Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2017; 5(4B):1297-1303 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com DOI: 10.36347/sjams.2017.v05i04.016

Original Research Article

Aminotransferase -to-Platelet Ratio Index as Predictive Marker for Liver Cirrhosis

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Abstract: Cirrhosis is a condition in which the liver slowly deteriorates and is unable to function normally due to chronic, or long lasting, injury. Liver biopsy is considered as a gold standard for the diagnosis of cirrhosis and has many problems like bleeding, infective peritonitis which limit use of liver biopsies in all patients. Until date there is no non-invasive marker to replace it. Aim to evaluate the Aspartate aminotransferase-to-platelet ratio index (APRI) as a predictive marker for liver cirrhosis. Material and Methods the present study was analytical cross-sectional study carried out during Aug 2016 to Dec 2016, at Al Khartoum State. A total one hundred individuals were enrolled in this study, and classified into two groups 50 patients with liver cirrhosis diagnosed by ultrasound as case group and 50 healthy individuals as control group. Platelet count and Aspartate aminotransferase (AST) were done using Mindary BC3000 plus hematology analyzer and mindary BA-88A Semi-auto Chemistry Analyzer respectively. APRI was calculated for every patient using the formula {(AST / ULN) x 100}/platelet count (109/L).The Predictive value of APRI was evaluated with a receiver-operating characteristics (ROC) curve. Results the level AST was significantly increased in cirrhosis cases than that in control and the platelet count was significantly lower in cirrhosis cases than that in control, furthermore the APRI level was significantly higher in cirrhosis cases than that in control cases (p-value 0.000, 0.000, 0.000) respectively. Also the study found that the level of AST, platelets count and APRI level was not significantly affected by cirrhosis gender (p-value 0.499, 0.870, 0.452) respectively. Also very strong and highly significant correlations were observed between level of AST and APRI (r=0.901**,p <0.01) and medium and highly significant correlations between the level of platelets count and APRI (r=0.413**,P<0.01) .Also the study found that the level of APRI can predict cirrhosis with high degree of efficiency, the sensitivity and specificity of APRI was found to be 96.0% and 100.0% respectively, also positive and negative predictive values were 100.0% and 96.0%respectively, with area under the ROC curve of 0.999,P<0.01 (95% CI) at cut-off 0.64 . This study conclude that there is APRI can predict cirrhosis with high degree of accuracy, and there is no significant difference was observed between cirrhosis genders for the level of APRI and it can be used in areas where facilities for liver biopsy and advanced imaging techniques are not available.
Keywords: liver cirrhosis, Aspartate aminotransferase, Aspartate aminotransferase-to-platelet ratio index

INTRODUCTION:

Cirrhosis is a condition in which the liver slowly deteriorates and is unable to function normally due to chronic, or long lasting, injury. Scar tissue replaces healthy liver tissue and partially blocks the flow of blood through the liver [1]. Liver biopsy is the gold standard for the overall evaluation of the liver histological lesions in any type of liver disease [2]. This is an invasive procedure subject to inter observer variability and sampling error of biopsies; biopsy length and fragmentation influences its reliability and histopathological results. There are a number of other complications like bleeding, pneumothorax, infective peritonitis which limit the use of liver biopsies in all patients [3]. Several non-invasive biochemical tests like Fibro Test , hepascore, transient electrography [4], fibrospect, forns index, AAR, etc. are currently in use

[5] requiring complex calculations and expensive biochemical assays.

An ideal non-invasive diagnostic test for hepatic fibrosis should be simple, readily available, reproducible, inexpensive, and accurate. Aspartate aminotransferase: Platelet Ratio Index (APRI) was reported as a novel index for prediction of significant fibrosis and cirrhosis [6]. Some of the previous studies demonstrate the APRI could identify cirrhosis with high degree of accuracy in the studied patients [7], APRI is closely associated with liver cirrhosis in patients undergoing surgery for HCC [8] and meta-analysis suggests that APRI show limited value in identifying hepatitis B-related significant fibrosis and cirrhosis [9].

