THE PERFORMANCE OF GPRI, FIB-4 AND LIVER ELASTOGRAPHY FOR DIAGNOSING LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B

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ABSTRACT

After assessing liver fibrosis stages of 83 patients with chronic hepatitis B using GPRI, FIB-4 and ElastPQ, we have the following conclusions:

GPRI had a good accuracy for diagnosing significant liver fibrosis and advanced fibrosis with AUROC > 0.7. With a cut-off of 0,38, GPRI had a high sensitivity and NPV for diagnosing significant fibrosis (> 80%). With a cuf-off of 0,59, GPRI had a very high sensitivity and NPV for diagnosing advanced fibrosis (> 90%). FIB-4 had sub-optimal accuracy for diagnosing significant fibrosis with AUROC of 0,64 and advanced fibrosis with AUROC of 0,65. With a cut-off of 2,34 for diagnosing significant fibrosis (≥F2): FIB-4 had very high specificity (92%), and NPV of 65%. With a cut-off of 2,65 for diagnosing advanced fibrosis (≥ F3): FIB-4 had a very high specificity and and also a very high NPV (>80%). ElastPQ had excellent accuracy for diagnosing both significant and advanced fibrosis (AUROC was 0,84 and 0,83, respectively). For diagnosing significant fibrosis: with cut-off of 6.07, ElastPQ had sensitivity of 86%, specificity 71%, PPV 68% and NPV 87%; For diagnosing advanced fibrosis: using cut-off of 9,43, ElastPQ had sensitivity of 67%, specificity 97%, PPV 87% and NPV 90%

All 3 tools GPRI, FIB-4 and ElastPQ had significant positive correlation with liver fibrosis stage ($p < 0,001$). Among them, liver elastography using ElastPQ had the strongest correlation ($r = 0,62$, $p < 0,001$).

Keywords: *ElastPQ, APRI, FIB-4, GPRI, liver fibrosis, cirrhosis, transient elastography, point shear wave elastography.*

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I. INTRODUCTION

Chronic hepatitis B infection is a major global health problem. In 2015, WHO estimated that 257 million people were living with chronic hepatitis B (CHB) infection and it resulted in an estimated 887 000 deaths due to chronic hepatitis B related liver diseases [18]

Vietnam is a country which has a high prevalence of hepatitis B infection, with approximately 8,6 million people infected with hepatitis B virus. The prevalence of chronic hepatitis B infection is estimated around 8.8% in female and 12.3% in male [1],[18]

Chronic hepatitis B infection is the main cause of liver diseases in Vietnam such as cirrhosis and hepatocellular carcinoma

Liver fibrosis is the result of chronic liver injury, manifested as the accumulation of extracellular matrix in almost all chronic liver diseases regardless of the causes [12]. Liver fibrosis progresses gradually to cirrhosis and this is the main cause of death in patients with CHB. Assessing stage of liver fibrosis plays an important role in treatment decision, prognosis and time for screening cirrhosis complications.

Liver biopsy is considered the gold standard to assess stages of liver fibrosis. However, liver biopsy is an invasive procedure and may cause potentially life threatening complications, so it is not commonly used nowadays. Moreover, liver biopsy also depends on the sample size, experiences of pathologist and these factors affect the results. Therefore, noninvasive methods for assessing liver fibrosis stages become more developed and are being widely used worldwide to limit the use of liver biopsy. These methods include biomarkers and imaging tools, mainly liver elastography. Among the biomarkers, The Aspartate aminotransferase to Platelet Ratio Index (APRI) is recommended by WHO to assess liver fibrosis in CHB patients in countries with limited resources[17]. In addition, other biomarkers such as FIB-4 (Fibrosis-4), GPRI (Gamma-glutamyl transpeptidase to platelet ratio index - GPRI),… are very valuable in assessing liver fibrosis in CHB patients according to studies of Qiang L (2016) [11], Lemoine M (2015) [6],…

Besides, liver elastography is a technique which has good accuracy for assessing liver fibrosis stages. Currently, in addition to transient elastography technique (TE) recommended by WHO for assessing liver fibrosis in CHB patients, point shear wave elastopraphy (pSWE) technique is being extensively studied and applied in clinical practice as in studies of Guzman AF (2011) [2], Lee JE (2017) [5],…. They showed that ElastPQ (PQ: point quantification) had a very high accuracy in diagnosing cirrhosis in CHB patients.

