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Research Article

ASPARTATE PLATELET RATIO INDEX AS A PREDICTOR OF SEVERITY OF FIBROSIS IN CHRONIC HEPATITS C

KANNAN NARAYANAN[1], SUE ANN ZACHARIAH[2]*, SHEELA KURIAN V[3]

Department of General Medicine, Government Medical College, Kottayam, Kerala, India. Email: zachsadr@gmail.com

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ABSTRACT

Objectives: Hepatitis C is an important emerging cause for chronic liver disease in India, with high risk for chronicity and hepatocellular carcinoma. Chronic hepatitis C (CHC) is the most common cause for chronic liver disease and cirrhosis, and liver transplantation. Liver biopsy is the gold standard for evaluation of fibrosis - however it remains fraught with drawbacks and limitations. The aspartate aminotransferase-to-platelet ratio index (APRI), a tool with limited expense and widespread availability is a promising non-invasive alternative to liver biopsy for detecting hepatic fibrosis in CHC. : (1) The objectives of the study were to determine the association between APRI and severity of fibrosis in Hepatitis C (2) and to describe the clinical profile of patients with Hepatitis C.

Methods: A cross-sectional descriptive study in 60 patients diagnosed with hepatitis C for more than 6 months admitted to the General Medicine and Medical Gastroenterology Departments of Govt Medical College, Kottayam. Data were collected with a structured pro forma and analyzed using SPSS.

Results: 35 of 60 patients belonged to METAVIR F3 (severe fibrosis) and F4 (cirrhosis). An APRI of 0.5 was associated with a finding of F3 or F4 with a sensitivity of 97.14% and a specificity of 88%. 31 of the 60 patients belonged to F4. An APRI of 1.5 or more was a predictor for cirrhosis with a sensitivity of 93.1% and specificity of 96.77%. The positive predictive value of cirrhosis APRI threshold >1.5 is 96.4%.

Keywords: Chronic hep C, APRI, Fibrosis, Predictor, Severity.

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INTRODUCTION

Hepatitis C is an emerging infection in India and an important pathogen causing chronic liver disease in India. The high risk of chronicity of this blood-borne infection and its association with hepatocellular carcinoma underscores its public health importance. Hepatitis C can present as acute or chronic hepatitis. Most of the cases of acute hepatitis C are asymptomatic with patients unaware of the underlying infection. Modes of transmission of HCV can be divided into percutaneous (blood transfusion and needle stick inoculation) and non-percutaneous (sexual contact and perinatal exposure). Total global HCV prevalence is estimated at 2.5% (177.5 million of HCV infected adults). The estimated prevalence of HCV infection in India is about 1–1.9%.

Chronic hepatitis C (CHC) is the most common cause of chronic liver disease and cirrhosis, and the most common indication for liver transplantation. Hepatitis C virus (HCV) is the most common chronic blood borne infection in the U.S. and is involved in 40% of chronic liver disease. Chronic hepatitis develops in 50–90% of persons with acute HCV infection. The hepatic complications of CHC usually occur only after progression to cirrhosis has taken place. HCV infection elicits an immune response in the host that involves both an initial innate response and a subsequent adaptive response. Hepatic fibrosis is the final common pathway for most chronic liver diseases. The cell responsible for hepatic fibrosis appears to be the activated myofibroblast. Chronic liver diseases progress from mild inflammation, to more severe inflammation, to fibrosis, and finally to cirrhosis. Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury that leads to portal hypertension and end-stage liver disease. Cirrhosis presents as various clinical complications, including ascites, jaundice, or hepatocellular carcinoma. During this process, hepatic stellate cells (HSCs) activation occurs. Platelet derived growth factor, tumor necrosis factor α, transforming growth factor β or reactive oxygen species play a role in the progression to liver cirrhosis. Multiple cells play a role in liver cirrhosis including hepatocytes and sinusoidal lining cells such as HSCs, sinusoidal endothelial cells (SECs), and Kupffer cells. Hepatocytes also are involved in the pathogenesis of cirrhosis, as damaged hepatocytes release reactive oxygen species and inflammatory mediators that can promote activating HSCs and liver fibrosis. Cirrhosis is frequently indolent, asymptomatic, and unsuspected for years before development of decompensating events such as jaundice, ascites, encephalopathy, and/or variceal hemorrhage. Early diagnosis of liver cirrhosis is therefore important to prevent cirrhosis related mortality.

Liver biopsy remains the gold standard for evaluation of liver fibrosis, but it is an invasive and inaccurate procedure with numerous drawbacks. There are several limitations. First, sampling error is common, and many liver diseases do not affect the liver uniformly. In a sentinel study involving 51 patients with nonalcoholic fatty liver disease in whom two biopsy samples were obtained on the same day, 35% of the patients with F3 fibrosis in one sample had F0 or F1 fibrosis in the other. Complicating matters further, both diagnostic accuracy and disease staging depend on specimen size. Small biopsy samples may be non-diagnostic or may not reveal cirrhosis. Second, biopsies are costly. Each biopsy involves an expert gastroenterologist or radiologist and a pathologist and must be performed in a facility with adequate periprocedural monitoring by nurses. Biopsies are associated with complications, including pain,serious bleeding, injury to other organs, and in rare cases, death. For these reasons, many patients refuse to undergo liver biopsy. To overcome the limitations of liver biopsy several non-invasive parameters had been developed. The aspartate aminotransferase-to-platelet ratio index (APRI), a tool with limited expense and widespread availability, is a promising noninvasive alternative to liver biopsy for detecting hepatic fibrosis in CHC. APRI can be calculated using formula.

$$APRI = \frac{AST\ \frac{levels}{AST}\left(Upper\ limit\ of\ normal\right)}{Platelet\ count\left(\frac{10^9}{L}\right)}100$$

The present study is being conducted to find out the accuracy of APRI in predicting severity of fibrosis in CHC.

Objectives

The objectives are as follows:

1. To determine the association between APRI and severity of fibrosis in patients with CHC.
2. To describe the clinical profile of patients with CHC.

METHODS

Study design

This was a cross-sectional descriptive study.

Table 1: Age distribution in the study population (n=60)

Age in years	Frequency	Percent
≤40	7	11.7
41–50	16	26.7
51–60	23	38.3
61–70	12	20
>70	2	3.3
Total	60	100

Table 2: Sex distribution in the study population (n=60)

Gender	Frequency	Percent
Male	31	51.7
Female	29	48.3
Total	60	100

Table 3: Descriptive analysis of fatigue among the study population (n=60)

Fatigue	Frequency	Percent
Absent	37	61.7
Present	23	38.3
Total	60	100

Table 4: Bleeding manifestations among the study population (n=60)

Bleeding manifestations	Frequency	Percent
Absent	56	93.3
Present	4	6.7
Total	60	100

Table 5: Percentage distribution of anemia among the study population (n=60)

Anemia	Frequency	Percent
Absent	42	70
Present	18	30
Total	60	100

Table 6: Percentage distribution of thrombocytopenia among the study population (n=60)

Thrombocytopenia	Frequency	Percent
Absent	33	55
Present	27	45
Total	60	100

Study period

The study was from July 1, 2019, to June 30, 2020.

Table 7: Percentage distribution of Ascitis in USG abdomen among the study population (n=60)

Ascites	Frequency	Percent
Absent	51	85
Present	9	15
Total	60	100

Table 8: Percentage distribution of Cirrhosis in USG abdomen among the study population (n=60)

Cirrhosis in USG abdomen	Frequency	Percent
Absent	41	68.3
Present	19	31.7
Total	60	100

Table 9: Percentage distribution of splenomegaly in USG abdomen among the study population (n=60)

Splenomegaly	Frequency	Percent
Absent	47	78.3
Present	13	21.7
Total	60	100

Table 10: Percentage distribution of portal hypertension in USG abdomen among the study population (n=60)

Portal HTN	Frequency	Percent
Absent	45	75
Present	15	25
Total	60	100

Table 11: Percentage distribution of Esophageal varices in OGD scopy among the study population (n=60)

Eso Varices	Frequency	Percent
Absent	46	76.7
Present	14	23.3
Total	60	100

Table 12: Percentage distribution of portal hypertensive gastropathy in OGD scopy among the study population (n=60)

PHG	Frequency	Percent
Absent	48	80
Present	12	20
Total	60	100

Table 13: Percentage distribution of HCV genotype among the study population (n=60)

HCV genotype	Frequency	Percent
1	7	11.7
2	1	1.7
3	32	53.3
4	20	33.3
Total	60	100

Study setting

This study was conducted at the Department of General Medicine, and Department of Gastroenterology, Govt Medical College, Kottayam.

Table 14: METAVIR staging based on fibroscan among the study population

METAVIR	Frequency	Percent
F0-F1	20	33.3
F2	5	8.3
F3	6	10
F4	29	48.3
Total	60	100

Table 15: Overview of the blood parameters among the study population

Parameter	N	Mean	SD	Min	Max	Median	Q1	Q3
Age	60	53.3	11.3	21	72	55	45.75	60
Hemoglobin	60	12.8	1.9	9	16	13	11	14
Platelet count	60	204.0	105.9	72	500	156.5	120	260
TB	60	1.12	0.83	0.2	3.9	0.9	0.6	1.2
DB	60	0.61	0.57	0.1	2.8	0.5	0.3	0.6
TP	60	6.8	0.8	3.9	8.3	7	6.275	7.275
ALB	60	3.4	0.6	1.3	4.2	3.5	3	3.9
SGOT	60	84.6	66.4	14	292	64.5	29.5	126
SGPT	60	63.0	47.2	10	248	56.5	25	85.75
ALP	60	127.4	52.7	59	335	109.5	90.5	160
INR	60	1.06	0.19	0.80	1.80	1.00	0.92	1.18
Fibroscan	60	17.2	11.9	3	40	13	6	29.6
APRI	60	2.2	2.2	0.1	9.7	1.3	0.3	3.5

Table 16: APRI versus gender

Sex	n	APRI		p-value
		Mean	SD	
Male	31	1.87	1.92	0.278
Female	29	2.49	2.46	

Table 17: APRI versus fatigue

Fatigue	N	APRI		p-value
		Mean	SD	
Absent	37	1.13	1.85	<0.001
Present	23	3.84	1.63	

Table 18: APRI versus ascitis in USG abdomen

Ascites	n	APRI		p-value
		Mean	SD	
Absent	51	2.08	2.24	0.446
Present	9	2.69	1.98	

Table 19: APRI and bleeding manifestations

Bleeding manifestations	n	APRI		p-value
		Mean	SD	
Absent	56	2.16	2.21	0.958
Present	4	2.23	2.38	

Study population

All patients with hepatitis C related chronic liver disease in department of General Medicine and Gastroenterology wards of Government Medical College Kottayam.

