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RESEARCH ARTICLE

CLINICAL USEFULNESS OF ASPARTATE AMINOTRANSFERASE TO PLATELET RATIO INDEX FOR THE DIAGNOSIS OF LIVER DISEASES

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Abstract

Chronic liver diseases are on the increase world wide among which Chronic Hepatitis C (CHC), Chronic Hepatitis B (CHB) are predominant. Several causative factors have been identified so far. In all such liver diseases, LFTs are the first line of testing done in clinical laboratories followed by CBC and other important microbiology tests if an infections microorganism is the causative agent. While advanced fibrosis factors like FIB-4 are used to confirm the degree of liver damage, simple LFT are routinely done. Aspartate Aminotransferase to Platelet Ratio Index (APRI) is now emerging as an additional calculated parameter to substantiate LFTs. This research article presents the association found between individual LFTs and APRI, and good association was found between liver specific tests and APRI, suggesting that APRI could be included as an additional diagnostically useful parameter for routine clinical use for the diagnosis of liver diseases.

INTRODUCTION

Chronic hepatitis C (CHC) is one of the most important causes of chronic liver disease in the world, potentially resulting in cirrhosis, Hepato Cellular Carcinoma (HCC), and the need for liver transplantation. Liver biopsy is currently performed before therapy indication. Although, it is the golden standard there are many reasons to avoid or delay the procedure. APRI Score is an easy, low cost alternative method for assessing structural changes in CHC. APRI is a serological marker that has satisfactory sensitivity and specificity together with a high predictive value and it can be useful either in the absence of a biopsy or to reduce the frequency with which biopsies need to be carried out to monitor the evolution of CHC and the right moment for treatment indication.(Borsoi Viana et al., 2009)

In CHC, liver biopsy is the gold standard method for assessing liver histology, however it is invasive and can have complications. Non-invasive markers have been proposed and APRI has been shown as an easy and inexpensive marker of liver fibrosis. The Area Under Receiver Operating Curve (AUROC) of APRI for predicting significant fibrosis and cirrhosis were 0.92 (0.83-1.00) and 0.92 (0.85-1.00), respectively. Using cut-off values recommended by prior studies, significant fibrosis could be identified in 44% of liver biopsy and 66% of cirrhosis patients. APRI could identify significant fibrosis and cirrhosis at a high degree of accuracy to differentiate the above two disorders. (Silva et al., 2008)

APRI will be useful as a non-invasive marker of fibrosis and cirrhosis in children with chronic viral hepatitis. The AURUC were 0.71 for fibrosis and 0.52 for cirrhosis. When examining subgroups, the APRI performed better in older patients and in those with vertically transmitted HCV. (Katherine E et al., 2010). An ideal noninvasive diagnostic test for hepatic fibrosis should be simple, inexpensive, and accurate. APRI showed a significant correlation with hepatic fibrosis, and was superior to AST, AST/ALT ratio and platelet in predicting patients with significant fibrosis (fibrosis stage 3, 4) can be identified to have APRI = 1 with sensitivity a 71.2% and specificity of 70.3%. The sensitivity and specificity of an APRI = 1.5 for cirrhosis (stage 4) were 83.3% and 75.0%. Simple index using AST and platelet value can predict the presence of significant fibrosis and cirrhosis in CHB patients without clinical evidence of cirrhosis. (Sim SJ et al., 2005). APRI has low sensitivity and specificity for the diagnosis of significant fibrosis in patients with Alcoholic Liver Disease (ALD) including patients who have hepatitis C. Given the frequent history of alcohol use in patients with hepatitis C, APRI may be of limited usefulness in the diagnosis of fibrosis in many patients (Lieber CS et al., 2006).

APRI may be a useful noninvasive marker in the exclusion of both significant fibrosis and cirrhosis in patients with CHB. However, it is not accurate in the prediction of either significant fibrosis or cirrhosis. (Güzelbulut F et al., 2012) An APRI score of 0.99 had a comparably high negative predictive value for significant fibrosis (F3-F4) in African American 0.90 and in white veterans 0.83. For cirrhosis (F4), an APRI score of 1.0 provided a negative predictive value of 0.96 in the African American subset and 0.94 in the White subset. No difference were found in the performance of the APRI score for predicting stages of fibrosis between the two groups. The APRI score displayed similar performance in African Americans and Whites. A threshold of 1.0 can reliably exclude cirrhosis in African American veterans with chronic HCV infection (Burton MJ et al., 2011).

The combination of APRI< or = 0.50 and APRI>1.50 classified correctly 36% of patients with or without significant fibrosis, while the combination of APRI< or = 1.00 and APRI>2.00 classified correctly 62% of patients with or without cirrhosis. There was no significant difference in the predictive values of APRI between patients with CHC and CHB. APRI is significantly associated with the extent of fibrosis, but it does not classify correctly 40-65% of patients with CHC or HBeAg-negative CHB and thus it cannot replace liver biopsy (Chrysanthos NV et al., 2006). Longitudinal comparison demonstrated a persistently higher APRI value in HBV patients who developed HCC during follow-up than those remaining cancer free. APRI might be a marker of HCC risk in HBV patients in cirrhosis-dependent and independent manners. Further studies are warranted to validate this finding and test its clinical applicability in HCC prevention (Hann HW et al., 2015). Liver fibrosis may be a risk factor for mortality during Antiretroviral Therapy among HIV-infected individuals in Africa. APRI is an inexpensive and potentially useful test for liver fibrosis in resource-constrained settings (Vinikoor MJ et al., 2015).