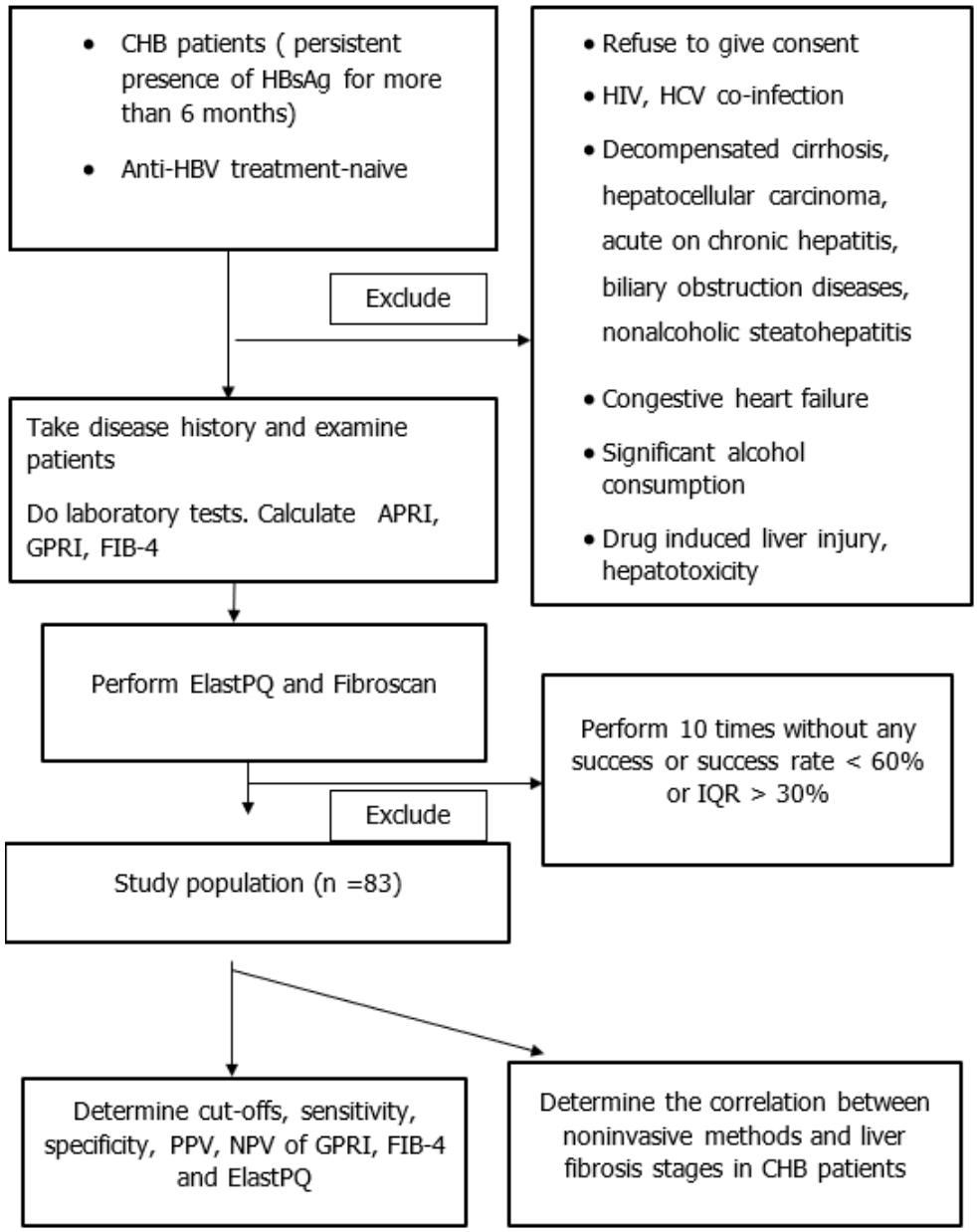
The noninvasive techniques for diagnosing liver fibrosis have been being studied and used in many countries. However, in Vietnam, there are only few studies regarding the diagnostic performance of these noninvasive methods. Therefore, we realized the need of a study to compare the performance of GPRI, FIB-4 and liver elastography using ElastPQ for diagnosing liver fibrosis in CHB patients. Subsequently, we could recommend the application of these techniques in clinical practice. This is the reason why we conducted this study.

II. STUDY DESIGN AND PATIENTS

Eighty three patients with CHB were included in this study. CHB was defined as the persistent presence of hepatitis B surface antigen (HBsAg) for more than 6 months. Inclusion criteria were patients older than 18 years old with CHB, no previous anti-HBV treatment. Patients with the following conditions were excluded: co-infection with HCV or HIV (anti HCV (+) or anti HIV (+)), significant alcohol consumption (male: > 210g/week, female: > 140g/week), decompensated cirrhosis with complications such as ascites, gastrointestinal variceal bleeding, hepatoencephalopathy, acute on chronic viral hepatitis: when ALT level abruptly rises to more than 10 times ULN, hepatocellular carcinoma (detected with B mode ultrasound), fatty liver (detected with B mode ultrasound), biliary obstruction diseases (detected with B mode ultrasound), congestive heart failure, drug induced liver injury, hepatotoxicity.

2.1. Study design: analytical cross sectional prospective study

Flow diagram



- Blood tests:

APRI:

The formula to calculate APRI is developed by CT. Wai et al (2003) [14]. Formula to calculate APRI :

$$\text{APRI} = \frac{\text{AST (patient)/AST(ULN)}}{\text{Platelet } (10^9/\text{L})} \times 100$$

* ULN (Upper Limit of Normal): upper limit of normal range of AST in the lab where blood sample is delivered for measuring serum AST level.

