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DIAGNOSTIC ACCURACY OF APRI SCORE FOR DETECTION OF ESOPHAGEAL VARICES IN PATIENTS WITH LIVER CIRRHOSIS

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Abstract:

Introduction: *Liver cirrhosis (LC) is the final evaluative stage of any chronic liver disease and it is a condition prone to multiple complications because of portal hypertension. Development of esophageal varices (EV) is a major complication that may occur in up to 90% of cirrhotic patients. It has been seen that more than 185 million people are infected with HCV worldwide. As many as 350,000 people die each year from HCV related complications. In Pakistan condition is very alarming as more than 10 million people are reported to be affected.*

Objective: *The objective of this study was to measure the PPV and NPV of APRI score for detecting esophageal varices by using Endoscopy as gold standard investigation.**Study Design**: Cross Sectional Study.**Setting**: Study was conducted in Jinnah hospital Lahore.**Study Duration**: Present research was conducted from 02-02-2017 to 01-01-2018.**Material and Methods:** 140 patients were admitted in the gastroenterology ward of Jinnah Hospital Lahore. All the patents were informed for the purpose of the study and a written informed consent was taken from the patients. Routine laboratory test (AST, ALT and PLT) was performed in hospital laboratory. Platelet counts were calculated manually on peripheral smear. The results of the lab reports were used to calculate the APRI score according to operational definition. All data was collected by using well defined proforma. Endoscopy was performed to check the presence of esophageal varices. Minimum grade I Esophageal varices was considered as significant. **Results**: From one hundred and forty patients it was observed that the minimum age was 18 years and maximum age was 70 years with mean ± standard deviation as 42.75 ± 9.69 years. The minimum duration of HCV was 1 year and maximum duration of HCV was 5 years with mean ± standard deviation as 42.75 ± 9.69 years. The minimum AST level was 13 IU/L and maximum AST level was 72 IU/L with mean ± standard deviation as 39.20 ± 18.06 IU/L. The minimum platelet count was 100 10^9/L and maximum platelet count was 380 10^9/L with mean ± standard deviation as 208.21 ± 82.70 10^9/L.There were 52.9% male patients and 47.1% female patients. APRI score was observed > 0.5 in 82.1% patients while APRI score was observed < 0.5 in 17.9%. Esophagal varices was present in 87.9% while esophagal varices was not found in 12.1% patients. Sensitivity of APRI score was calculated as 88.71%, specificity was 75 %, positive predictive value was 95.65% and negative predictive value was 48%.After stratification and by using chi-square test, significant association was found between APRI score and presence of esophageal varices in age group of < 40 years and age group of ≥ 40 years having p-value of 0.000 and 0.000 respectively. APRI score was significantly associated with the presence of esophageal varices in males and females having p-value of 0.000 and 0.016 respectively. Significant association was not found between APRI score and presence of esophageal varices in HCV duration of ≤ 3 years having p-value of 1.000 whereas significant association was found between APRI score and presence of esophageal varices in HCV duration of > 3 years having p-value of 0.000.**Conclusion:** Esophagal varices was present in 87.9% and the sensitivity of APRI score was calculated as 88.71%, specificity was 75 %, positive predictive value was 95.65% and negative predictive value was 48%. Effect modifiers have significant effect for the presence of esophageal varices except duration of HCV ≤ 3 years.*

Key words: *Esophagal Varices, APRI Score, Endoscopy, Positive and Negative Predictive Value.*

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INTRODUCTION:

Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stages at which point the only option may be liver transplantation. However, reversal of cirrhosis (in its earlier stages) has been documented in several forms of liver disease following treatment of the underlying cause. Patients with cirrhosis are susceptible to a variety of complications and their life expectancy is markedly reduced.

Patients with cirrhosis may present in a variety of ways [1].

- They may have stigmata of chronic liver disease discovered on routine physical examination
- They may have undergone laboratory or radiologic testing or an unrelated surgical procedure that incidentally uncovered the presence of cirrhosis
- They may present with decompensated cirrhosis, which is characterized by the presence of dramatic and life-threatening complications, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis (SBP), or hepatic encephalopathy
- Some patients never come to clinical attention. In older reviews, cirrhosis was diagnosed at autopsy in up to 30 to 40 percent of patients [2,3]

A meta-analysis found that the factors with the best ability to predict cirrhosis in adults with known or suspected liver disease included [4]:

- Presence of ascites (likelihood ratio [LR] 7.2)
- Platelet count <160,000/mm ^{3} (LR 6.3)
- Spider nevi (LR 4.3)
- Bonacini cirrhosis discriminant score greater than 7 (LR 9.4)