Sample size

According to the study conducted by Lin *et al*. [1], sensitivity of APRI index is 77. According to Amarapurkar *et al*. [2], the prevalence of

Table 20: APRI versus Anemia

Anemia	n	APRI		p-value
		mean	SD	
Absent	42	1.82	1.97	0.063
Present	18	2.97	2.55	

Table 21: APRI versus HCV genotype

HCV genotype	n	APRI		p-value
		Mean	SD	
1	7	1.50	1.39	0.337
2	1	4.60	.	
3	32	1.91	2.24	
4	20	2.69	2.32	

Table 22: APRI versus cirrhosis in USG abdomen

Cirrhosis in USG abdomen	n	APRI		p-value
		Mean	SD	
Absent	41	1.36	1.95	<0.001
Present	19	3.91	1.66	

Table 23: APRI versus splenomegaly in USG abdomen

Splenomegaly	n	APRI		p-value
		Mean	SD	
Absent	47	1.67	2.13	<0.001
Present	13	3.98	1.38	

Table 24: APRI versus portal hypertension in USG abdomen

Portal HTN	n	APRI		p-value
		Mean	SD	
Absent	45	1.44	1.92	<0.001
Present	15	4.35	1.42	

Table 25: APRI versus esophageal varices

Esophageal varices	n	APRI		p-value
		Mean	SD	
Absent	46	1.60	2.10	<0.001
Present	14	4.04	1.36	

Table 26: APRI versus portal hypertensive gastropathy

PHG	n	APRI		p-value
		Mean	SD	
Absent	48	1.65	2.04	<0.001
Present	12	4.23	1.55	

chronic liver disease due to hepatitis C in is 16%. Substituting these values in the formula

$$\frac{Z\alpha^2(sensitivity\,(1-sensitivity))}{d^2(p)}$$

Where $Z\alpha^2$=3.814
p = prevalence of hepatitis C in patients with chronic liver disease
d= 3.2
Minimum sample size will be 50.

Study stools
Structured questionnaire and lab reports.

Inclusion criteria
Consecutive patients who diagnosed to have Hepatitis C by RNA polymerase chain reaction for more than 6 months, who already underwent HCV genotyping and who were treatment naïve presented to the outpatient department and wards of General Medicine and Gastroenterology, Government Medical College Kottayam.

Exclusion criteria
All other causes of chronic liver disease were excluded from the study.

Study procedure
After receiving Institutional Review Board clearance and consent from patients cross-sectional observational study was conducted on patients in the outpatient department and wards of departments of General Medicine and Gastroenterology Govt Medical College Kottayam from July 1, 2019 to June 30, 2020. Written consent was taken from patients who met the inclusion criteria for the study. Consecutive patients who diagnosed to have Hepatitis C by RNA polymerase chain reaction for more than 6 months, who already underwent HCV genotyping and who were treatment naïve were included in the study. Detailed history regarding symptoms was taken. Fatigue was assessed using fatigue scale. Investigations including complete blood count, tests for liver function, liver injury, ultrasonography abdomen, oesophagogastroduodenoscopy and ultrasound shear wave elastography were done. Platelet count was done using automated analyzers. Liver function test were done using automated analyzers. Ultrasonography abdomen was done in radiology department.

Ultrasound shear wave elastography was done with a small transducer where a 50-MHz wave was passed into the liver from the transducer on the end of an ultrasound probe. The probe also had a transducer on the end that measured the velocity of the shear wave, in meters per second as this wave passed through the liver. Liver stiffness was evaluated by measuring the velocity of a vibration wave, also called a shear wave, generated on the skin. Shear wave velocity was determined by measuring the time the vibration wave took to travel to a particular depth inside the liver. To improve test reliability a minimum of 10 valid readings, with at least a 60% success rate and an interquartile range of ≤30% of the median value, were taken with the results expressed in kilopascals (kPa). The liver stiffness which indicates the severity of fibrosis was expressed in kilopascals. These values were then categorized into Metavir staging as per the study conducted by Castéra *et al*. As per Castéra *et al*., values below 7.0 kilopascals belong to F0-F1 stage which denotes absent fibrosis or mild fibrosis.

Table 27: METAVIR staging versus age group

Age in years	METAVIR								Total	
	F0-F1		F2		F3		F4			
	n	%	n	%	n	%	n	%	n	%
≤40	3	42.9	0	0	1	14.3	3	42.9	7	100
41–50	6	37.5	1	6.3	2	12.5	7	43.8	16	100
51–60	7	30.4	1	4.3	2	8.7	13	56.5	23	100
61–70	3	25	2	16.7	1	8.3	6	50	12	100
>70	1	50	1	50	0	0	0	0	2	100
Total	20	33.3	5	8.3	6	10	29	48.3	60	100

χ^2=8.9, df=12, p=0.709

Table 28: METAVIR staging versus gender

Sex	METAVIR								Total	
	F0-F1		F2		F3		F4			
	n	%	n	%	n	%	n	%	n	%
Male	10	32.3	3	9.7	3	9.7	15	48.4	31	100
Female	10	34.5	2	6.9	3	10.3	14	48.3	29	100
Total	20	33.3	5	8.3	6	10	29	48.3	60	100

χ^2=0.2, df=3, p=0.983

Table 29: APRI versus METAVIR scoring

METAVIR	n	APRI		p-value
		Mean	SD	
F0-F1	20	0.31	0.17	<0.001
F2	5	0.60	0.46	
F3	6	1.15	0.85	
F4	29	3.93	1.92	

Table 30: Distribution of METAVIR in the study population

Statistical parameter	METAVIR			
	F0-F1	F2	F3	F4
n	20	5	6	29
Mean	0.31	0.6	1.15	3.931
SD	0.17	0.46	0.85	1.92
Median	0.3	0.5	0.95	3.5
25% Percentile	0.1	0.2	0.525	2.5
75% Percentile	0.4	1.05	1.775	5.35
Minimum	0.1	0.2	0.3	0.7
Maximum	0.7	1.3	2.6	9.7
Range	0.6	1.1	2.3	9

Table 31: Comparison between APRI and fibroscan values in the study population

Statistical parameter	APRI	Fibroscan (kPa)
N	60	60
Mean	2.20	17.17
Std. Deviation	2.21	11.85
Median	1.3	13
25% Percentile	0.3	6
75% Percentile	3.5	29.6
Minimum	0.1	3
Maximum	9.7	40

Table 32: Correlation of APRI and other parameters

Correlation of APRI with other parameters	Pearson correlation	
	Correlation coefficient r	p-value
Fibroscan	0.848	<0.001
Age	0.003	0.984
Hemoglobin	−0.303	0.019
TB	0.549	<0.001
DB	0.526	<0.001
TP	−0.174	0.185
ALB	−0.146	0.267
SGPT	0.718	<0.001
ALP	0.454	<0.001
INR	0.449	<0.001

Values between 7.0 kilopascals and 9.5 kilopascals belong to F2 stage which denotes significant fibrosis. Values between 9.5 kilopascals and 12.5 kilopascals belong to F3 stage which denotes severe fibrosis. Values above 12.5 kilopascals belong to F4 stage which denotes cirrhosis. All patients were then categorized into four M ETAVIR stages.

APRI scores were calculated for all patients.

APRI index was calculated using the formula

$$APRI = \frac{AST\ \frac{levels}{AST}\left(Upper\ limit\ of\ normal\right)}{Platelet\ count\left(\frac{10^9}{L}\right)} \times 100$$

