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RESEARCH ARTICLE

PAPAS INDEX FOR NON-INVASIVE ASSESSMENT OF LIVER FIBROSIS IN EGYPTIAN PATIENTS WITH CHRONIC HEPATITIS C: COMPARISON WITH FIB-4 AND FIBROQ

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ABSTRACT

Background And Aim: The diagnostic value of serum markers of liver fibrosis has been investigated in numerous studies. This study aimed to investigate the value of PAPAS index for non-invasive assessment of liver fibrosis in Egyptian patients with chronic hepatitis C in comparison to FIB-4 and FibroQ.
Methods: Forty naïve Egyptian patients with chronic hepatitis C virus prior to treatment with antiviral therapy were included. All were subjected to clinical evaluation, laboratory investigations, abdominal ultrasonography, transient elastography (Fibroscan) in addition to non-invasive indices (PAPAS index, FIB-4 and Fibro Q).
Results: The mean stiffness score of studied patients by transient elastography was 11.3±7.6 kpascal where 9 cases (22.5%) were F1, 12 cases (30%) were F2, 9 cases (22.5%) were F3 and 10 cases (25%) were F4. PAPAS index was significantly higher in F3-F4 (advanced fibrosis) than F1-F2 (non advanced fibrosis) (P<0.001). PAPAS showed highly significant diagnostic performance in differentiating advanced from non-advanced fibrosis in comparison to FIB-4 and FibroQ. The AUC of ROC curve of PAPAS, FIB-4 and FibroQ was 0.987, 0.787 and 0.714 respectively. Using cutoff value of ≥ 2.05 PAPAS index could predict advanced fibrosis with PPV 95%, sensiti vity 100% and <2.05 could exclude advanced fibrosis with NPV 100%, and specificity 95.2%.
Conclusion: PAPAS index was superior to FIB-4 and FibroQ in differentiating between advanced and non-advanced fibrosis.

INTRODUCTION

Chronic hepatitis C has a significant prevalence worldwide reaching alarming levels at some regions such as Egypt (Kamal and Nasser, 2008). One of the mainstays of management of HCV is the detection of the stage of liver fibrosis (Mitchell *et al*., 2010). To date, liver biopsy is still the gold standard for staging of liver fibrosis, however, it has several well-documented drawbacks including sampling error and inaccuracy due to inter- and intraobserver variability of histopathologic interpretation in addition to significant risks for the patient (Bedossa *et al*., 2003). Thus, it cannot be used as a standard follow-up procedure for disease monitoring (Seeff *et al*., 2010).

For these reasons, non-invasive methods for assessing the severity of fibrosis may someday completely replace liver biopsy and are constantly being searched for. Among the non-invasive tests, the best results were obtained with liver stiffness measurement (LSM) by means of transient elastography (TE) (Fibroscan). This non-invasive method is expensive and requires equipment that is not widely available (Beaugrand, 2006 and Stasi *et al*., 2009).

Therefore simpler and cheaper methods for the prediction of hepatic fibrosis were sought for. One of these non-invasive tests is FibroQ, which is calculated from common laboratory test results as (10 × age × AST × PT INR)/ (ALT × platelet count) (Hsieh *et al*., 2009).

The FIB-4 index is another index based on standard biochemical values and age. It is calculated as: [Age (yr) × AST (U/L)]/[platelet count (109/L) × ALT (U/L) $^{1/2}$]. It has been reported to be markedly useful for the prediction of

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advanced liver fibrosis (Sterling *et al*., 2006 and Vallet-Pichard *et al*., 2007).

PAPAS (Platelet/Age/Phosphatase/AFP/AST) index is a new non-invasive test that can predict significant fibrosis and cirrhosis. Its predictive power was superior to other non-invasive models using common parameters, including the AST/platelet/GGT/AFP (APGA) index, AST/platelet ratio index (APRI), and the FIB-4 index (Seto *et al*., 2011 and Ozel *et al*., 2015).