MATERIALS AND METHODS:

The study was conducted in Khartoum state, during Aug 2016__Dec 2016, Patient enrolled in this study were from Ibn Sina Hospital.

Study population and Sample size:

One hundred individuals were enrolled in this study, and classified into two groups, 50 patients with liver cirrhosis diagnosed by ultrasound as case group and 50 healthy individuals as control group

Selection criteria:

Inclusion criteria:

Patients with liver cirrhosis and healthy control

Exclusion criteria:

The exclusion criteria were liver disorders other than cirrhosis, Hematological disorders like (hemophilia, malignancy, Drug-induced Thrombocytopenia) and chronic disorders like (diabetes, hypertension, cardiac diseases, and renal failure), any surgical history or patient's unwillingness to participate in the study.

Data collection:

Standard questionnaire was used to obtain the clinical data for each participant in this study.

Sample collection:

Samples were collected using dry, plastic syringes, tourniquet was used to make the veins more prominent, 5ml blood samples was collected in two containers, 2.5 ml of blood samples was collected in EDTA blood container for platelet count by use fully automatic Mindary BC3000 plus Auto analyzer and 2.5 ml of blood samples was collected in plane containers were allowed to clot at 25°, and then they were centrifuged at 4000 rpm to obtain the serum samples, and stored in -20° until used to measure of Aspartate aminotransferase(AST).

Biochemical measurements:

a. Platelet count:

A complete haemogram was done by using a Mindary BC3000 plus hematology analyzer within four hours of the blood collection. Dedicated reagents and standard methodologies were used. The two level quality controls were run and the analyzer was maintained according to the manufacturer's instructions during the entire period of the study.

b. Quantitative determination of aspartate aminotransferase (AST)

Aspartate aminotransferase (AST) was measured by kinetic method by using mindary BA-88A Semi-auto Chemistry Analyzer.

Ethical consideration:

Ethical Clearance was obtain from Chemical Pathology department (University of Alzaim Alazhari) and Informed Consent was taken from every Participant .

Statistical Analysis:

All data were analyzed using SPSS (statistical packages for social science), version 11.5. Descriptive statistics, student t test was used to compare between two groups, correlation test was used to fine any correlation between AST and PLT count with APRI and ROC curve was used to calculate the cut-off points for APRI. P-value < 0.05 was considered significant.

RESULTS:

The present study was conducted using a total of hundred participants, 50 patients of liver cirrhosis diagnosed by Ultrasound (case), 34 (68.0%) were male and 16 (32.0%) were female, and 50 healthy participants (control), 26(52%) were male corresponding to 24 (48%) were female (table 3-1). This study revealed that the mean ± SD of the AST level in the case and control were (76.2±42.7 IU) and (24.2±5.5) with significantly increased in cirrhosis cases than that in control cases by about 214.9 %, and the mean ± SD of the platelet count in the case and control were (110.7±30.9×103/µl) and (297.5±73.5×103/µl) with significantly lower in cirrhosis cases than that in control cases by about 214.9 %, furthermore in table 2 shows the mean ± SD of the APRI level in the case and control were (1.85±1.18) and (0.22±0.07) with significantly higher in cirrhosis cases than that in control cases by about 740.9% (table 3-2).

This study indicate that level of AST, platelets count and APRI level was not significantly affected by cirrhosis gender p value (0.499, 0.870, 0.452) respectively table (3-3) . Also in figure 1, 2 show very strong and highly significant correlations were observed between level of level of AST and APRI (r=0.901**, p <0.01) and medium and highly significant correlations between the level of platelets count and APRI (r=0.413**, P<0.01). Based on ROC curve selected different cut-off for the predict the absence or presence of cirrhosis and chose the suitable cut-off with high specificity and sensitivity .In this study the cut-off was chosen (0.64) with sensitivity and specificity of APRI was found to be 96.0% and 100.0% respectively, and the positive and negative predictive values were 100.0% and 96.0% respectively with significantly Area under the curve (AUC) (0.999, P<0.01).