The Bonacini cirrhosis discriminant score is calculated by giving points for the following parameters [5]:

- Platelets (x1000/mm ^{3}): >340 zero points, 280 to 399 one point, 220 to 279 two points, 160 to 219 three points, 100 to 159 four points, 40 to 99 five points, and <40 six points
- Alanine aminotransferase to aspartate aminotransferase (ALT/AST) ratio: >1.7 zero points, 1.2 to 1.7 one point, 0.6 to 1.19 two points, <0.6 three points
- International normalized ratio (INR): <1.1 zero points, 1.1 to 1.4 one point, >1.4 two points

Factors associated with a low likelihood of cirrhosis included:

- Lok index <20 percent (LR 0.09)
- Platelet count of 160,000/mm ^{3} or higher (LR 0.29)
- Absence of hepatomegaly (LR 0.37)

The Lok index is calculated using the platelet count, AST, ALT, and INR [6].

History

The history should include questioning about risk factors for chronic liver disease including a history of hepatitis, alcohol consumption, diabetes mellitus, use of illicit drugs (by injection or inhalation), transfusions, family history of liver disease, travel, and the presence of autoimmune diseases (including inflammatory bowel disease, rheumatoid arthritis and thyroid disease). The review of systems should include questioning related to fatigue, easy bruisability, lower extremity edema, fever, weight loss, diarrhea, pruritus, increasing abdominal girth, and confusion or sleep disturbance (possibly indicating encephalopathy).

Physical findings

A number of physical findings have been described in patients with cirrhosis.

- Spider angiomata

Spider angiomata (also referred to as spider telangiectasias) are vascular lesions consisting of a central arteriole surrounded by many smaller vessels. They are most frequently found on the trunk, face, and upper limbs. The body (the central arteriole) can be seen pulsating when compressed with a glass slide. Blood fills the central arteriole first before traveling to the peripheral tips of each leg after blanching. There are usually multiple radiating "legs" and surrounding erythema that may encompass the entire lesion or only its central portion.

While their pathogenesis is incompletely understood, they are believed to result from alterations in sex hormone metabolism. One study suggested that the presence of spider angiomata in men was associated with an increase in the estradiol/free testosterone ratio [7].

MATERIAL AND METHODS:

Study design:

It's a cross sectional study.

Settings:

Jinnah Hospital Lahore

Duration of study:

The present research was conducted from 00-00-2017 to 00-00-2017.

Sample Size:

Sample size of 140 cases is calculated with 95% confidence interval and taking expected percentage of EV as 90% and sensitivity as 64.7% and

specificity as 72.7% of APRI.

Sampling Technique:

Non probability, consecutive sampling.

Sample Selection:

Inclusion criteria:

1. Liver cirrhosis due to HCV for atleast one year (as per operational definition)
2. Age between 18-70 years for either gender.

Exclusion criteria:

1. Liver cirrhosis due to HBV
2. Alcoholic liver Disease
3. Metabolic and autoimmune causes of Liver cirrhosis
4. Platelet disorders
5. Patients taking drugs that are likely to alter serum AST levels
6. Acute hepatitis

Data Collection Procedure:

140 patients were admitted in the gastroenterology ward of Jinnah Hospital Lahore. All the patents were informed for the purpose of the study and a written informed consent was taken from the patients. Routine laboratory test (AST, ALT and PLT) was performed in hospital laboratory. Platelet counts were calculated manually on peripheral smear. The results of the lab reports were used to calculate the APRI score according to operational definition. All data was collected by using well defined performa. Endoscopy was performed to check the presence of esophageal varices. Minimum grade I Esophageal varices was considered as significant.

Data Analysis Procedure

All the collected data was entered into SPSS version 16. Numerical variables i-e age, APRI score were presented by mean ±SD. Categorical variables i-e gender were presented as frequencies and percentages. 2x2 tables were constructed and PPV and NPV was calculated. Stratification was done for age, duration of HCV and gender for effect modifiers. Post stratification Chi-square test was used and p value of ≤ 0.05 was considered as statistically significant.

RESULTS:

From one hundred and forty patients it was observed that the minimum age was 18 years and maximum age was 70 years with mean $\pm$ standard deviation as 42.75 $\pm$ 9.69 years. The minimum duration of HCV was 1 year and maximum duration of HCV was 5 years with mean $\pm$ standard deviation as 42.75 $\pm$ 9.69 years. The minimum AST level was 13 IU/L and maximum AST level was 72 IU/L with mean $\pm$ standard deviation as 39.20 $\pm$ 18.06 IU/L. The minimum platelet count was 100 10^9/L and maximum platelet count was 380 10^9/L with mean $\pm$ standard deviation as 208.21 $\pm$ 82.70 10^9/L. There were 74 (52.9%) male patients and 66 (47.1%) female patients. APRI score was observed > 0.5 in 115 (82.1%) patients while APRI score was observed < 0.5 in 25 (17.9%). Esophagal varices was present in 123 (87.9%) while esophagal varices was not found in 17 (12.1%) patients. Sensitivity of APRI score was calculated as 88.71%, specificity was 75 %, positive predictive value was 95.65% and negative predictive value was 48%.