This study was performed to investigate the value of PAPAS index for non-invasive assessment of liver fibrosis in Egyptian patients with chronic hepatitis C in comparison to FIB-4 and FibroQ.

PATIENTS AND METHODS

This cross-sectional study was conducted on 40 naïve Egyptian patients with chronic hepatitis C virus prior to treatment with antiviral therapy. Patients were diagnosed by positive HCV Ab by ELISA and quantitative PCR. They were presented to Internal Medicine and Tropical Medicine Departments and outpatient clinics at Ain Shams University Hospital, during the period from April 2015 to December 2015.

Informed written consent was obtained from each patient prior to inclusion. The study protocol was approved by the Research Ethical Committee of Faculty of Medicine, Ain Shams University according to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients with any other etiology for chronic hepatitis (other than HCV), chronic alcohol abuse, obesity (BMI>30), biliharziasis, Diabetes Mellitus, those with decompensated liver disease, hepatocellular carcinoma, previous antiviral, immunosuppressive or anticoagulant therapy, liver transplantation, as well as those with any other co-morbidities were excluded.

All included patients were subjected to the following:

1- Complete clinical evaluation.
2- Laboratory investigations:
   a) CBC: white blood cells, platelet counts and haemoglobin level,
   b) Liver profile: alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, total and direct bilirubin, alkaline phosphatase, prothrombin time and INR.
   c) Renal profile: creatinine and blood urea.
   d) Alpha Feto-protein.
   e) Viral markers including: HCV Ab by third generation ELISA, HBsAg, HBcAb IgM and IgG.
   f) Quantitative PCR for HCV.
3- Abdominal ultrasonography: for liver size, echogenicity, spleen size, echogenicity and confirming absence of ascites, liver or spleen focal lesions or portal vein thrombosis.
4- Transient elastography (Fibroscan): FibroScan (M probe, Echosens, 502 Touch, Paris) was carried out by an experienced examiner in all patients (fasting for at least six hours). During the examination, the patient was lying in dorsal decubitus and the right arm in maximal abduction so as to enlarge the intercostal space in which the probe was placed. The median liver stiffness of 10 successful measurements fulfilling the criteria was noted in kilopascal (Kpa).

The cut-off values used to assess liver stiffness in HCV were measured according to *Ziol et al., 2005*:

a) F1: 7-8.4 Kpa
b) F2: 8.5-9.4 Kpa
c) F3: 9.5-14.4 Kpa
d) F4: 14.5-75 Kpa

We classified the cases in our study according to the results of transient elastography by Fibroscan into:

a) Non-advanced fibrosis including (F1– F2).
b) Advanced fibrosis including (F3-F4).

5- Non-invasive indices:

Fibrosis test	Calculation
PAPAS index (Seto *et al*., 2011)	Log (index+1) = 0.0255+0.0031×age (years)+0.1483×log{ALP (U/L)}+0.004×log{AST (U/L)}+0.0908×log{AFP (ng/L)+1}-0.028×log{platelet count (10^9/L)}
FIB-4 index (Sterling *et al*., 2006)	[Age (yr) × AST (U/L)]/[platelet count (10^9/L) × ALT (U/L) $^{1/2}$] If FIB-4 < 1.45: no or minimal fibrosis. If FIB-4 > 3.25: significant fibrosis.
Fibro Q (Hsieh *et al*., 2009)	(10 × age × AST × INR)/ (PLT × ALT)

Statistical analysis

The collected data were coded, tabulated, and statistically analysed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0.

Descriptive statistics were done for quantitative data as minimum & maximum of the range as well as mean ± SD (standard deviation) for quantitative parametric data, median and 1st& 3rd inter-quartile range for quantitative non-parametric data, while it was done for qualitative data as number and percentage.

Correlations were done using Pearson Correlation for numerical parametric data, and Spearman Rho test for numerical non parametric and qualitative data. Receiver operating characteristics (ROC) curve was used to evaluate the performance of different tests differentiate between certain groups, DeLong test was used to compare between area under ROC curve (AUCs). P value < 0.05 was considered statistically significant & P< 0.01 as highly significant.