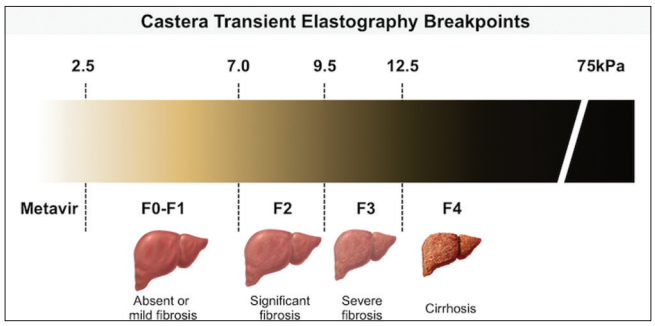

Fig. 1: METAVIR staging according to Fibroscan

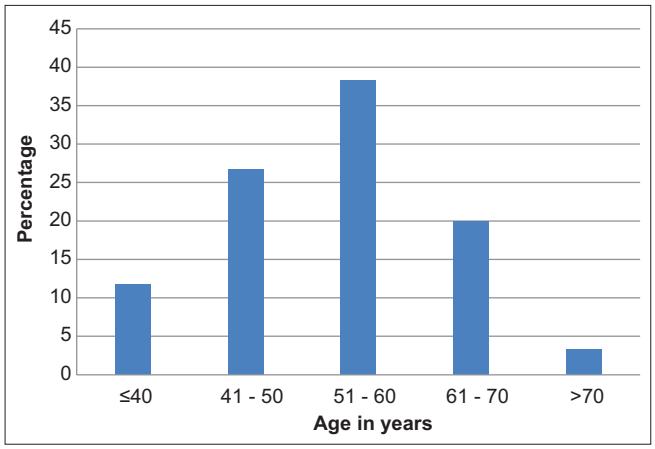

Fig. 2: Age distribution among study population

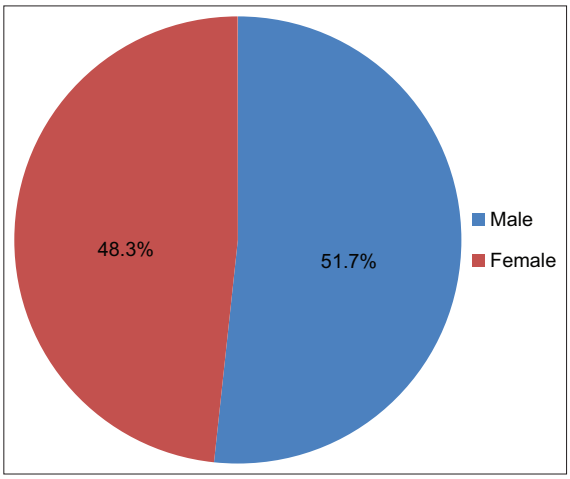

Fig. 3: Sex distribution of the study population

Data management and statistical analysis

The data's obtained were entered into Microsoft excel and analyzed using IBM SPSS version 25 software. During the analysis, the patients are grouped into survivors and non survivors. The data were coded in SPSS for easy data analysis.

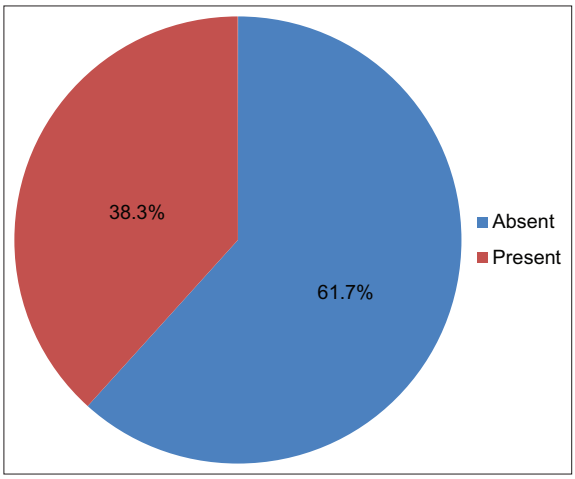

Fig. 4: Fatigue among the study population

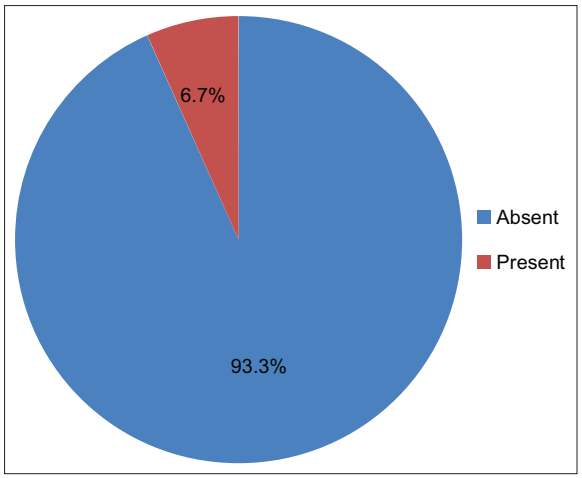

Fig. 5: Bleeding manifestations among the study population

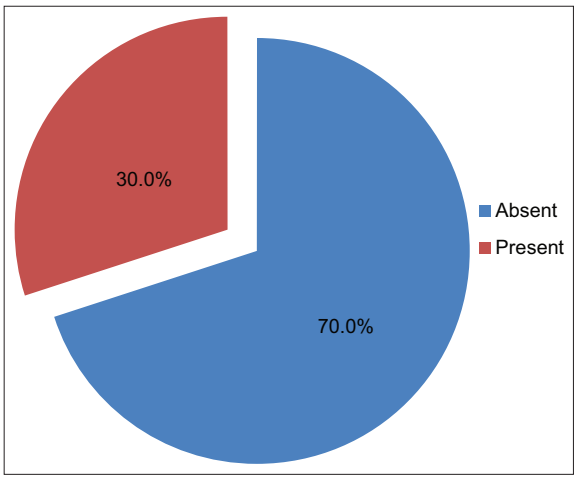

Fig. 6: Percentage distribution of anemia among the study population

Case definitions

1. Chronic hepatitis C-Defined as inflammation of the liver caused by hepatitis C that lasts for at least 6 months. Diagnosis of HCV infection was done HCV RNA polymerase chain reaction. Inflammation liver was assessed by liver function tests.
2. APRI score parameters-APRI score is calculated using patient's platelet count, patient's aspartate aminotransferase levels and upper limit of normal aspartate aminotransferase levels.
3. Platelet count - normal platelet count is taken between 1.5 lakhs and 4.5 lakhs. Thrombocytopenia is defined as platelet count below 1.5 lakh.
4. Transaminases - Normal level of aspartate aminotransferase was taken 30 IU/L for men and 19 IU/L for women.
5. Anemia - Defined as quantitative or qualitative reduction in hemoglobin or circulating red blood cells or both resulting in