After stratification and by using chi-square test, significant association was found between APRI score and presence of esophageal varices in age group of < 40 years and age group of $\geq$ 40 years having p-value of 0.000 and 0.000 respectively. APRI score was significantly associated with the presence of esophageal varices in males and females having p-value of 0.000 and 0.016 respectively. Significant association was not found between APRI score and presence of esophageal varices in HCV duration of $\leq$ 3 years having p-value of 1.000 whereas significant association was found between APRI score and presence of esophageal varices in HCV duration of > 3 years having p-value of 0.000.

Table. 1 Descriptive Statistics
(n = 140)

	Minimum	Maximum	Mean	Std. Deviation
Age	18	70	42.75	16.81
Duration of HCV	1	5	3.00	1.42
AST	13	72	39.20	18.06
Platelet	100	380	208.21	82.70

Table.2 Distribution of Gender
(n = 140)

Gender	Frequency	Percentage
Male	74	52.9
Female	66	47.1
Total	140	100.0

Table.3 Distribution of APRI Score

APRI Score	Frequency	Percentage
> 0.5	115	82.1
< 0.5	25	17.9
Total	140	100.0

Table.4 Distribution of Esophageal Varices

Esophageal Varices	Frequency	Percentage
Yes	123	87.9
No	17	12.1
Total	140	100.0

Table 5: 2x2 Table of Esophageal Varices and APRI Score
(n = 140)

APRI Score	Esophageal Varices		Total
	Yes	**No**	
> 0.5	TP= 110 [a]	FP= 5 [b]	115
< 0.5	FN= 13 [c]	TN= 12 [d]	25
Total	123	17	140

Sensitivity = $\frac{TP}{TP+FN}$ x 100 = 88.71%

Specificity = $\frac{TN}{TN+FP}$ x 100 = 75%

Positive Predictive Value = $\frac{TP}{TP+FP}$ x 100 = 95.65%

Negative Predictive Value = $\frac{TN}{TN+FN}$ x 100 = 48%

Table.6 Stratification for APRI Score with respect to Age
(n = 140)

APRI Score	Esophageal Varices		Total	P-Value
	Yes	**No**		
Age < 40 years				
> 0.5	48	5	53	0.000
< 0.5	3	6	9	
Age ≥ 40 years				
> 0.5	62	0	62	0.000
< 0.5	10	6	16	
Total	123	17	140	

*Chi-square test was applied.

Table.7 Stratification for APRI Score with respect to Gender (n = 140)

APRI Score	Esophageal Varices		Total	P-Value
	Yes	No		
Male				
> 0.5	58	0	58	0.000
< 0.5	8	8	16	
Female				
> 0.5	52	5	57	0.016
< 0.5	5	4	9	
Total	123	17	140	

*Chi-square test was applied.

Table.14 Stratification for APRI Score with respect to Duration of HCV (n = 140)

APRI Score	Esophageal Varices		Total	P-Value
	Yes	No		
Duration of HCV ≤ 3 years				
> 0.5	68	5	73	1.000
< 0.5	11	0	11	
Duration of HCV > 3 years				
> 0.5	42	0	42	0.000
< 0.5	2	12	14	
Total	123	17	140	

*Chi-square test was applied.

DISCUSSION:

The objective of the present research was to measure the PPV and NPV of APRI score for detecting esophageal varices by using Endoscopy as gold standard investigation. In this regard the present cross sectional study was conducted in Jinnah hospital Lahore. So one hundred and forty patients of liver cirrhosis were included by fulfilling the inclusion and exclusion criteria by using non probability purposive sampling.

From one hundred and forty patients it was observed that the minimum age was 18 years and maximum age was 70 years with mean ± standard deviation as 42.75 ± 9.69 years. The minimum duration of HCV was 1 year and maximum duration of HCV was 5 years with mean ± standard deviation as 42.75 ± 9.69 years. The minimum AST level was 13 IU/L and maximum AST level was 72 IU/L with mean ± standard deviation as 39.20 ± 18.06 IU/L. The minimum platelet count was 100 10^9/L and maximum platelet count was 380 10^9/L with mean ± standard deviation as 208.21 ± 82.70 10^9/L.