Diagnostic characteristics were calculated as follows

- Sensitivity = (True positive test / Total positive golden) x 100
- Specificity = (True negative test / Total negative golden) x 100
- Predictive positive value = (True positive test / Total positive test) x 100
- Predictive negative value = (True negative test / Total negative test) x 100

- Positive likelihood ratio (LR+) = (True positive test / False positive test) x 100
- Negative likelihood ratio (LR-) = (False negative test / True negative test) x 100
- Diagnostic accuracy = [(True positive test + True negative test) / Total cases] x 100

RESULTS

This cross-sectional study was conducted on 40 Egyptian patients with chronic hepatitis C. They were 31 males (77.5%) and 9 females (22.5%). Their mean age was 47.7±13.6 years.

The mean Fibro Q, FIB-4, PAPAS index of the studied cases were 2.8 ± 1.4, 1.9 ± 1.1, and 2.0 ± 0.3 respectively. Their mean stiffness score (kpascal) by transient elastography was 11.3±7.6 where 9 cases (22.5%) were F1, 12 cases (30%) were F2, 9 cases (22.5%) were F3 and 10 cases (25%) were F4.

Table (1) shows the mean values and ranges of non-invasive indices in different fibrosis stages.

Table 1 The mean values and ranges of non-invasive indices in different fibrosis stages.

Stage	N	FibroQ		FIB-4		PAPAS	
		Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
F1	9	2.0±1.0	0.8–4.1	1.1±0.6	0.5–2.2	1.6±0.3	1.1–2.0
F2	12	2.6±1.8	0.4–5.7	1.7±1.3	0.3–4.0	1.8±0.3	1.3–2.1
F3	9	3.1±0.9	2.4–4.5	2.0±0.7	1.3–3.2	2.3±0.1	2.1–2.4
F4	10	3.5±1.3	2.2–5.6	2.8±0.9	1.3–4.6	2.2±0.1	2.1–2.4
F1–2	21	2.3±1.5	0.4–5.7	1.5±1.1	0.3–4.0	1.7±0.3	1.1–2.1
F3–4	19	3.3±1.1	2.2–5.6	2.4±0.9	1.3–4.6	2.2±0.1	2.1–2.4

Table (2) shows that there was highly significant positive correlation between the 3 non invasive indices

Table 2 Correlation between non-invasive measurements with patients' characteristics and laboratory data.

Variables		Stiffness	PAPAS	FibroQ	Fib-4
Age	^r	0.241	0.755	0.707	**0.692**
	p	0.134	<0.001*	<0.001*	<0.001*
BMI	^r	0.098	0.065	-0.182	**-0.101**
	p	0.548	0.691	0.262	0.534
HB	^r	0.040	0.080	0.031	0.185
	P	0.805	0.624	0.850	0.253
PLT	^r	-0.334	-0.317	-0.611	-0.591
	P	0.035*	0.047*	<0.001*	<0.001*
TLC	^r	-0.199	0.088	0.084	-0.037
	P	0.218	0.591	0.606	0.818
PT	^r	0.350	0.338	0.370	0.378
	P	0.027*	0.033*	0.019*	0.016*
INR	^r	0.307	0.339	0.355	0.344
	P	0.050*	0.032*	0.025*	0.030*
ALB	^r	-0.101	-0.483	-0.389	-0.292
	P	0.535	0.002*	0.013*	0.067
AST	#r	0.464	0.296	0.059	0.585
	p	0.003*	0.064	0.718	<0.001*
ALT	#r	0.354	0.182	-0.131	0.422
	p	0.025*	0.261	0.421	0.007*
ALP	#r	-0.037	0.084	0.000	-0.195
	p	0.819	0.604	0.998	0.228
AFP	#r	0.560	0.750	0.467	0.467
	p	<0.001*	<0.001*	0.002*	0.002*
D.BIL	#r	0.264	0.181	0.001	0.199
	p	0.100	0.264	0.994	0.219
T.BIL	#r	0.353	0.434	-0.020	0.129
	p	0.026*	0.005*	0.900	0.427
HCV PCR	#r	0.325	0.484	0.097	0.191
	p	0.041*	0.002*	0.552	0.239