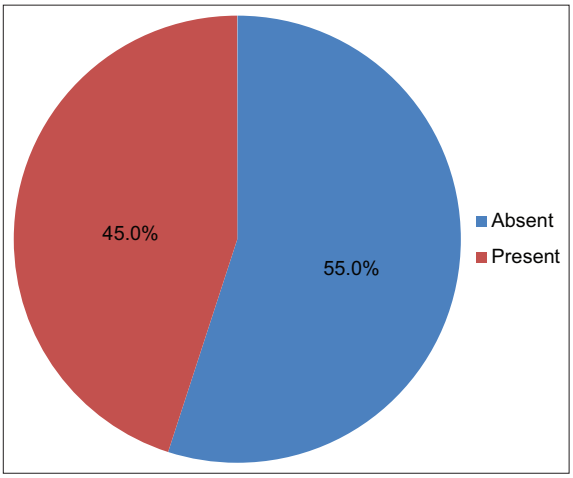

Fig. 7: Thrombocytopenia among the study population

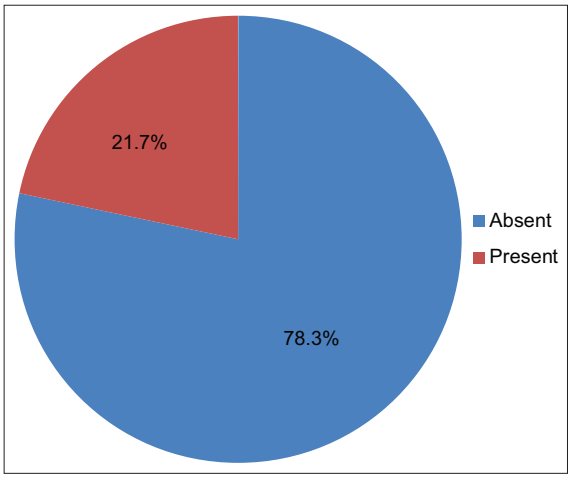

Fig. 10: Splenomegaly in USG Abdomen

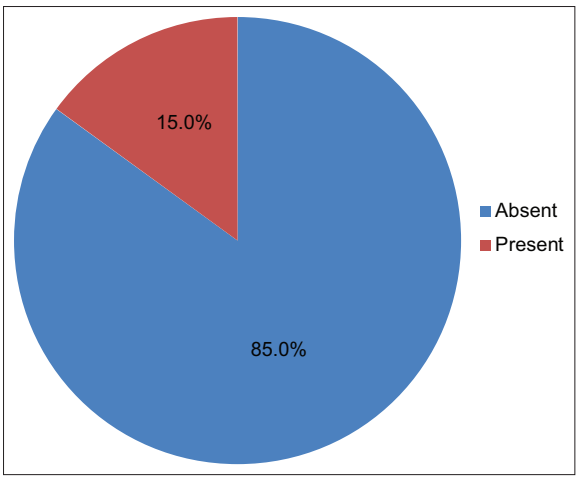

Fig. 8: Ascites in USG abdomen among the study population

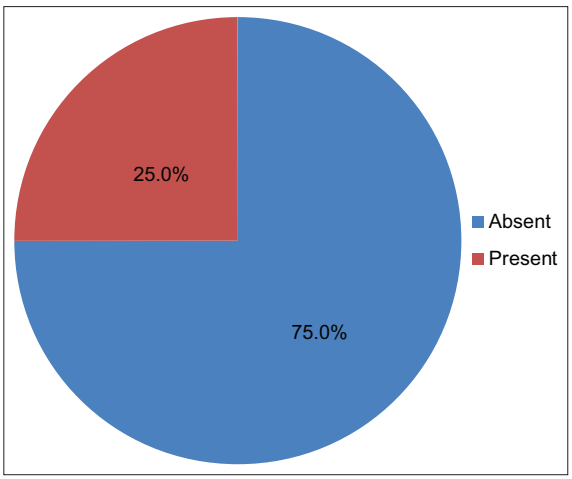

Fig. 11: Portal HTN among the study population

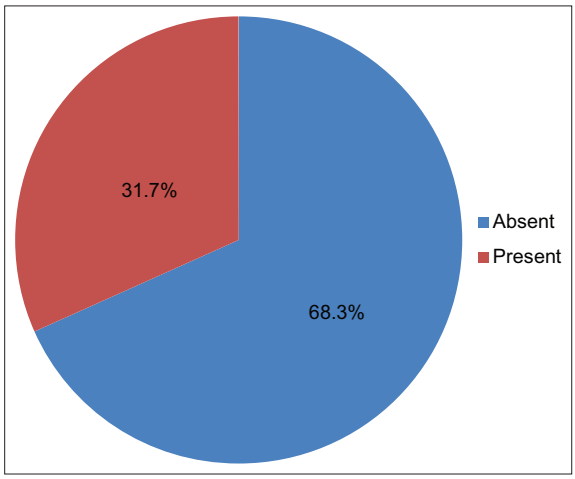

Fig. 9: Cirrhosis in USG Abdomen among the study population

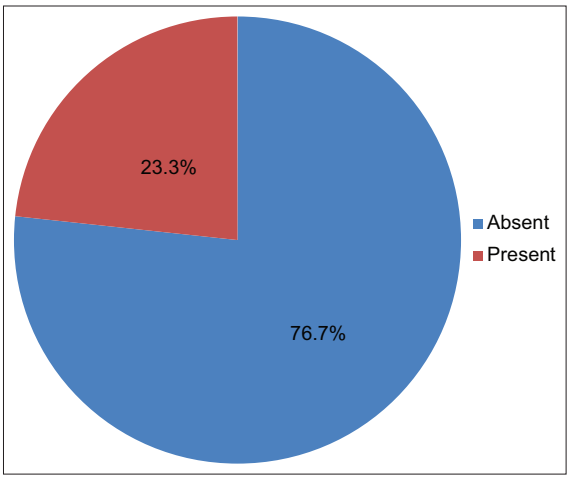

Fig. 12: Esophageal varices among the study population

decreased oxygen carrying capacity. As per the WHO anemia is defined as hemoglobin level <13 g/dL in men and 12 g/dL in women.

6. Fatigue-defined as a feeling of tiredness or exhaustion combined with impairment in the ability to perform daily activities and to find solutions in the absence of the usual strategies to recover energy, thereby negatively impacting quality of life [72]. Fatigue was assessed by daily fatigue impact scale.
7. Splenomegaly-Splenomegaly was determined by ultrasonography abdomen and was defined as maximum spleen length more than 12 cm.
8. Cirrhosis-Sonographical appearance of cirrhosis includes increase in surface nodularity, overall coarse and heterogeneous echotexture, segmental hypertrophy or atrophy along with signs of portal hypertension, splenomegaly, and ascites.
9. Portal hypertension - signs of portal hypertension in ultrasonography include enlarged portal vein - >13 mm (42% sensitive, 95–100% specific), slow portal venous flow <15 cm/sec, reversal or to-and-fro portal venous flow, portal venous thrombosis with or without cavernous transformation enlarged SMV and splenic vein which is more than 10 mm.
10. Esophageal varices-esophageal varices are dilated submucosal distal esophageal veins connecting the portal and systemic circulations. This happens due to portal hypertension (most commonly a result of cirrhosis), resistance to portal blood flow, and increased

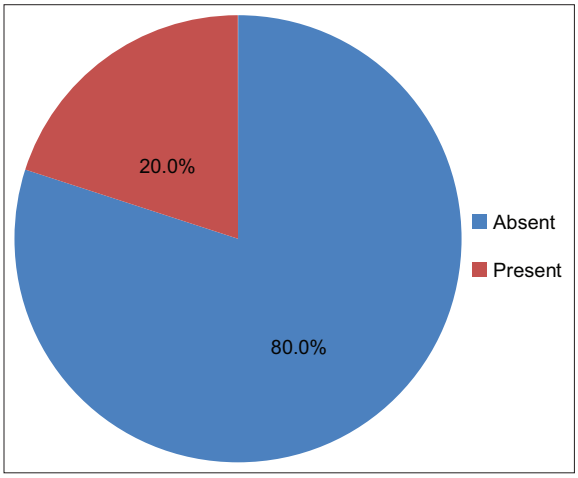

Fig. 13: PHG among the study population

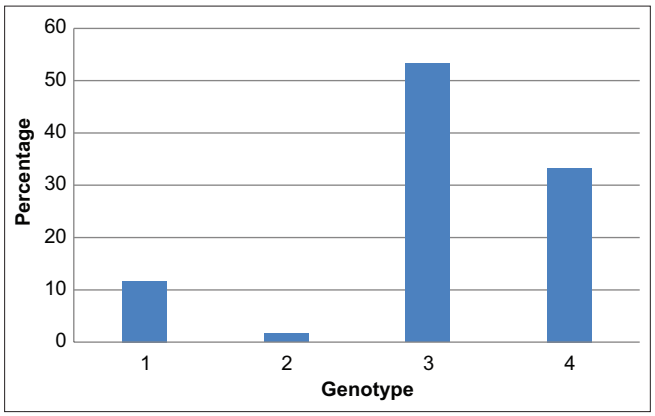

Fig. 14: HCV Genotype among the study population

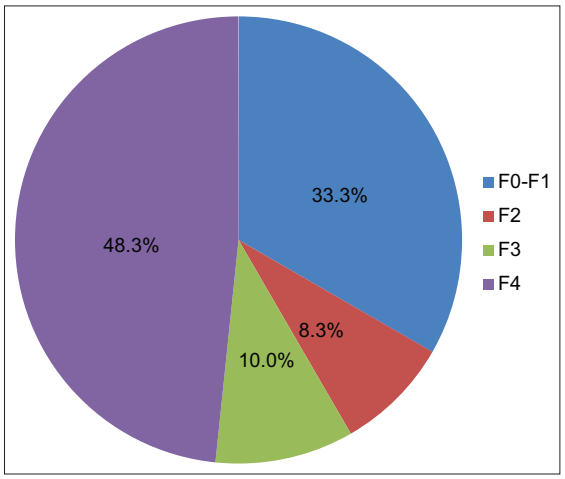

Fig. 15: METAVIR staging among the study population

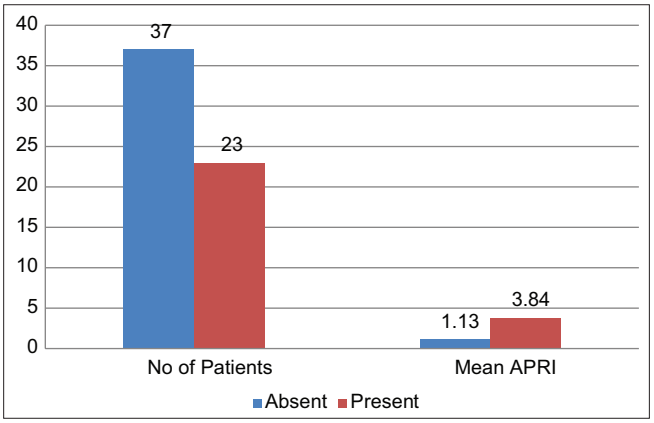

Fig. 16: APRI versus Fatigue

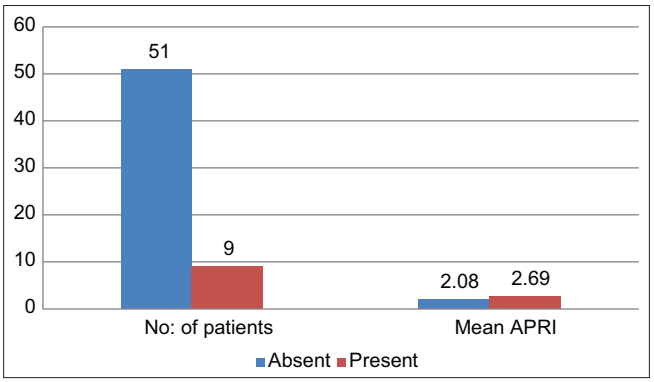

Fig. 17: Mean APRI in patients with Ascitis in USG abdomen

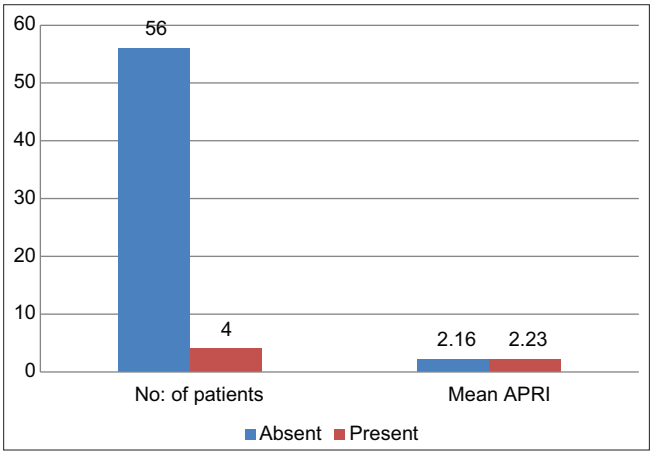

Fig. 18: Mean APRI in Patients with bleeding manifestations

portal venous blood inflow. Esophageal varices can be detected by oesophagogastroduodenoscopy.

11. Portal hypertensive gastropathy (PHG): PHGIs diagnosed by characteristic endoscopic findings of variably erythematous, small, polygonal areas surrounded by a whitish, reticular border in a mosaic pattern in the gastric fundus/body in a patient with portal hypertension.

RESULTS AND OBSERVATIONS

Total number of patient's studied-60.

Clinical profile

Minimum age in this study was 21 years and maximum age was 72 years (Table 1 and Fig. 2).

Out of 140 patients studied, 51.7% constituted males and rest 48.3% were females (Table 2 and Fig. 3).

Out of 60 patients studied, 23 had fatigue which constitutes about 38.3% of the study population (Table 3 and Fig. 4).

Out of 60 patients studied, 4 patients (6.7%) had bleeding manifestations (Table 4 and Fig. 5).