Previous study described that the Lok Score was the best among all the serum scores for diagnosing the varices. For a value higher than 0.8, it had a 45.5% positive predictive value, 86.4% negative predictive value and 67.72% diagnostic accuracy for prediction of large varices. For liver stiffness higher than 30.8KPa, the positive predictive value was 47.3%, negative predictive value 81% and diagnostic accuracy 68.32%. Using both tests simultaneously, the presence of large varices was predicted with a diagnostic accuracy of 78.12%, obtaining an increment in NPV and -LR up to 93.67% and 0.21, respectively. The Lok Score is a good predictor for excluding the presence of large varices in cirrhotic patients, similarly with liver stiffness. The two methods can be successfully combined into a noninvasive algorithm for the assessment of esophageal varices in cirrhotic patients. [108]

In our study, there were 52.9% male patients and 47.1% female patients. APRI score was observed > 0.5 in 82.1% patients while APRI score was observed < 0.5 in 17.9%. Esophagal varices was present in 87.9% while esophagal varices was not found in 12.1% patients. Sensitivity of APRI score was calculated as 88.71%, specificity was 75 %, positive predictive value was 95.65% and negative predictive value was 48%.

In existing literature, liver biopsies examination

revealed that out of 120 patients 10 (8.3%) had no fibrosis (F0), 46 (38%) portal fibrosis (F1), 34 (28%) septal fibrosis (F2), 21 (18%) bridging fibrosis (F3) and 9 (8%) cirrhosis (F4). APRI correctly classified 58 (48%) patients of significant fibrosis with AUC = 0.82 (95% CI, 0.73-0.88) at cut-off 0.5 and 1.5 with negative predictive value (NPV), Positive predictive value (PPV), sensitivity and specificity of 78%, 72%, 66%, 83% and 58%, 90%, 41% and 90% respectively. Eighty-seven (66%) CHC patients were correctly classified for advanced fibrosis with AUC = 0.87 (95% CI 0.79-0.94) at cutoffs 0.90 and 1.75 with a 95%NPV at 0.90 and 78% PPV at 1.75. APRI could correctly identify significant fibrosis in 48% and advanced fibrosis in 66% cases with acceptable degree of diagnostic accuracy in CHC patients in our clinical practice. [109]

In present research, after stratification and by using chi-square test, significant association was found between APRI score and presence of esophageal varices in age group of < 40 years and age group of $\geq$ 40 years having p-value of 0.000 and 0.000 respectively. APRI score was significantly associated with the presence of esophageal varices in males and females having p-value of 0.000 and 0.016 respectively. Significant association was not found between APRI score and presence of esophageal varices in HCV duration of $\leq$ 3 years having p-value of 1.000 whereas significant association was found between APRI score and presence of esophageal varices in HCV duration of > 3 years having p-value of 0.000.

In 22 studies (n = 4,266), the summary AUCs of the APRI for significant fibrosis and cirrhosis were 0.76 [95% confidence interval (CI), 0.74–0.79] and 0.82 (95%CI, 0.79–0.86), respectively. For significant fibrosis, an APRI threshold of 0.5 was 81% sensitive and 50% specific. At a 40% prevalence of significant fibrosis, this threshold had a negative predictive value (NPV) of 80%, but could reduce the necessity of liver biopsy by only 35%. For cirrhosis, a threshold of 1.0 was 76% sensitive and 71% specific. At a 15% cirrhosis prevalence, the NPV of this threshold was 91%. Higher APRI thresholds had suboptimal positive predictive values except in settings with a high prevalence of cirrhosis. APRI accuracy was not affected by the prevalence of advanced fibrosis, or study and biopsy quality. However, the accuracy for cirrhosis was greater in studies including human immunodeficiency virus (HIV)/HCV–co-infected patients. The major strength of the APRI is the exclusion of significant HCV-related fibrosis. [110].

CONCLUSION:

Esophagal varices was present in 87.9% and the sensitivity of APRI score was calculated as 88.71%, specificity was 75 %, positive predictive value was 95.65% and negative predictive value was 48%. Effect modifiers have significant effect for the presence of esophageal varices except duration of HCV $\leq$ 3 years.

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PROFORMA

Diagnostic Accuracy of APRI Score for Detection of Esophageal Varices in Patients With Liver Cirrhosis

CASE NO: _____

Name of Patient: _____ S/D/W/O: _____

Reg. #: _____Age: _____

Sex: Male ☐ Female ☐

Date of Admission: _____
Address: _____

Study Variables:

1. Serum AST Levels _____
2. Platelet count _____
3. APRI Score
- > 0.5
- < 0.5

4. Esophageal Varices
- Present

Absent