^Pearson correlation, #Spearman correlation, *Significant

(PAPAS, FibroQ and FIB-4) and age (P<0.001), between FIB-4 and AST (P <0.001) and between each of stiffness score and PAPAS index with AFP (P <0.001).

PT was significantly positively correlated with stiffness score (P=0.027), PAPAS index (P=0.033), FIB-4 (P=0.016) and Fibro Q (P=0.019). HCV PCR was significantly positively correlated with stiffness score (P=0.041) and PAPAS index (P=0.002).

There was highly significant negative correlation between each of FibroQ and FIB-4 with platelets (P <0.001),

There were significant negative correlations between stiffness score and platelets, PAPAS index and platelets, PAPAS index and albumin and FibroQ and albumin (P = 0.035, 0.047, 0.002 and 0.013 respectively).

Table (3) shows that PAPAS index was significantly higher in F3-F4 (advanced fibrosis) than F1-F2 (non advanced fibrosis) with P value <0.001 compared to FIB-4 (P=0.004) and Fibro Q (P=0.028). Only PAPAS was significantly higher in F3 than F2 with P value <0.001.

Table 3 Comparison between non-invasive indices in different fibrosis stages**.**

Non-invasive indices		FibroQ		FIB-4		PAPAS	
Stage		t	p	t	p	t	p
F1	F2	0.858	0.402	1.252	0.226	0.884	0.388
F2	F3	0.747	0.464	0.661	0.517	5.323	<0.001*
F3	F4	0.855	0.404	1.959	0.067	1.693	0.109
F1–2	F3–4	2.283	0.028*	3.033	0.004*	6.878	<0.001*

Independent t-test
*Significant

Table (4) shows that PAPAS ≥ 2.05 (best cut-off value) had excellent diagnostic characteristics in differentiating advanced from non-advanced fibrosis. Using cutoff value of ≥ 2.05, PAPAS index could predict advanced fibrosis with PPV 95%, sensitivity 100% and <2.05 could exclude advanced fibrosis with NPV 100%, and specificity 95.2%.

Table 4 Diagnostic characteristics of PAPAS ≥2.05 (best cut off value) in differentiating advanced from non-advanced fibrosis.

Character	Value	95% CI
Sensitivity	100.0%	85.4%–100.0%
Specificity	95.2%	82.1%–95.2%
Positive Predictive value (PPV)	95.0%	81.2%–95.0%
Negative Predictive value (NPV)	100.0%	86.2%–100.0%
Positive likelihood ratio (LR+)	21.0	4.8–21.0
Negative likelihood ratio (LR-)	0.0	0.0–17.8
Diagnostic accuracy (DA)	97.5%	83.7%–97.5%

CI: Confidence interval

Table (5) shows that FIB-4 ≥ 1.2 (best cut-off value) had excellent sensitivity, NPV and LR-, but low other characteristics in differentiating advanced from non-advanced fibrosis.

Table (6) shows that Fibro Q ≥ 2.3 (best cut-off value) had excellent sensitivity, NPV and LR-, but low other characteristics in differentiating advanced from non-advanced fibrosis.

Table 5 Diagnostic characteristics of FIB-4 ≥ 1.2 (best cut off value) in differentiating advanced from non-advanced fibrosis**.**

Character	Value	95% CI
Sensitivity	100.0%	83.8%–100.0%
Specificity	61.9%	47.3%–61.9%
Positive Predictive value (PPV)	70.4%	59.0%–70.4%
Negative Predictive value (NPV)	100.0%	76.3%–100.0%
Positive likelihood ratio (LR+)	2.6	1.6–2.6
Negative likelihood ratio (LR-)	0.0	0.0–0.3
Diagnostic accuracy (DA)	80.0%	64.6%–80.0%

CI: Confidence interval

Table 6 Diagnostic characteristics of FibroQ ≥ 2.3 (best cut off value) in differentiating advanced from non-advanced fibrosis.