Table: 3-1: The frequency and percentage of gender for control and cirrhosis cases

Variable	Control n=50	Case n =50	P-value
Male	26(52%)	34(68%)	0.000
Female	24(48%)	16(32%)	0.016

Table 3- 2: Mean differences of AST, Platelet count and APRI level in cirrhosis cases and control group :

Variable	Control n = 50	Cases n = 50	P-value
AST	24.2±5.5 (12.0 - 36.0)	76.2±42.7 (21.0 -204.0)	0.000
Platelet count	297.1±73.5 (154.0 - 482.0)	110.7±30.9 (56.0 -220.0)	0.000
APRI	0.22±0.07 (0.08 – 0.37)	1.85±1.20 (0.35 – 6.07)	0.000

T test was used to calculate P value.
P value less than 0.05 considered significant.
Mean ±SD.
Minimum – Maximum between the brackets.

Table: 3- 3: Mean differences of AST, Platelet count and APRI level in cirrhosis cases regarding to gender:

Variable	Male	Female	P-value
AST	73.3±39.1	88.2±50.3	0.499
Platelet count	111.2±34.4	109.6±22.8	0.870
APRI	1.77±1.04	2.04±1.45	0.452

T test was used to calculate P value.
P value less than 0.05 considered significant.
Mean ± SD

Table: 3-4: Diagnostic efficiency of the APRI in predicting cirrhosis with different cut-off :

Cut-off	Sensitivity	specificity	PPV	NPV
(0.36)	98%	96%	96.1%	97.9%
(0.64)	96%	100%	100%	96.1%
(0.79)	94%	100%	100%	94%
(0.88)	92%	100%	100%	92.6%
(1.00)	82%	100%	100%	84.8%

ROC curve used to calculate the cut-off.
PPV (Positive Predictive Value).
NPV (Negative Predictive Value).

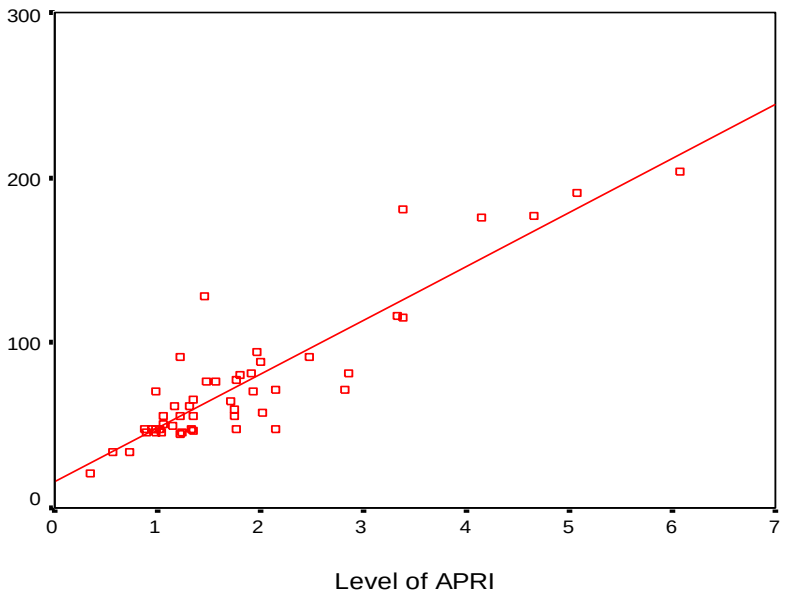

Fig 3-1: correlation between the level of AST and APRI in cirrhosis cases (R 0.901, P 0.000).