APRI score has been studied as a marker of liver cirrhosis and portal hypertension, but has not been evaluated in the setting of acute Upper Gastrointestinal Bleeding (UGIB). The APRI score performed well in predicting a variceal etiology of acute UGIB, with AUROC 0.89. The APRI score is an objective metric that helps predict a variceal etiology of acute UGIB. Using this rule could improve adherence to guidelines on management of UGIB. Although studies are unable to demonstrate a survival benefit, improved adherence to evidence-based guidelines serves as a metric related to this most important outcome measure. Prospective study to validate these findings is indicated (Civan JM et al., 2015). The AUROC to study the performance of APRI for predicting High Portal Pessure (HPP) >12 mmHg) had AUROC of 0.716 (95% CI 0.574–0.858). An APRI of ≥1.09 had a sensitivity 66%, specificity 73%, positive predictive value 85%, negative predictive value 47%, and diagnostic accuracy 68% for predicting HPP >12 mmHg. APRI correlates fairly with HVPG in patients of cirrhosis. An APRI score of ≥1.09 seems to have an acceptable accuracy for prediction of high portal pressure. APRI is a fair, bedside, cost-effective parameter for diagnosis of HPP in patients with cirrhosis (Vipin Verma et al., 2014). APRI could significantly predict cirrhosis but not significant fibrosis. AUROC for cirrhosis was 0.67 (95% CI= 0.45-0.89; p=0.13). APRI, a non invasive, easy to obtain bedside test which significantly predicts cirrhosis but not fibrosis in pediatric patients with Intestinal failure Associated Liver Disease (IFALD). As the clinicians need a non invasive test to differentiate among different stages of liver fibrosis rather than differentiating cirrhosis from normal, one cannot recommend the use of this test in pediatric patients with IFALD for this purpose (Juan J Díaz et al., 2013).

Meta-regression analysis indicated that the accuracy of APRI for both significant fibrosis and cirrhosis was affected by histological classification systems, but not influenced by the interval between Biopsy & APRI or blind biopsy. Meta-analysis suggests that APRI show limited value in identifying hepatitis B-related significant fibrosis and cirrhosis (Wenwen Jin et al., 2014). In discriminating patients with histological fibrosis score >2, APRI provided the best AUROC of 0.80 in comparison to the other four non-invasive liver fibrosis tests. The AUROC of APRI was better in female (0.871) than in male (0.753) recipients. Among female recipients, an APRI value >1.4

was 91% sensitive and 75% specific in detecting a staging score >2. The corresponding values among male recipients were 60% and 77%, respectively. Among non-invasive liver fibrosis tests, APRI has the highest diagnostic value in discriminating liver transplant patients with progression to significant liver fibrosis, although its accuracy is influenced by recipient sex (Pierluigi Toniutto et al., 2007). APRI was significantly associated with fibrosis scores in patients with CHC and NAFLD, but not in those with CHB In patients with CHC, the APRI showed a sensitivity of 72.7% and a specificity of 62.4% for detection of fibrosis. In the NAFLD group, the APRI showed a sensitivity of 60.0% and specificity of 73.3% for detection of fibrosis ($p<0.01$). In patients with CHB, the APRI showed a sensitivity of 55.0% and a specificity of 75.4% for fibrosis (p=NS). The APRI shows an acceptable accuracy for the assessment of liver fibrosis in patients with CHC and NAFLD, but not in those with CHB (Yusuf Yilmaz et al., 2011).

MATERIALS AND METHODS

30 patients in the age group of 16-77 years consisting of males and female were selected for this study. All 30 patients attended the Liver clinic and the control group patients of an equal number were selected from those attending the Master Health Check up. The main aim of this study is to find out the association between each LFT test between patients and normal controls with respect to LFT and APRI.

Diuri CS 1300 B analyser and Dialab reagents were used to measure LFT and routine haematological parameters are processed using Siemens Advia 2120i fully automatic analyser. While the accuracy of all LFT were validated by the use of Bio-Rad accuracy controls at two levels, the accuracy of haematological parameters were validated by Siemens commercial controls available.

Inclusion Criteria

Patients who attended Liver Clinic and whose AST values were >200 U/L and routine Master Health Checkup patients who were investigated for the analytes used in this study were included.

Exclusion Criteria

All other patients attending the liver clinic and whose AST value was <200 U/L were excluded.

For Statistical analysis of data, a software downloaded from the website http:// www.vssarstats.com was used to calculate correlation coefficient (r), Student 't' distribution (t) and probability (p) between liver infected patients and controls.