Out of 60 patients studied, 18 patients (30 %) had anemia (Table 5 and Fig. 6).

Out of 60 patients studied, 27 patients (45%) had thrombocytopenia (Table 6 and Fig. 7).

Out of 60 patients studied, 9 patients (15%) had ascites in ultrasonography abdomen (Table 7 and Fig. 8).

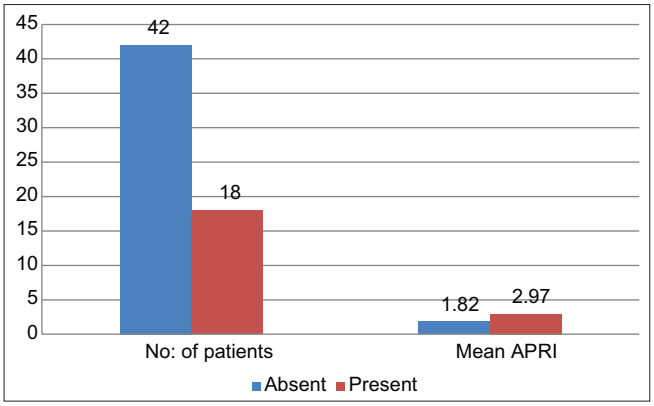

Fig. 19: Mean APRI in patients with anemia

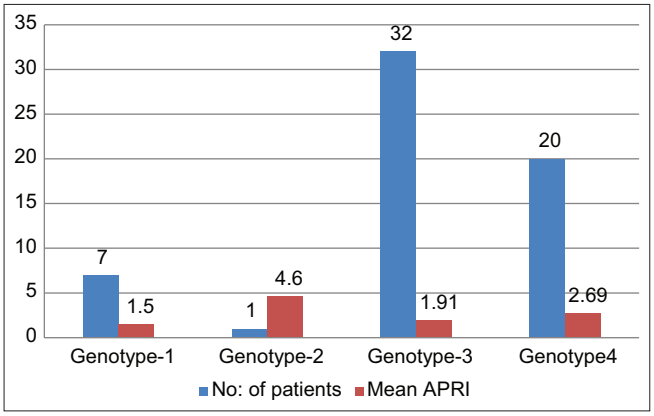

Fig. 20: Mean APRI versus HCV genotype

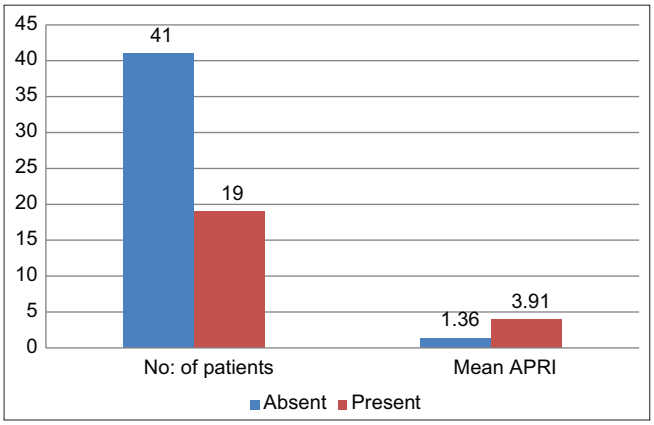

Fig. 21: Mean APRI in patients with cirrhosis in USG abdomen

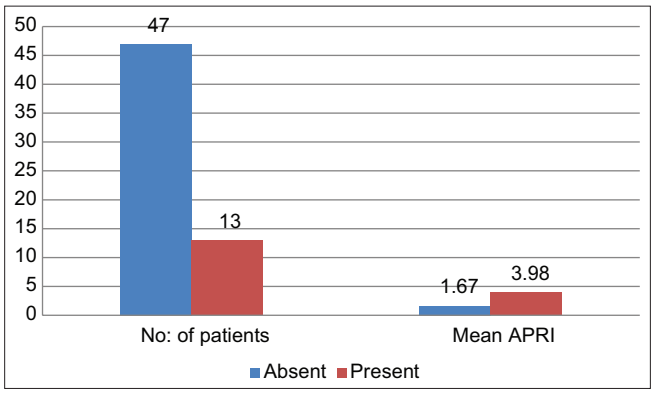

Fig. 22: Mean APRI in patients with splenomegaly in patients

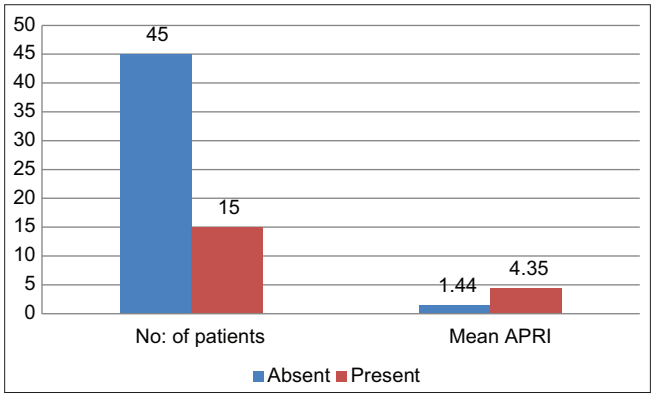

Fig. 23: Mean APRI in patients with portal hypertension on USG abdomen

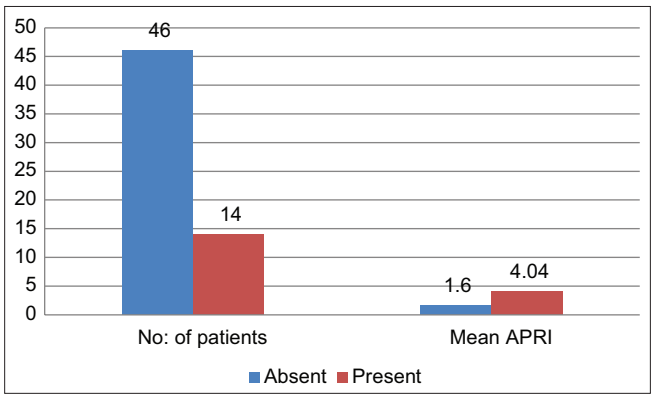

Fig. 24: Mean APRI in patients with Esophageal varices in OGDscopy

Out of 60 patients studied, 31.7% had cirrhosis in abdominal ultrasonography (Table 8 and Fig. 9).

Out of 60 patients studied, 13 patents (21.7%) had splenomegaly in abdominal ultrasonography (Table 9 and Fig. 10).

Out of 60 patients studied, 15 patients (25%) had portal hypertension in ultrasonography abdomen (Table 10 and Fig. 11).

Out of 60 patients studied, 14 patients (23.3%) had esophageal varices in esophagogastroduodenoscopy (Table 11 and Fig. 12).

Out of 60 patients studied, 12 patients (20%) had portal hypertensive gastropathy in esophagogastroduodenoscopy (Table 12 and Fig. 13).

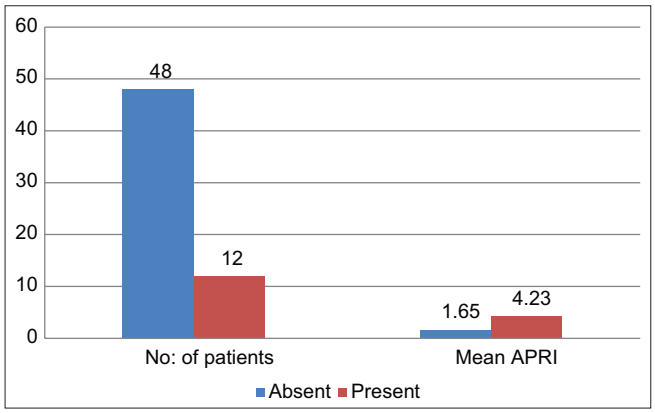

Fig. 25: APRI and portal hypertensive gastropathy in OGDscopy

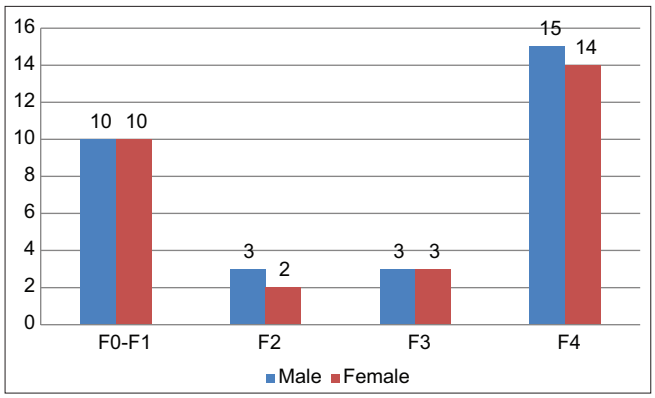

Fig. 26: METAVIR staging and gender

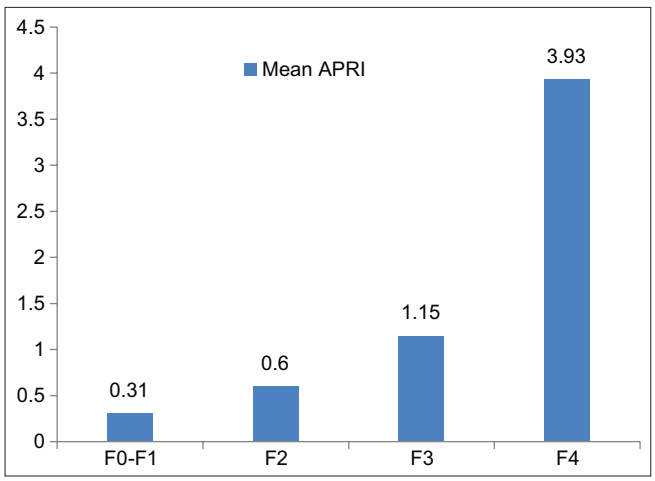

Fig. 27: Mean APRI versus Metavir staging

Most common phenotype of HCV among the study population was genotype type 3 (Table 13 and Fig. 14).