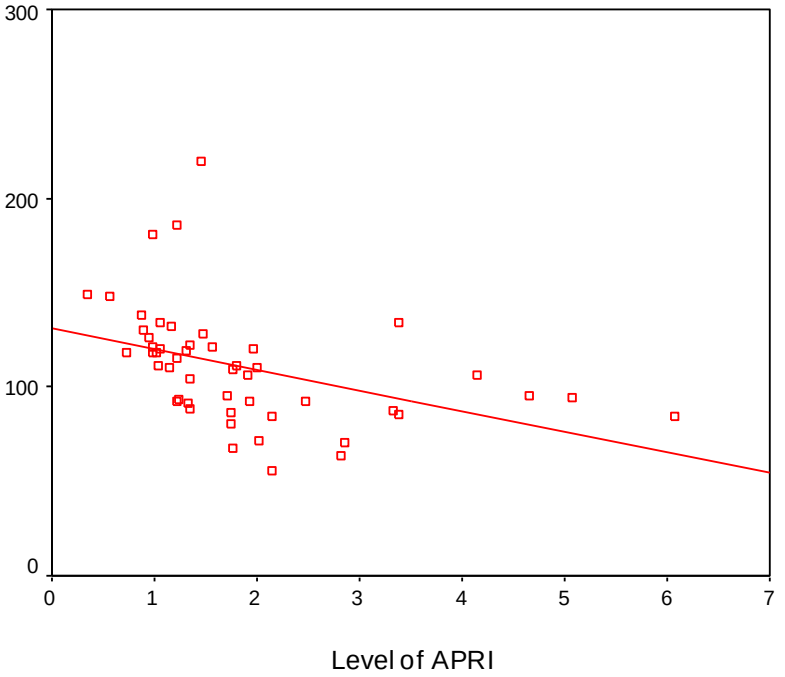

Fig 3-2: correlation between the level of platelet count and APRI in cirrhosis cases (R 0.413, P 0.003).

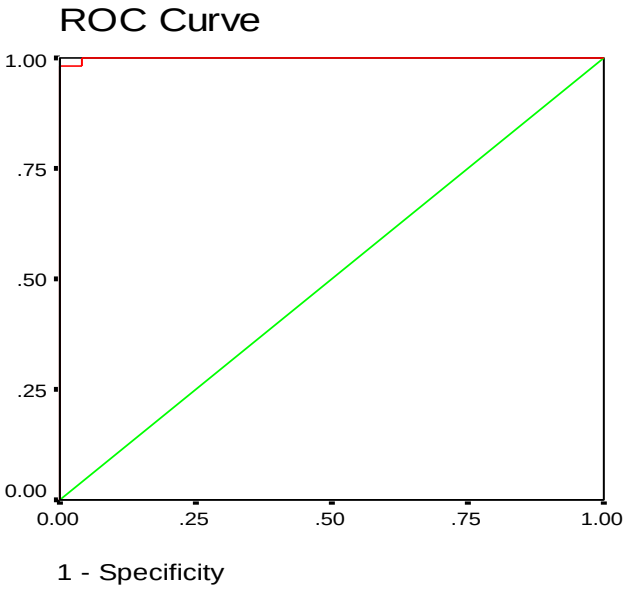

Fig 3-3: Receiver Operating Characteristic (ROC) Curve for Aspartate aminotransferase-to-platelet ratio index (APRI) as predictive marker for liver cirrhosis (AUC 0.999, p-value 0.000)

DISCUSSION:

The present study predicted the efficiency of APRI as a bedside non-invasive marker for cirrhosis in Khartoum state and this study showed that APRI is a fair and accurate non-invasive marker for cirrhosis with high specificity and sensitivity. The low cost and easy availability of two variables (AST and platelets) makes APRI a useful and simple bedside test [10]. In this study showed the AST level in cirrhosis patients was significantly increased (76.2±42.7 IU) than that in control (24.2±5.5) by about 214.9 %. This may be attributed to Chronic liver disease with associated hepatocyte death, as evidenced by elevated serum transaminase levels, results in inflammation followed by fibrosis [11]. And the platelet count was significantly lower in cirrhosis cases (110.7±30.9×103/µl) as compared to control (297.5±73.5×103/µl), with a reduction estimated by about 62.8 %. This may be due to defect in the function of liver which produced most of coagulation factors and thrombopoitien hormone and some of complication of liver cirrhosis(secondary hyperfibrinolysis, accelerated intravascular coagulation and splenomegaly) may be lead to reduce the platelet count [12].. On the other hand the level of APRI was also significantly higher in cirrhosis cases (1.85±1.18) in comparison to that in control subjects (0.22±0.07), with an increase estimated by about 740.9% as show in (table 2), also in this study the level of AST and platelet count was not significantly affected by gender, Furthermore, no significant difference was observed between cirrhosis genders for the level of APRI (table4). Based on these statements, the matrix correlation in table 5, shows that there was very strong and highly significant (P<0.01) correlation between level of AST and APRI (r=0.901**), whereas the correlation between the level of platelets count and APRI was medium and highly significant (r=0.413**, P<0.01). finally based on the diagnostic efficiency of APRI by ROC curve Table 6,7 shown the Area under the curve (AUC) of APRI for predicting cirrhosis was significantly 0.999 and sensitivity and specificity of APRI was found to be 96.0% and 100.0% respectively. Also the positive and negative predictive values were 100.0% and 96.0%respectively. Many of the studies show agree with this result and other will not , Jain, Princi *et al.;* the sensitivity and specificity of the APRI test was found to be 96% and 96.1% respectively with negative predictive value (NPV) and Positive predictive value (PPV) of 96% and 96.1% respectively. Under area the ROC curve of 0.973 (95% CI) at cut-off 0.65(7). Whereas Wai *et al.;* have found that using the cut-off APRI values of 1.00 and 2.00, as determined by the ROC curves, significant fibrosis could be predicted accurately in 51% and cirrhosis in 81% of patients. The AUC of APRI for predicting significant fibrosis and cirrhosis in the validation set were 0.88 and 0.94, respectively [13]. In a study by Roger *et al.;* the APRI performed substantially better than the AST/ALT ratio for diagnosing fibrosis or cirrhosis [14]. Also, Sirli R *et al.;* APRI results had 81% sensitivity and 50%

specificity in predicting significant fibrosis and that with a cut-off value of 1, the sensitivity and specificity for predicting cirrhosis were 76% and 71%, respectively [15]. However the Meta analysis by Jin *et al.;* suggested limited value of APRI in identifying Hepatitis B related significant fibrosis and cirrhosis [16], and Jason *et al.;* in 2015 reported Serum and imaging non-invasive markers of fibrosis may have insufficient accuracy when used in isolation; however, a combination of markers may allow sufficient accuracy to systematically identify patients with cirrhosis [17].

CONCLUSION:

This study conclude that the APRI can predict cirrhosis with high degree of efficiency, the sensitivity and specificity of APRI was found to be 96.0% and 100.0% respectively, also positive and negative predictive values were 100.0% and 96.0%respectively. Also conclude that there is no significant difference was observed between cirrhosis genders for the level of APRI and it can be used in areas where facilities for liver biopsy and advanced imaging techniques are not available. Further prospective studies are recommended to validate the APRI with liver biopsy which is the gold standard for the diagnosis of cirrhosis, and find a relationship of APRI score with patients of cirrhosis caused by different a etiology, and take up the issue of histopathological diagnosis of cirrhosis where APRI score can be correlated with the grade of fibrosis.

ACKNOWLEDGEMENTS

First of all I thanks full for god to give me the power and the ability to complete this great work .I would like to express my deepest thanks to my Supervisor Dr: Nasr Eldin Mohamed Ahmed Shrif who had been a great help for me in this work. My thank also extend to Dr. Abdelgadir Eltom and all the staff of Al zaeim Al Azhari university faculty of Medical laboratory science specially department of Clinical Chemistry

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