ASPARTATE AMINOTRANSFERASE PLATELET RATIO INDEX AS A NON-INVASIVE PREDICTOR FOR ESOPHAGEAL VARICES

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ABSTRACT

Objective: To determine the diagnostic accuracy of Aspartate Aminotransferase Platelet Ratio Index (APRI) as a predictor for esophageal varices.

Study Design: Cross-sectional validation study.

Place and Duration of Study: Department of Medicine, PNS Shifa Hospital Karachi, from Oct 2015 to Sep 2016.

Patients and Methods: One hundred and thirty five patients were enrolled in this study. Patients included in this study belonged to both genders, and were aged between 18 to 80 years. Cirrhosis was detected by Ultrasonography. Platelet count and Serum Aspartate Aminotransferase (AST) levels were performed in pathology laboratory. APRI ratio was calculated by using the formula AST (times above upper limit of normal)/ platelets x (10^9/L) x 100. For each patient APRI was determined with a cutoff value of 1.3. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value of APRI were calculated by comparing it with upper gastrointestinal endoscopy as a gold-standard.

Results: In this cross sectional validation study, 27.4% (n=37) were aged between 18-40 years, 52.6% (n=71) were aged between 41 to 60 years and 27% (n=20) were aged between 61 to 80 years of age respectively, and mean ± SD was calculated as 48.6 ± 14.3. Amongst the total, 63.7% (n=86) were males whereas 36.3% (n=49) were females. The diagnostic accuracy of APRI was determined, considering endoscopy as gold standard, 65 % (n=65) were true positive, 35% (n=35) were false positive, 51.4% (n=18) were false negative and 48.57% (n=17) were true negative. Sensitivity, specificity and accuracy of APRI were 78.3%, 32.7% and 60.7%, respectively. Positive predictive value, negative predictive and diagnostic accuracy of APRI was 65.0%, 48.5% and 60.7% respectively.

Conclusion: Our study results signify that APRI is an unsuitable replacement for endoscopy and cannot help in the screening of esophageal varices among cirrhotics because of low specificity and negative predictive value hence proved that we need further evaluation/trials to use APRI as a screening test in our domestic population.

Keywords: Aspartate Aminotransferase, Aspartate aminotransferase platelet ratio index, Esophageal Varices.

INTRODUCTION

Esophageal varices (EV) are dilated collateral veins in the esophageal wall that project directly into the lumen. They are the second principle cause of death in cirrhotics and its prevalence in decompensated cirrhotics is 60% where as in compensated cirrhotics which is 30%[1]. About 30% of these patients will experience a episode of variceal hemorrhage within a year of diagnosis[2]. In patients with Child Class A and Child Class C disease, 6-week mortality for a single event of variceal bleed ranges from 0% to 30% respectively[3].

The evolution of EV is clinically mute and there is no current non-invasive screening technique to identify its development, progression and diagnosis. Keeping in view the above, the Beveno IV, consensus report recommended screening of all cirrhotics with endoscopy for EV[4].Invasive procedures like endoscopy are hazardous so non-invasive procedures are being formulated to decrease the financial burden on tax payers and health care systems. EV develop very slowly and silently over a span of many years in cirrhotic patients, endoscopy is scheduled after 2 to 3 years in patients without

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EV and in decompensated cirrhosis it is done yearly[5].

World wide data has shown that factors like splenomegaly, ascites, spider naevi, Child's grade, platelet count, prothrombin time/activity, portal vein diameter, serum albumin, and serum bilirubin as noteworthy forecasters to perceive the early existence of esophageal varices[6]. A large number of non-invasive screening tests e.g. liver stiffness measurement (LSM), platelet count/ spleen diameter ratio (PSR), spleen stiffness measurement (SSM) etc are being thoroughly researched. PSR appears to be the most accurate and validated non-invasive screening test for EV in patients with compensated cirrhosis with a cut-off of 909, and it could be clinically useful to avoid endoscopies in a large population of patients[7]. Similarly, like PSR an index Aspartate Aminotransferase-To-Platelet Ratio Index (APRI) has restricted financial insinuations and extensive accessibility[8]. In the identification of fibrosis the sensitivities and specificities of APRI fluctuate from 41% to 91% and 47% to 95% respectively. Cheung *et al.* postulated that in chronic hepatitis C patients, APRI was superior in foretelling progressive fibrosis. According to the writers, in order to identify hepatic fibrosis APRI's with a cutoff of 0.5 and 1.5 can be employed in daily clinics[9].