RESULTS

Table I Mean & SD for Patients & Controls (n=30)

Group / Mean & SD		TBIL	DBIL	TP	ALB	SGOT	SGPT	GGT	ALP	PLT	WBC	ESR	APRI
Abnormal (n=30)	Mean	2.06	1.25	5.69	3.46	1291	653.6	133.7	119.4	155.5	14.1	15.4	43.5
	SD	1.97	1.72	1.17	0.64	3039.2	1416.7	176.5	82.04	85.91	7.36	18.5	115.3
Normal (n=30)	Mean	0.63	0.19	7.11	4.25	23.5	27	21	80.43	243.8	7.91	13.67	0.32
	SD	0.23	0.13	0.35	0.2	4.93	10.5	10.74	18.28	70.71	1.59	9.53	0.42

Table I shows the Mean & SD values obtained for LFT, WBC, ESR & calculated APRI for patients and controls. From Table I, it is clear that in liver disease patients, LFTs are mostly elevated as observed by increases

in bilirubin and all enzymes. Haematological Indices WBC, APRI, Platelet and A/G shows decrease confirming that liver function is indeed affected in liver disorders.

Table II : Statistical Parameters for Controls (n=30)

Analytes compared	r	t	p
AST VS APRI	0.66101	4.661	0.000635
ALT VS APRI	0.701832	5.213	0.0000075
PLT VS APRI	-0.6744	-4.833	0.000022
WBC VS APRI	-0.26301	-1.442	0.08016
ESR VS APRI	-0.26025	-1.427	0.0824

Table II presents statistical parameters (r, t & p) to find out the association between AST, ALT, PLT, WBC and ESR to APRI for the controls. From this Table, it is clear that APRI shows highest significant of <0.001 when compared with AST, ALT and Platelet and a modest significant of 0.08 when compared with both WBC and ESR. From this statistical analysis, it is confirmed that APRI value is indeed associated with the liver specific enzymes AST and ALT as well as to PLT justifying that APRI is a useful marker to identify liver related disorders like cirrhosis, fibrosis and cancer.

Table III : Statistical Parameters for Patients with AST >200 U/L (n=30)

Analytes compared	r	t	p
TP VS APRI	-0.3370	-1.894	0.034
ALB VS APRI	-0.3906	2.245	0.0164
AST VS APRI	0.9100	11.614	0.000001
ALT VS APRI	0.7849	6.793	0.000001
PLT VS APRI	-0.3638	-2.067	0.024

Table III shows the statistical parameters obtained for patients whose AST level was > 200 U/L. While both AST and ALT showed a highly significant association to APRI (P <0.00001), TP, albumin and PLT gave a significant association with a P value of <0.05, confirming that APRI is an additional useful parameter to diagnose patients with liver diseases.

Table IV : Statistical Parameters (Patients Vs Controls) (n=30)

Analytes compared	r	t	p
N.TP VS A.TP	0.259	1.419	0.08
N.AST VS A.AST	0.498	3.039	0.0026
N.ALT VS A.ALT	0.568	3.652	0.00053
N.GGTP VS A.GGTP	0.461	2.749	0.00518
N.APRI VS A.APRI	0.524	3.255	0.001479

Table IV presents similar statistical data but between patients and controls when individual LFT tests are compared. A highly significant association was noted for the liver specific enzyme ALT (P< 0.001) followed by good correlations for AST, GGT and APRI at a P value of <0.01. These data indicates strongly that APRI could be used as additional diagnostically useful calculated parameter derived from CBC test.

DISCUSSION

Chronic liver diseases are on the increase and in most conditons, LFTs are generally used for diagnosis. Many studies done in the past have recommended the use of advanced fibrosis scoring systems to grade the degree of liver damage. Further, CBC is a routine test usually investigated along with LFT, but however the use of APRI has not been investigated extensively. Few studies done have correlated APRI to liver fibrosis scores but not with individual LFTs [(2)]. Most of the studies done earlier have correlated APRI to FIB-4 scores and suggested its clinical use [(5,7,8,910)]. Studied have also been done in all CHC, CHB & HCC patients linking APRI to NAFLD and but they did not do any correlation of such results to LFT & CBC [(11,12,13)]. The outcome of this study has strongly established associations between APRI and LFTs and recommends that APRI be included along with LFT and CBC as an additional parameter for patients attending liver clinic.

CONCLUSION

Generally in all liver related disorders like cirrhosis, hepatitis, virus infections, LFT is routinely done to assess the degree of liver damage. While advanced fibrosis factors and liver biopsies are used to diagnose severe liver damage, routine LFTs are sufficient for the preliminary diagnosis. APRI is now emerging as a diagnostically useful calculated parameter and this research work done by correlating LFTs with APRI has given solid information to include APRI as a routine test for all liver related disorders. Further research are required to confirm the findings of this study on a large number of patients and to recommend APRI as routine test along with other investigations for patients attending liver clinic.

Conflict of Interest : None

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