Character	Value	95% CI
Sensitivity	94.7%	77.5%–99.7%
Specificity	57.1%	41.5%–61.7%
Positive Predictive value (PPV)	66.7%	54.5%–70.2%
Negative Predictive value (NPV)	92.3%	67.1%–99.6%
Positive likelihood ratio (LR+)	2.2	1.3–2.6
Negative likelihood ratio (LR-)	0.1	0.0–0.5
Diagnostic accuracy (DA)	75.0%	58.6%–79.7%

CI: Confidence interval

Table (7) shows the diagnostic performance of non-invasive indices in differentiation between advanced and non-advanced liver fibrosis. The AUC of ROC curve of PAPAS, FIB-4 and FibroQ was 0.987, 0.787 and 0.714 respectively. PAPAS showed highly significant diagnostic performance, while FIB-4 and FibroQ showed fair significant diagnostic performance in differentiating F3–4 (advanced fibrosis) from F1–2 (non-advanced fibrosis) with P value <0.001, 0.002 and 0.021 respectively.

Table 7 Diagnostic performance of non-invasive indices in differentiation between advanced and non-advanced liver fibrosis

Stages		Variables	AUC	SE	P	95 CI
		PAPAS	0.987	0.014	<0.001*	0.500–1.000
F1–2	F3–4	FibroQ	0.714	0.085	0.021*	0.549–0.880
		FIB-4	0.787	0.077	0.002*	0.635–0.939

AUC: Area under curve, SE: Standard error, CI: Confidence interval, *Significant

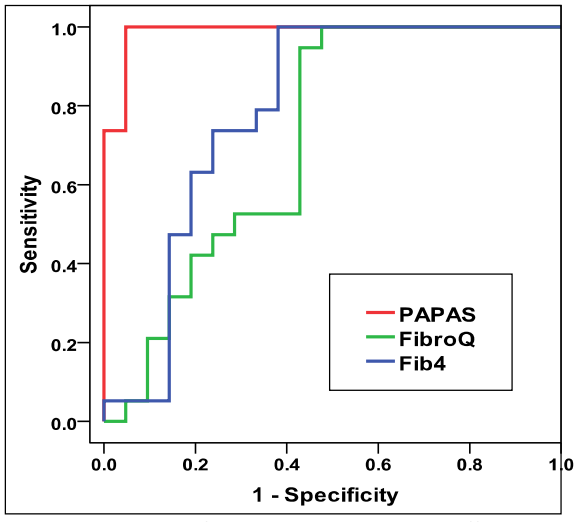

Figure 1 ROC curve for non-invasive indices in differentiating advanced from non-advanced fibrosis.

Figure (1) shows ROC curve for non-invasive indices in differentiating advanced from non-advanced fibrosis. On comparing the AUC of ROC curve of PAPAS index to that of FIB-4 and FibroQ, in differentiating between advanced and non-advanced fibrosis, P-value was found to be highly significant (P< 0.001). While on comparing the AUC of ROC curve of FIB-4 to that of FibroQ in differentiating advanced from non-advanced fibrosis, P-value was non significant (P=0.302)**.**

Figure 2 demonstrates transient elastography (Fibroscan) examination of the liver showing liver stiffness measurement of 16 Kpa (F4).