Among the 60 patients in this study, 29 patients (48.3%) belonged to F4 stage (cirrhosis). 6 patients (10%) patients belonged to F3 stage (severe fibrosis). 5 patients (8.3%) belonged to significant fibrosis. 20 (33.3%) patients belonged to F0-F1 stage (no fibrosis or absent fibrosis) (Table 14 and Fig. 15).

The mean value of fibroscan in the study was 17.2 with a standard deviation of 11.9. The median value of fibroscan is 13. Maximum value of fibroscan was 40. The minimum value of fibroscan was 3 (Table 15).

The mean value of APRI in the study was 2.2. The median value of APRI was 1.3.Maximum value of APRI was 9.7 The minimum value of APRI was 0.1.

The mean age of the study was 53.3 with a maximum of 72 and minimum of 21.

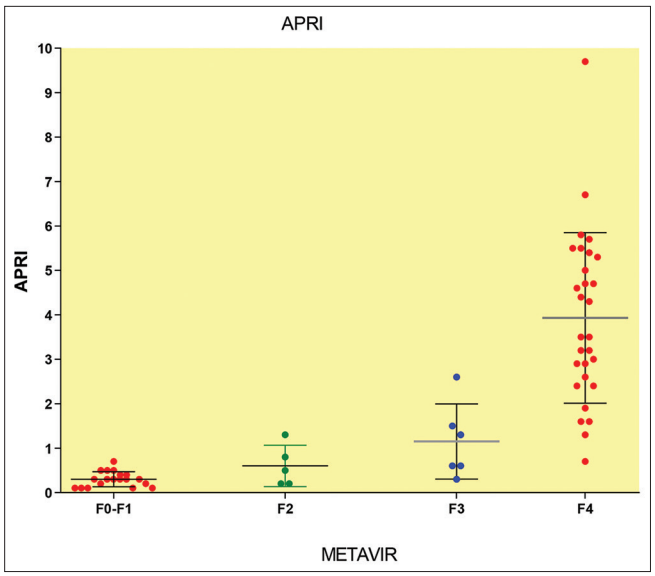

Fig. 28: Scatter dot plot diagram describing APRI according to METAVIR classification

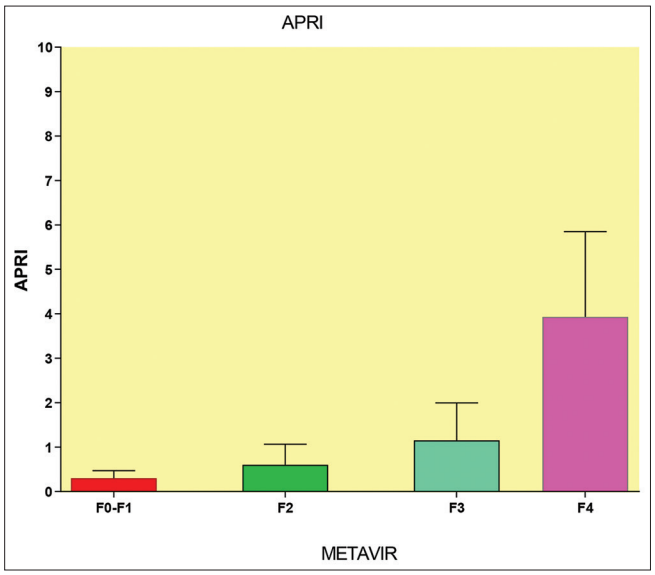

Fig. 29: APRI expressed in mean and standard deviation

The mean value of hemoglobin in the study was 12.8 with standard deviation of 2.9. Maximum value of hemoglobin was 16. Minimum value of hemoglobin was 9.

The mean value of platelet count in the study was 204 × 10^9 with a standard deviation of 105 × 10^9. Maximum value of platelet count was 500 × 10^9. The minimum value platelet count was 72 × 10^9.

The mean value of total bilirubin in the study was 1.6 with a standard deviation of 0.83. Maximum value of total bilirubin was 3.9. The minimum value of total bilirubin was 0.2.

The mean value of direct bilirubin in the study was 1.6 with a standard deviation of 0.61. Maximum value of direct bilirubin was 2.8. The minimum value of direct bilirubin was 0.1.

The mean value of total protein in the study was 6.8 with a standard deviation of 0.8. Maximum value of total protein was 8.3. The minimum value of total protein was 3.9.

The mean value of albumin in the study was 3.4 with a standard deviation of 0.6. Maximum value of albumin was 4.2.The minimum value of albumin was 1.3.

The mean value of SGOT in the study was 84.6 with a standard deviation of 66.4. Maximum value of SGOT was 292. The minimum value of SGOT was 14.

The mean value of SGPT in the study was 63 with a standard deviation of 47.2. Maximum value of SGPT was 248. The minimum value of SGPT was 10.

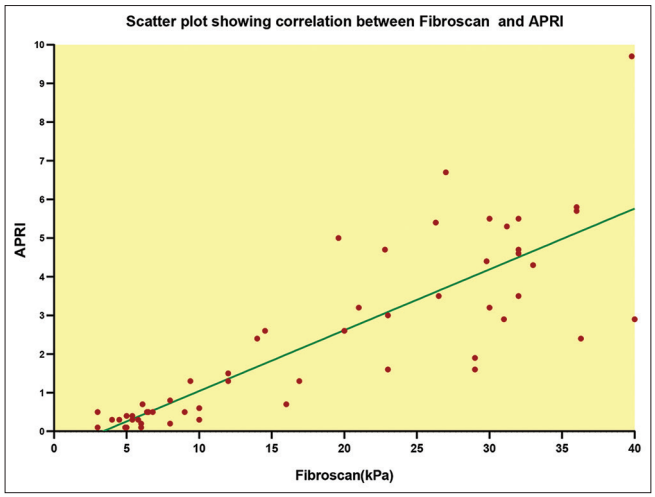

Fig. 30: Scatter plot showing correlation between Fibroscan and APRI

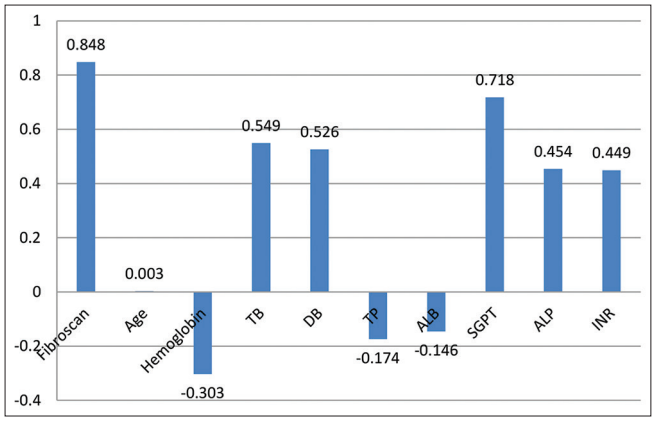

Fig. 31: Correlation of APRI and other parameters

The mean value of alkaline phosphatase in the study was 127.4 with a standard deviation of 52.7. Maximum value of alkaline phosphatase was 335. The minimum value of alkaline phosphatase was 59.

The mean value of INR in the study was 1.06 with a standard deviation of 0.19. Maximum value of INR was 1.80. The minimum value of INR was 0.80.

Out of the 60 patients studied, 31 were male and 29 were female. Mean APRI among males was 1.87 and mean APRI among females was 1.92. There was no statistical significance between APRI and gender with p value of 0.278 using student T test (Table 16).

Out of the 60 patients studied, 23 patients had fatigue. Mean APRI among the patients who had fatigue was 3.84 with a standard deviation of 1. There was statistical significance between APRI and fatigue with p<000.1 using student t-test (Table 17 and Fig. 16).

Out of the 60 patients studied, 9 patients had ascites in ultrasonography abdomen. Mean APRI among patients who had ascites in USG abdomen was 2.69 with a standard deviation of 1.98. There was no statistical significance between APRI and ascites in ultrasonography abdomen as the p value is >0.05 using student t-test (Table 18 and Fig. 17).

Out of the 60 patients studied, 4 patients had bleeding manifestations. Mean APRI among patients who had bleeding manifestation was 2.23 with a standard deviation of 2.38. There was no statistical significance between APRI and bleeding manifestations as p value is >0.05 using student t-test (Table 19 and Fig. 18).

Out of the 60 patients studied 18 patients had anemia. Mean APRI among patients who had anemia was 2.97 with a standard deviation of 2.55. There was no statistical significance between APRI and anemia as p value is >0.05 using student t-test (Table 20 and Fig. 19).

Out of the 60 patients studied, 7 patients had HCV genotype 1. Mean APRI among patients who had genotype-1 was 1.5 with a standard deviation of 1.39. 32 patients had genotype-3. Mean APRI of patients with genotype-3 was 1.91 with standard deviation of 2.24. Among the 60 patients, 20 patients had genotype - 4 which had mean APRI of 2.69 with standard deviation of 2.32 (Table 21 and Fig. 20).