Various causes like portal hypertension, viral hepatitis, platelet destruction by antibodies, alcohol etc may lead to a diminished platelet count in cirrhotics. With the advancement of liver disease, hepatic toxicity and membrane seepage may lead to an upsurge of AST levels resulting in modification in splenic blood course and diminution of platelet count[10]. Stark alteration in parenchyma of liver epitomized by fibrosis, escalating resistance of intrahepatic circulation and capillarization of sinusoids may result in portal hypertension in cirrhotics with an APRI greater than 1.64[11]. APRI is a decent pointer of fibrosis and employs platelet count as its denominator, whereas the existence of esophageal varices with a sensitivity of 64.70% and a specificity of 72.7% can be envisaged by an APRI cutoff value greater than 1.3[12].

Ours is a developing country and health care sources are very limited. Basic invasive procedures like upper gastrointestinal endoscopy are costly and available at limited tertiary care hospitals. Keeping in view the alarming situation of the rise in number of cirrhotic patients secondary to various causes in our country, it is necessary to devise/find a cheap yet accurate method of non-invasively predicting esophageal varices. APRI is an easily available and cost effective parameter. The purpose of this study is to devise a non-invasive marker like APRI for predicting esophageal varices. This ratio can help us to screen high risk patients with esophageal varices so that these patients can be put on primary prophylaxis against bleeding before being transferred to teritiary health centres for invasive endoscopy if necessary.

PATIENTS AND METHODS

The institute's ethical committee approved the study for research and all procedures followed in harmony with the ethical principles of the responsible committee on human experimentation and in the line with Helsinki Declaration of 1975, as revised in 2000. The cross sectional validation study was conducted at the Department of Medicine, PNS Shifa Hospital Karachi from October 2015 to September 2016. One hundred and thirty five known cirrhotic patients (irrespective of the cause) from both genders, aged 18-80 years were selected from outpatient departments via non-probability convenient sampling. Patients with muscular disorders, cardiac issues or any other cause of thrombocytopenia were excluded. Sample size was calculated by world health organization (WHO) sample size calculator, keeping sensitivity: 64.70%[12], specificity: 72.7%[12], expected prevalence: 60%[12] and confidence interval: 95.

Each patient was explained about the technique and protocol of ultrasound examination of abdomen in detail and related instructions were given for the procedure. The patient

was examined in supine position with arms resting by the side during quiet respiration and liver echotexture was identify by an expert ultrasonologist. APRI was calculated, using the above mentioned formula. Within 24 hours of admission, blood sample was drawn under aseptic technique and sent to specified laboratory of the hospital on the same day. Aspartate Aminotransferase (AST) and platelet levels were measured under the supervision of an experienced pathologist. EV were confirmed on upper gastrointestinal endoscopy by a consultant gastroenterologist. All relevant data was collected on a predesigned proforma. All the data were analyzed using SPSS version 17.0.2 x 2 table was constructed to calculate sensitivity, specificity, predictive values and accuracy. Mean and standard deviation (mean ± SD) was calculated for quantitative variables like age. Frequency and percentages were calculated for qualitative measures like gender.

RESULTS

Total 135 patients of this study group segregated on the basis of the inclusion/ exclusion criteria were analyzed and the diagnostic accuracy of APRI to predict EV was calculated. Table-I & II are depicting the age and gender wise distribution of patients respectively, whereas table-III gives the comparison of

Table-I: Distribution of cases by age

Age (Year)	Number	Percentage
18-40	37	27.4
41-60	71	52.6
61-80	27	20.0
Total	135	100.0
Mean ± SD	48.6 ± 14.3	

Table-II: Distribution of cases by gender

Gender	Number	Percentage
Male	86	63.7
Female	49	36.3
Total	135	100.0

Table-III: Comparison ofAspartate amino transferase platelet ratio index (APRI) and endoscopic findings (n=135).