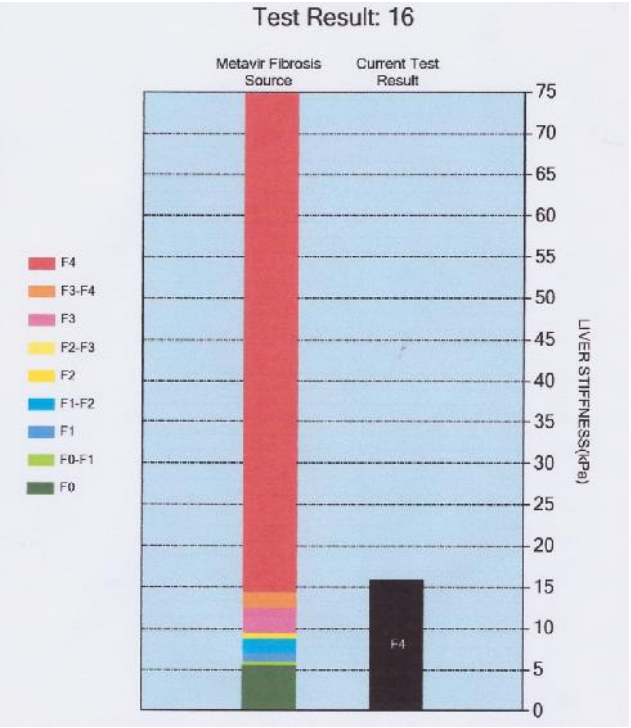

Figure 2 Transient elastography (Fibroscan) examination showing liver stiffness measurement of 16 Kpa (F4).

DISCUSSION

The diagnostic value of serum markers of liver fibrosis has been investigated in numerous studies. The ideal marker for liver fibrosis would be highly sensitive and specific to identify different stages of fibrosis and readily available, safe, inexpensive and reproducible to allow the monitoring of disease progression or regression as a part of natural history of liver disease or treatment regimens *(Baranova et al., 2011).*

It has been previously reported that age, serum AST, ALT, and platelet count were independent predictors of liver fibrosis. These 4 variables were used to derive the novel FIB-4 index *(Sterling et al., 2004)***.**

The FibroQ test was proposed by Hsieh *et al* in 2009. It is calculated based on age, AST, prothrombin time (PT-INR), platelet count, and ALT. In their study, using a cutoff value of 1.6, the AUC for the detection of significant fibrosis was 0.783, and the negative predictive value was 100% for the exclusion of cirrhosis. These values were both higher than those obtained

when using the AST-to-Platelet Ratio Index (APRI) and AST/ALT ratio (AAR) in the same cohort *(Hsieh et al., 2009).* A similar study showed that FibroQ was superior to FIB-4, AAR, APRI, and Lok's model in predicting significant fibrosis in patients with chronic hepatitis C *(Hsieh et al., 2012).*

PAPAS (Platelet/Age/Phosphatase/AFP/AST) index was developed by *Seto et al. (2011)* to predict significant liver fibrosis from the five best parameters in their study. Using the formula:Log(index+1)=0.0255+0.0031×age(years)+0.1483×log{ALP(U/L)}+0.004×log{AST(U/L)}+0.0908×log{AFP(ng/L)+1}-0.028×log{platelet count(10^9/L)}.

The current study was performed to investigate the value of PAPAS index for non-invasive assessment of liver fibrosis in Egyptian patients with chronic hepatitis C in comparison to FIB-4 and FibroQ.

As regard platelet count, significant negative correlation was found with the degree of hepatic fibrosis measured by transient elastography (P=0.035), PAPAS (P=0.047), FibroQ (P<0.001) and FIB-4 (P<0.001). This was in agreement with several studies as *Ozel et al (2015)* and *Hsieh et al (2012).*

As regard INR, significant positive correlation was found between INR and degree of hepatic fibrosis measured by transient elastography, PAPAS, FibroQ and FIB-4 (P = 0.050, 0.032, 0.025 and 0.030 respectively). This was in agreement with *Hsieh et al (2012).* But our results regarding INR contradicted with *Lu et al (2003)* who reported that there was no significant difference in PT at different stages and grades of liver fibrosis.