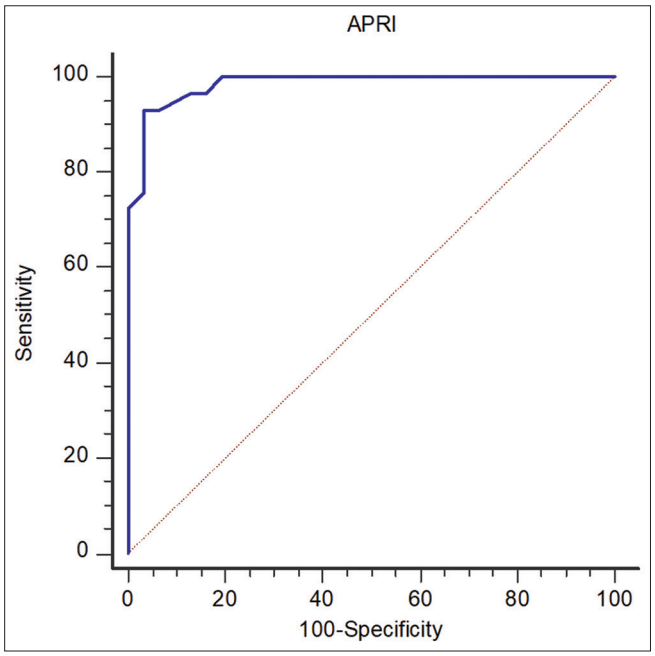

Fig. 32: ROC Curve of APRI to predict METAVIR >F2

There is no statistical significance between APRI and HCV genotype as p-value is >0.337 using ANOVA test.

Out of the 60 patients studied, 19 patients had cirrhosis in ultrasonography abdomen. Mean APRI among patients who had cirrhosis in USG abdomen was 3.91 with a standard deviation of 1.66. There was statistical significance between APRI and cirrhosis in ultrasonography abdomen as p value is >0.001 using student t-test (Table 22 and Fig. 21).

Out of the 60 patients studied, 13 patients had splenomegaly in ultrasonography abdomen. Mean APRI among patients who had splenomegaly in USG abdomen was 3.98 with a standard deviation of 1.38. There was statistical significance between APRI and splenomegaly in ultrasonography abdomen as p value is <0.001 using student t-test (Table 23 and Fig. 22).

Out of the 60 patients studied, 15 patients had portal hypertension in ultrasonography abdomen. Mean APRI among patients who had portal hypertension in USG abdomen was 4.35 with a standard deviation of 1.42. There was statistical significance between APRI and portal hypertension in ultrasonography abdomen as p value is <0.001 using student t-test (Table 24 and Fig. 23).

Out of the 60 patients studied, 14 patients had esophageal varices in esophagogastroduodenoscopy. Mean APRI among patients who had esophageal varices in esophagogastroduodenoscopy was 4.04 with a standard deviation of 1.36. There was statistical significance between APRI and esophageal varices in esophagogastroduodenoscopy as p value is <0.001 using student t-test (Table 25 and Fig. 24).

Out of the 60 patients studied 12 patients had portal hypertensive gastropathy in esophagogastroduodenoscopy. Mean APRI among patients who had portal hypertensive gastropathy in esophagogastroduodenoscopy was 4.23 with a standard deviation of 1.55. There was statistical significance between APRI and portal hypertensive gastropathy in esophagogastroduodenoscopy as p value is <0.001 using student T test (Table 26 and Fig. 25).

Out of the 60 patients studied in this study, 7 patients were under the age 40 years. Among the 3 patients under the age of 40 years. Among this, 7 patients and 3 patients belonged to F4 stage and F1 stage. 1 patient belonged to F3 stage. 16 patients belonged to the age group 41–50. Among the 16 patients belonged to the age group 41–50, 6 patients belonged to F0-F1 stage, 1 patient belonged to F1 stage, 2 patients belonged to F3 stage and 7 patients belonged to F4 stage. 23 patients belonged to the age group 51–60. Among the patients belonged to the age group 51–60, 7 patients belonged to F0-F1 stage, 1 patient belonged to F2 stage, 2 patients belonged to F3 stage, and 13 patients belonged to F4 stage. 12 patients belonged to the age group 61–70. Among the 12 patients belonged to the age group 61–70, 3 belonged to F0-F1, 2 belonged to F2, 1 belonged to F3, and 6 patients belonged to F4 stage. Above the age of 70 years, there were 2 patients.

There is no statistical significance between METAVIR staging and age as p value is more than 0.709 using Chi-square test. In all age groups (Table 27).

Out of the 60 patients studied, 29 patients belonged to the F4 stage. Among the 29 patients belonged to F4 stage, 14 (48.3%) were females and 15 (48.3%) were males.

6 patients belonged to the F3 stage in which males and females were equal in number.

5 patients belonged to F2 stage in which 3(9.7%) were males and 2 (6.9%) were females. There was no statistical significance for METAVIR and sex in any of the stages of fibrosis as p-value is >0.05 (Table 28 and Fig. 26).

Out of the 60 patients studied, 20 patients were in F0-F1 group. Mean APRI among patients in F0-F1 was 0.31 with a standard deviation of 0.17. F2 group had 5 patients and F3 group had 6 patients with mean APRI of 0.60 and 1.15, respectively. There is progressive rising trend of APRI from F0-F1 to F4. There was statistical significance between APRI and Metavir scoring with a p value <0.001 using ANOVA test (Table 29 and Fig. 27).

Middle horizontal line is the mean and error bar represents standard deviation

Among the 60 patients studied mean APRI score in F0-F1 stage was 0.31 with a standard deviation of 0.17. Maximum value of APRI in F0-F1 stage is 0.7 and minimum value is 0.1. Mean APRI score in F2 stage is 0.6 with a standard deviation of 0.46. Minimum value of APRI score in F2 stage is 0.2 and maximum value is 1.3. Mean APRI score in F3 stage is 1.15 with standard deviation of 0.85. Maximum value of APRI score in F3 stage is 2.6. Minimum value of APRI score in F3 stage is 0.3. Mean APRI score in F4 stage is 3.931 with standard deviation of 1.92. Maximum value of APRI score in F4 stage is 9.7 and minimum value for APRI in F4 stage is 0.7 (Table 30 and 31 and Fig. 28).

Correlation between fibroscan and APRI

The correlation coefficient r of APRI with Fibroscan value is 0.848 with p<0.001. This suggests a strong positive correlation between APRI score and METAVIR stages determined by fibroscan. Higher the value of APRI, higher will be the fibroscan value.

The correlation coefficient r of APRI with total bilirubin value is 0.549 with p<0.001. This suggests a positive correlation between APRI score and total bilirubin. Higher the value of total bilirubin, higher will be the APRI value.

The correlation coefficient r of APRI with direct bilirubin value is 0.549 with p<0.001. This suggests a positive correlation between APRI score and total bilirubin. Higher the value of total bilirubin, higher will be the APRI value.

The correlation coefficient r of APRI with SGPT value is 0.718 with p<0.001. This suggests a positive correlation between APRI score and SGPT. Higher the value of SGPT, higher will be the APRI value.

The correlation coefficient r of APRI with ALP value is 0.454 with p<0.001. This suggests a positive correlation between APRI score and ALP. Higher the value of ALP, higher will be the APRI value.

The correlation coefficient r of APRI with INR value is 0.449 with p<0.001. This suggests a positive correlation between INR score and total bilirubin. Higher the value of INR, higher will be the APRI value (Table 32 and Fig. 29-31).

Sample size		60
Positive group:	F>2	35
Negative group:	F≤2	25
Area under the ROC curve (AUC)		
Area under the ROC curve (AUC)	0.974	
Standard Error	0.0172	
95% Confidence interval	0.896 to 0.998	
Optimum cutoff	>0.5	
Sensitivity	97.14	
Specificity	88	

APRI	Sensitivity	Specificity	+PV	-PV
>0.2	100	36	68.6	100
>0.3	97.14	60	77.3	93.7
>0.5	97.14	88	91.9	95.7
>0.6	91.43	88	91.4	88
>0.7	88.57	92	93.9	85.2
>0.8	88.57	96	96.9	85.7

Among the 60 patients studied, 35 patients belong to METAVIR stage F3 and F4. The optimum cutoff value of APRI for finding F3 and F4 stages among this patients was more than 0.5 with a sensitivity of 97.14% and a specificity of 88%.The area under ROC curve for finding stages F3 and F4 is 0.974 with a confidence interval of 0.896–0.998. The positive predictive value for F3 and F4 METAVIR stages with APRI value 0.5 is 91.9% and negative predictive value for F3 and F4 METAVIR stages with APRI value 0.5 is 95.7% (Table 33 and Fig. 32).

Sample size		60
Positive group:	F>3	29
Negative group:	F≤3	31
Area under the ROC curve (AUC)	0.984	
Standard Error	0.0112	
95% Confidence interval	0.912–1.000	
Optimum cutoff	>1.5	
Sensitivity	93.1	
Specificity	96.77	

Among the 60 patients studied, 31 patients belong to METAVIR stage F4. The optimum cutoff value of APRI for finding F4 stage among this patients was more than 1.5 with a sensitivity of 93.1% and a specificity of 96.77%. The area under ROC curve for finding stage F4 is 0.984 with a confidence interval of 0.912–1.000. The positive predictive value F4 METAVIR stage with APRI value more than 1.5 is 96.4% and negative predictive value for F4 METAVIR stage with APRI more than 1.5 is 93.7%. Among the 29 patients with cirrhosis by fibroscan, 25 patients had APRI >1.5 (Fig. 33).

Criterion	Sensitivity	Specificity	+PV	-PV
>0.6	100	80.65	82.9	100
>0.7	96.55	83.87	84.8	96.3
>0.8	96.55	87.1	87.5	96.4
>1.3	93.1	93.55	93.1	93.5
>1.5	93.1	96.77	96.4	93.7
>2.4	75.86	96.77	95.7	81.1
>2.6	72.41	100	100	79.5

DISCUSSION

This study was conducted at Government Medical College Kottayam, to determine the association between APRI and severity of fibrosis in patients with chronic hepatitis C and to describe the clinical profile of patients with chronic hepatitis C.

A total of 60 patients were studied and the following observations were made regarding the age and sex distribution, clinical features, blood investigations, USG abdomen, OGD scopy FIBROSCAN, and APRI score.