Aspartate Aminotransferase Platelet Ratio Index	Endoscopy (Gold Standard)		Total
	Esophageal varices (Positive)	Esophageal varices (Negative)	
>1.3	True Positive(a) 65 (65%)	False Positive (b) 35 (35%)	100
<1.3	False Negative (c) 18 (51.4%)	True Negative(d) 17 (48.57%)	35
Total	83 (61.4%)	52 (38.5)	135

Table-IV: Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic Accuracy of Aspartate aminotransferase platelet ratio index(APRI) (n=135).

Sensitivity	78.3%
Specificity	32.7%
Positive Predictive Value	65.0%
Negative Predictive	48.5%
Diagnostic accuracy	60.7%

Sensitivity = a / (a+c), Specificity = d / (b+d), Positive predictive value = a / (a+b), Negative predictive value = d / (c+d), Diagnostic accuracy = (a+d) / (a+b+c+d) x 100

APRI and endoscopic finding. Table-IV shows sensitivity, specificity, predictive values and diagnostic accuracy. Figure shows area under the receiver operating characteristic (ROC) curve was 0.559 [95% CI (0.471 to 0.644)]. Left corner of the curve shows perfect prediction with 100% sensitivity and 100% specificity.

DISCUSSION

A total of 30-40% of the cirrhotics may have a dreadful complication of portal hypertension like upper GI bleed. Amassed cases of liver diseases may result in variceal hemorrhage,concomitant with a high morbidity/ mortality rate, and huge financial implications.

According to the Benevo IV consensus screening of all cirrhotics is obligatory for the growth of EVs[13].

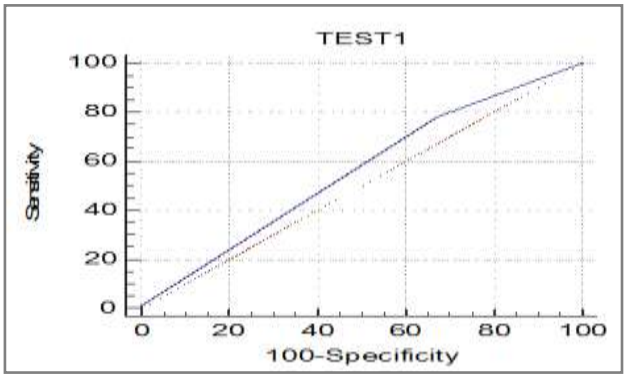

Figure: Receiver operating characteristic curves for the diagnosis.

However there are certain issues in third world countries due to which maximal treatment and screening is not possible. Besides the lack of trained staff including gastroenterologist and facilities like endoscopy units, poor socio-economic and educational status of patients also play a role. In such setup transferring every patient to big cities is not possible as it is not financially affordable by everyone. So in such a situation we need to have a non invasive test which can be carried out at district hospital level and does not require sophisticated laboratory equipment. In order to reduce the social, monetary and medical liability of the disease on the entire health organization, there is a dire need for a non-invasive test for the recognition of EVs[14].

Hepatic fibrosis is anticipated by APRI in a better way. Significant calculation errors are not seen in variables like platelet count and AST. Other existing possibilities of non-invasive measures to distinguish the existence of EV, conversely have not yet been recognized to be used as an alternative to endoscopy[15].

It has been reported that APRI is correlated with histologic degree of liver fibrosis and cirrhosis[16]. APRI may well be interrelated to the existence of EV was postulated by innovators like Sanyal, *et al*, while potal hypertension and APRI were correlated by Berzigotti, *et al*. Various studies have proposed different cutoff values for APRI like for Castéra, *et al* it was 1.3. The sensitivity, specificity, positive and negative predictive value of 68%, 64%, 51% and 78% respectively in their study. However as compared to our study these values were different.