As regard AST, significant positive correlation was found between AST and degree of hepatic fibrosis measured by transient elastography with (P=0.003). Only FIB-4 showed highly significant positive correlation with AST (P<0.001). PAPAS and FibroQ showed no correlations with AST. This was in agreement with *Hsieh et al. (2012)* and *Ozel et al (2015).*

As regard AFP, there was significant positive correlation between AFP and degree of hepatic fibrosis measured by transient elastography (P <0.001), PAPAS index (P <0.001), Fibro Q (P =0.002) and FIB-4 (P =0.002). This was in agreement with *Khairy et al. (2012), Liu et al. (2014) and Ozel et al. (2015).*

Regarding ALT, there was significant correlation between ALT and degree of hepatic fibrosis measured by transient elastography (P=0.025) and FIB-4 (P=0.007). This contradicted with *Hsieh et al (2012)* who reported non-significant relation between ALT and degree of hepatic fibrosis.

As regard serum albumin, significant negative correlation was found between it and each of PAPAS index (P = 0.002) and Fibro Q index (P= 0.013). This was in agreement with *Khairy et al (2012).*

In the current study, we found that PAPAS index, FIB-4 and FibroQ were significantly higher in patients with advanced fibrosis (F3-F4) than in those with non-advanced fibrosis (F1-F2) (P <0.001, 0.004 and 0.028 respectively). Using cutoff value ≥2.05 for PAPAS index in detecting advanced fibrosis (F3-F4), PAPAS index showed highly significant diagnostic performance with AUC 0.987 (P <0.001), sensitivity 100%, specificity 95.2%,PPV 95% and NPV 100%.

Ozel et al (2015) reported that AUC of PAPAS index for detecting significant fibrosis and cirrhosis were 0.71(0.61-0.81) and 0.71(0.61-.081). Using cutoff value of 0.86 or less to exclude significant fibrosis, PAPAS index had sensitivity 59.5%, specificity 69.8%, PPV 75.8% and NPV 52.1%. At a cutoff value of 1.33 or more to exclude cirrhosis, it had sensitivity 67.6%, specificity 68% PPV 39.7 and NPV 83.8%. *Ozel et al (2015)* observed that PAPAS index was useful for differentiation of cirrhosis in patients with chronic hepatitis C with NPV 83.8%.

Seto et al (2011) firstly derived and validated PAPAS index in a cohort of 237 Chinese patients with chronic hepatitis B. They reported that AUC of PAPAS index for prediction of significant fibrosis was 0.776 and improved to 0.797 for patient with ALT <2×ULN. At cutoff value of 1.662, sensitivity was 73.3%, specificity 78.2%, PPV 56.4% and NPV to exclude significant fibrosis was 88.4%. They reported that by using PAPAS index, 67.5% of liver biopsies for patients being considered for treatment with ALT < 2×ULN could be avoided. On comparing the best cutoff values of PAPAS index, FibroQ and FIB-4 in differentiating between advanced and non-advanced fibrosis, we found that PAPAS index had the best specificity (95.2%) in excluding advanced fibrosis in comparison to FibroQ that had specificity of 57.1% and FIB-4 that had specificity of 61.9%. Regarding sensitivity, PAPAS index and FIB-4 had sensitivity of 100% while FibroQ had sensitivity of 94.5%.

On comparing the AUC of ROC curve of PAPAS index in differentiating between advanced and non-advanced fibrosis, it was found that P-value was highly significant (P< 0.001) when compared to FIB-4 and FibroQ.

While on comparing the AUC of ROC curve of FIB-4 to that of FibroQ in differentiating advanced from non-advanced fibrosis, P-value was non significant (P=0.302).

In conclusion, PAPAS index is a new non-invasive test for assessment of liver fibrosis. Using cutoff value of ≥ 2.05 PAPAS index could predict advanced fibrosis with PPV 95%, sensitivity 100% and <2.05 could exclude advanced fibrosis with NPV 100%, and specificity 95.2%. PAPAS index was superior to FIB-4 and FibroQ in differentiating between advanced and non-advanced fibrosis.

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