Age and gender

The mean age of the study population was 53.3±11.33 years of which 48.3% were females and 51.7% were males. The study by Wai *et al*. [3] revealed a mean age of 46.8±0.6 years and males constituted 64%. The population of the study by Viana *et al*. [4] had a mean age of 51±11.6 years with 53.5% males and 46.5% females. The study by Papadopoulos *et al.* [5] had a mean age of 51.54±12.4 years and 63.5% of them were male.

Clinical features

In this study, 27 (45%) patients had thrombocytopenia. The mean value of platelet count in the study was 204 × 10^9 with a standard deviation of 105 ×10^9. Maximum value of platelet count was 500 ×10^9 and the minimum value was 72 ×10^9. In the study by Wai *et al*. [3], the mean platelet count was 219 × 10^9, which is comparable to our study. There was statistical association between platelet count and stages of fibrosis. As the platelet count decreased, severity of fibrosis increased.

In this study, 19 (31.7%) patients had cirrhosis in ultrasonography abdomen. There was statistical significance between APRI and cirrhosis in USG abdomen.

In this study, 13 (21.7%) patients had splenomegaly in ultrasonography abdomen. There was statistical association between APRI and splenomegaly in ultrasonography abdomen, similar to the study by Wai *et al*. [3] 18% of patients with chronic hepatitis C had splenomegaly in ultrasonography abdomen and there was statistical association between APRI and splenomegaly in ultrasonography abdomen.

In this study, predominant HCV genotype was Genotype-3. 32 patients (53.3%) had genotype 3 and 20 (33.3%) patients had Genotype 4. This is similar to the study by Papadopoulos *et al*. [6], where HCV genotype 3 was the predominant genotype(38.5%). In the study by Loaeza-del-Castillo *et al*. [7], Genotype 3 was the predominant genotype (40%). In the study by Taneja *et al*. [76], the predominant HCV genotype being HCV-3 (n=214; 64.8%) followed by HCV-1 (n=116; 35.2%).

In the present study, 15 (25%) patients had portal hypertension in ultrasonography abdomen. Mean APRI among patients with portal hypertension was 4.35. There was statistical significance between APRI score and portal hypertension with p<0.001. Among the patients with portal hypertension all of them belonged to METAVIR stage F4 (cirrhosis). The mean APRI among the patients who had portal hypertension with cirrhosis was 4.353. The mean APRI among the patients who had cirrhosis but without portal hypertension was 3.479. There was no statistical significance for APRI in patients with cirrhosis and portal hypertension and cirrhosis without portal hypertension.

In this study, 14 (23.3%) patients have esophageal varices in esophagogastroduodenoscopy. Mean APRI among patients with esophageal varices was 4.04. There was statistical significance between APRI score and esophageal varices with p<0.001. Among the patients with esophageal varices all of them belonged to METAVIR stage F4 (cirrhosis). The mean APRI among the patients who had esophageal varices with cirrhosis was 4.154. The mean APRI among the patients who had cirrhosis but without esophageal varices was 3.750. There was no statistical significance for APRI in patients with cirrhosis and esophageal varices and cirrhosis without esophageal varices.

In this study, 12 (20%) patients have portal hypertensive gastropathy in esophagogastroduodenoscopy. There was statistical significance between APRI score and portal hypertensive gastropathy with p<0.001.

The mean value of SGOT in the study was 84.6 IU/L with a standard deviation of 66.4. Maximum value of SGOT was 292.The minimum value of SGOT was 14. There was statistical significance between APRI score and SGOT with p<0.001. In the study by Papadopoulos *et al*. [5], mean value of SGOT in the study was 62.3±48 IU/L and found that SGOT was an independent predictor of fibrosis in chronic hepatitis C.

The mean value of SGPT in the study was 63 with a standard deviation of 47.2. Maximum value of SGPT was 248. The minimum value of SGPT was 10. There was statistical significance between APRI score and SGPT with p<0.001. In the study by Papadopoulos *et al*. [5], mean value of SGOT in the study was 71.8±62.

The mean value of alkaline phosphatase in the study was 127.4 with a standard deviation of 52.7. Maximum value of alkaline phosphatase was 335. The minimum value of alkaline phosphatase was 59. There was statistical significance between APRI score and alkaline phosphatase with p<0.001.

The mean value of INR in the study was 1.06 with a standard deviation of 0.19. Maximum value of INR was 1.80. The minimum value of INR was 0.80. There was statistical association between APRI and INR value in this study.

The mean value of fibroscan in the study was 17.2 with a standard deviation of 11.9. Maximum value of fibroscan was 40. The minimum value of fibroscan was 3.

In this study, on the basis of the validated cut offs by Castéra *et al*. [9], 29(48.3%) patients belong to F4 stage which indicate cirrhosis

(≥12.5 kPa). In this study, 6 (10%) patients belong to F3 stage which indicates severe fibrosis, but no cirrhosis (9.5–12.4 kPa). In this study, 5 (8.3%) patients belong to F2 stage which indicates significant fibrosis (7.1–9.4 kPa). In this study, 20 (33.3%) patients belonged to F0-F1 stage which indicates mild fibrosis or no fibrosis (≤7 kPa).

In the study conducted by Taneja *et al.* (8), 95 (28.8%) patients had cirrhosis (≥12.5 kPa), 39 (11.8%) had severe fibrosis but no cirrhosis (9.5–12.4 kPa), 49 (14.8%) had moderate fibrosis (7.1–9.4 kPa), and no or minimal fibrosis (≤7 kPa) was seen in 147 (44.5%) patients.

The mean value of APRI in the study was 2.2. Maximum value of APRI was 9.7. The minimum value of APRI was 0.1.

Median APRI values in CHC patients increased according to fibrosis stage. Median APRI score in F0-F1 stage was 0.3. Median APRI score in F2 stage is 0.5. Median APRI score in F3 stage is 0.95. Median APRI score in F4 stage is 3.5. In the study by Loaeza-del-Castillo *et al.* [7], median APRI values in CHC patients increased according to fibrosis stage, namely 0.39 for F0, 0.505 for F1, 0.545 for F2, 0.745 for F3, and 1.64 for F4. The correlation coefficient r of APRI with Fibroscan value is 0.848 with p<0.001. This suggests a strong positive correlation between APRI score and METAVIR stages determined by fibroscan. Higher the value of APRI, higher will be the fibroscan value.

Among the 60 patients studied, 35 patients belong to METAVIR stage F3 (severe fibrosis) and F4 (Cirrhosis). The optimum cutoff value of APRI for finding severe fibrosis or cirrhosis among this patients was more than 0.5 with a sensitivity of 97.14% and a specificity of 88%. The area under ROC curve for finding severe fibrosis or cirrhosis is 0.974 with a confidence interval of 0.896–0.998.The positive predictive value for severe fibrosis and cirrhosis with APRI value 0.5 is 91.9% and negative predictive value for severe fibrosis or cirrhosis with APRI value 0.5 is 95.7%. Among the 60 patients studied 31 patients belong to METAVIR stage F4 (cirrhosis). The optimum cutoff value of APRI for finding cirrhosis stage among this patients was >1.5 with a sensitivity of 93.1% and a specificity of 96.77%. The area under ROC curve for finding cirrhosis is 0.984 with a confidence interval of 0.912–1.000. The positive predictive value cirrhosis with APRI threshold >1.5 is 96.4 % and negative predictive value for cirrhosis with APRI more than 1.5 is 93.7%.

In the study conducted by Wai *et al.* [3], it was found that ROC curves of APRI for predicting significant fibrosis and cirrhosis with AUC of 0.80 and 0.89, respectively. For patients with APRI of 0.50 or less, 47 of 55 (85%) would not have significant fibrosis. In that study patients who had significant fibrosis, only 8 (9%) would have APRI of 0.50 or less.

In the study by Loaeza-del-Castillo *et al.* [7] for the diagnosis of significant fibrosis (METAVIR F3) in CHC patients, APRI values delimited an AUC of 0.803 (95%CI 0.735–0.872; p<0.001), with a threshold of APRI score 0.7. At this threshold, sensitivity was 77.6% (95%CI 65.8–86.9%), specificity 75.3% (65.5–83.5%), positive predictive value 68.4% (56.7–78.6%), negative predictive value 83% (73.4–90.1%), and accuracy 76.2% (69–82.5%).

In the study by Papadopoulos *et al.* [5], the optimal APRI score for cirrhosis patients was calculated as >0.65 with area under the curve 0.871, with p<0.0001, giving sensitivity of 85.5%, Specificity of 77%, with a positive predictive value of 76%, and negative predictive value of 86%. The optimal APRI score to predict F3/F4 patients as one group indicating advanced fibrosis or cirrhosis was calculated as >0.64 with an area under curve of 0.82, and p value of <0.0001), giving a sensitivity of 72%, specificity of 83%. The positive predictive value of APRI score >0.64 in predicting advanced fibrosis or cirrhosis is 88% with negative predictive value of 63%.

In the study by Mendes *et al.* [9], APRI classification for advanced fibrosis/cirrhosis was possible in 77% of patients (APRI >2.0). Cirrhosis (F≥3) was found to be likely (APRI>2.0) in 7 patients (4%) and unlikely (APRI<1.0) in 134 (74%) patients, with 98% specificity and 97% PPV with AUROC of 0.76.

The difference in APRI cutoff score with other studies may be due to difference in SGOT levels according with body mass and different cutoff levels used in those studies.

CONCLUSIONS

1. APRI score was found to have strong positive correlation with fibroscan values. APRI score can be used as a predictor of fibrosis in patients with chronic hepatitis C.
2. Most of the patients with chronic hepatitis C were asymptomatic, with fatigue being the most common symptom.

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