Amongst the many non-invasive predictors being researched APRI is also being given considerable weightage. It is readily availabe and simple calculations without the requirement of complex gadgetries makes it more advantageous over other methods. It has a strong pathogeneic basis i.e. portal hypertension is associated with low levels of platelets and thrombopoietin resulting in hepatic parenchymal fibrosis.

Advanced fibrosis can also be predicted by AST/ALT ratio and research work is under consideration for its ability to identify EV. According to a study APRI score can be used as a preliminary test to discriminate patients who need a liver biopsy from those who do not, in resource poor settings where facilities for liver biopsy are not available[17]. In a study conducted by Civan and his companions an APRI score of 0.4 was used to guide early management of acute upper gastrointestinal bleed[18]. Similarly another study with a value of ≥1.0 showed a sensitivity, specificity, positive predictive value and negative predictive 68%, 89%, 77%, and 83% respectively for envisaging EV[19]. Globally, the AST/ALT ratio

detected EV in 81% patients. The AST/ALT ratio cutoffs were different for different pathological basis, however,they cannot foretell EVaccurately.

Based on our study with sensitivity, specificity and accuracy of aminotransferase platelet ratio index (APRI) of 78.3%, 32.7% and 60.7%, respectively and from data around the world, APRI, had low diagnostic precision in envisaging the occurrence of varices. Thus, they might not be acceptable to replace upper gastrointestinal endoscopy as a gold standard.

The gold standard procedure to detect EV is upper GI endoscopy. Spiegel conducted a study that showed that "Do Nothing" strategy was cheap though least effective. An incremental cost of $12,408 per additional variceal bleed prevented was associated with beta blocker therapy. In head to head comparision wih empirical beta-blocker treatment alone, endoscopy alongwith beta blocker and endoscopic variceal band ligation approaches costed nearby $175,000 additionally per variceal hemorrhage that could be prevented. The primary prophylaxis with beta blockers to prevent further incidence of variceal bleed is quite cheap, however if we additionally use endoscopy for screening purposes it increases the overall burden on financial resources with a low therapeutic advantage. In our setup this could be a viable options for our resource poor patients. We need further studies with different subsets of patient to further validate and revalidate such formulas. Amongst the newer predictors, acoustic radiation force impulse-virtual touch tissue quantification values of liver and spleen has certain predictive value for esophageal varices and it might be useful for primary screening of esophageal varices in post-hepatitis B cirrhosis patients[20].

CONCLUSIONS

Our study results signify that APRI is an unsuitable replacement for endoscopy and cannot help in the screening of esophageal varices among cirrhotics because of low specificity and negative predictive value hence proved that we need further evaluation/trials to use APRI as a screening test in our domestic population.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Zainab S, Qureshi HJ, Bukhari MR. Study of etiology and prevalence of esophageal varices in patients of liver cirrhosis. Pak J Med Health Sci 2012; 6(2): 459-462.
2. Jamil Z, Malik M, Durrani AA. Platelet count to splenic diameter ratio and other noninvasive markers as predictors of esophageal varices in patients with liver cirrhosis. Turk J Gastroenterol 2017; 28: 347-52.
3. Yeon S. Prevention and management of Esophageal Varices. Clin Mol Hepatol 2018; 24: 20-42.
4. Gillani SFM, Naseer M, Bhatti FSK, Saeed F,SamiUllah R. Fibroscan: A noninvasive tool for predicting early esophageal varices in chronic liver disease secondary to Hepatitis C virus infection. Pak Armed Forces Med J 2012; 4: 1-3.
5. Hussein HA, Tamer WM, Khalaf MS. AST/ALT Ratio for detection andseverity classification of Esophageal Varices in Child a HCV Liver cirrhosis Egyptian Patients. Life Sci J 2015; 12(4): 12-17.
6. Cherian JV, Deepak N, Ponnusamy RP, Somasundaram A, Jayanthi V. Non-invasive predictors of esophageal varices. Saudi J Gastroenterol 2011; 17: 64-68.
7. Sami SS, Harman D, Ragunath K,Bohning D, Parkes J, Guha IN.Non-invasive tests for the detection of oesophageal varices in compensated cirrhosis: systematic review and meta-analysis. United European Gastroenterol J 2018; 6(6): 806-818.
8. Zhijian Y, Hui L, Weiming Y,Zhanzhou L,Zhong C, Jinxin Z, et al. Role of the Aspartate Transaminase and Platelet Ratio Index in Assessing Hepatic Fibrosis and Liver Inflammation in Adolescent Patients with HBeAg-Positive Chronic Hepatitis B. Gastroenterology Research and Practice 2015; 1: 1-6.
9. Xiao G, Yang J, Yan L.Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis.Hepatology 2015; 61(1): 292-302.
10. Sert A, Pirgon O, Aypar E, Yılmaz H, Dündar B. Relationship between aspartate aminotransferase-to-platelet ratio index and carotid intima-media thickness in obese adolescents with non-alcoholic fatty liver disease. J Clin Res Pediatr Endocrinol 2013; 5: 182–88.
11. Tafarel JR, Tolentino LHL, Correa LM, Bonilha DB , Piauilino P, Fernanda Prata et al. Prediction of esophageal varices in hepatic cirrhosis by noninvasive markers. Eur J GastroenterolHepatol 2011; 23: 754-758.
12. Mattoss Z, Mattos A, Daros LF, Musskopf MI. Aspartate amino-transferase-to-platelet ratio index (APRI) for the non-invasive prediction of esophageal varices. Ann Hepatol 2013; 12: 810-814.
13. Grace ND. Diagnosis and treatment of gastro-intestinal bleeding secondary to portal hypertension. American College of Gastro-enterology Practice Parameter Committee. Am J Gastroenterol 1997; 92: 1081-91.
14. Sarangapani A, Shanmugam C, Kalyanasundaram M, Rangachari B, Thangavelu P, Subbarayan JK. Noninvasive prediction of large esophageal varices in chronic liver disease patients. Brief Communication 2010; 16: 38-42.

15. De Franchis R. Noninvasive diagnosis of esophageal varices: is it feasible? Am J Gastroenterol 2006; 101: 2520-22.
16. Cheng J, Zhao P, Liu J, Liu X, Wu X. Preoperative aspartate aminotransferase-to-platelet ratio index (APRI) is a predictor on postoperative outcomes of hepatocellular carcinoma. Medicine . 2016; 95(48): 1-6.
17. Wadhva RK, Haque MM, Luck NH, Tasneem AA, Abbas Z, Mubarak M. Diagnostic Accuracy of Aspartate Amino-transferase to Platelet Ratio Index and Fibrosis 4 Scores in Predicting Advanced Liver Fibrosis in Patients with End-stage Renal Disease and Chronic Viral Hepatitis: Experience from Pakistan. J Transl Int Med 2018; 6(1): 38–42.
18. Civan JM, Lindenmeyer CC, Whitsett M, Herrine SK.A Clinical decision rule based on the ast-to-platelet ratio index imp-roves adherence to published guidelines on the management of acute variceal bleeding. J Clin Gastroenterol 2015; 49(7): 599-606
19. Deng H, Qi X, Peng Y. Diagnostic Accuracy of APRI, AAR, FIB-4, FI, King, Lok, Forns, and FibroIndex Scores in Predicting the Presence of Esophageal Varices in Liver Cirrhosis: A Systematic Review and Meta-Analysis. Med SciMonit 2015; 21: 3961-77
20. Wang CY, Wen J, Zhou YH, Li S, Zhang Y, Lu W et al. Predictive value for esophageal varices using acoustic radiation force impulse elastography in post-hepatitis B cirrhosis patients. Zhonghua Gan Zang Bing Za Zhi 2018; 26(7): 499-502

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