FIB-4:

FIB-4 is calculated as shown below:

FIB-4 = (age x AST (IU/L)) / (Platelet (10^9/L x [ALT (IU/L)$^{1/2}$])

GPRI:

The formula to calculate GPRI :

$$\text{GPRI} = \frac{\text{GGT(patient)/GGT(ULN)}}{\text{Platelet } (10^9/\text{L})} \times 100$$

* ULN (Upper Limit of Normal): upper limit of normal range of GGT in the lab where blood sample is delivered for measuring serum GGT activity

Fibroscan:

M-mode transient elastography technique by Fibroscan 502 machine (Echosen, France) was performed on all patients in Ho Chi Minh City Medical Diagnostic Center (Medic). This procedure was performed at least 2 hours after meal.

The interval between the liver stiffness measurements was less than 2 weeks. A doctor in Medic would measure liver stiffness, this doctor had much experience and had done more than 1000 cases until the time of study

Measuring liver stiffness using ElastPQ:

In Thong Nhat Hospital in Ho Chi Minh City, patients were measured liver stiffness using Philips Affinity Machine equipped with ElastPQ tool on curved transducer, with frequency of 5MHz (image 2.1). When performing this technique, it would also provide information of B-mode ultrasound imaging.

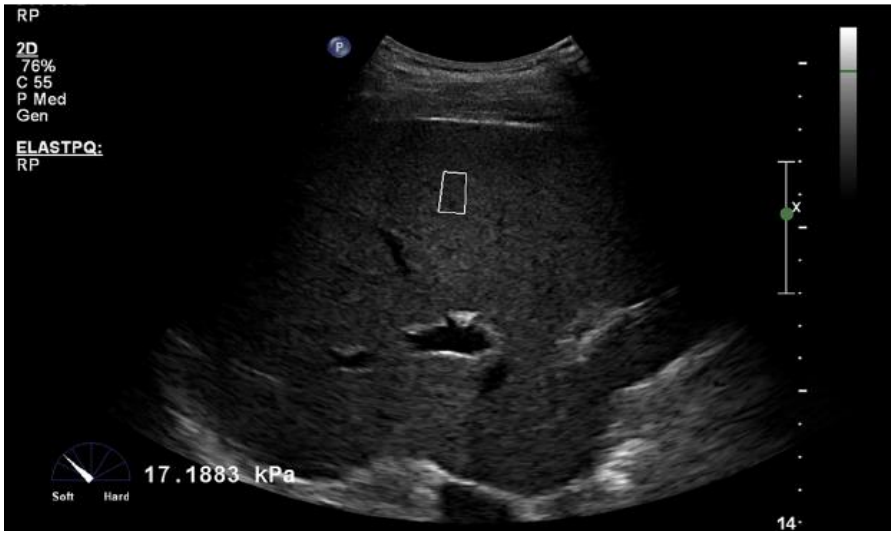


Image 2.1: Ultrasound image used for measuring shear wave velocity [5]
Source: Lee JE, Ultrasound in Med. & Biol, 2017

Table 2.1. Summary of ElastPQ values according to Metavir fibrosis stage[5]

Fibrosis stage	Metavir score	kPa	m/s
Normal	F0	2.0 - 4.5	0.81 - 1.22
Mild fibrosis	F0 - F1	4.5 - 5.7	1.22 - 1.37
Significant fibrosis	F2 - F3	5.7 - 12.0	1.37 - 2.00
Advanced fibrosis	F3 - F4	12.0 - 21.0 +	2.00- 2.64 +

- Fibrosis staging with the combination of Fibroscan and APRI

+ The performance of APRI for diagnosing liver fibrosis compared with that of liver biopsy in the study of Wang H (2013) [15] and the performance of Fibroscan for diagnosing liver fibrosis compared with that of liver biopsy in CHB patients in the study of Ledinghen VD (2008) [4] are shown in the following table:

Table 2.2. Staging liver fibrosis with the combination of APRI and Fibroscan

APRI	Fibroscan (kPa)	Liver fibrosis stage
< 0.5	< 7.2	F0 - F1
0.5 - < 1.0	7.2 - < 8.1	F2
1.0 - < 2.0	8.1 - < 11	F3
> 2.0	> 11	F4

+ The combination of Fibroscan and APRI used these following combined cut-off values: APRI = 0.5 and TE = 7.2 kPa for diagnosing significant fibrosis (≥ F2); APRI =1 and TE = 8.1 kPa for diagnosing advanced fibrosis (≥ F3)

- For diagnosing significant fibrosis (≥ F2): in cases with APRI ≥ 0.5 and TE ≥ 7.2 kPa, the combination of both 2 positive cut-off values gave the positive diagnosis; in all other cases, it was considered negative.
- For advanced fibrosis (≥ F3), in cases with APRI ≥ 1 and TE ≥ 8.1 kPa, the combination of both 2 positive cut-off values gave the positive diagnosis; in all other cases, it was considered negative.

2.2. Data processing method

Data was managed and processed by SPSS 20.0.

Statistical analysis methods: t-test to compare the means of 2 independent groups, One-wave Anova to compare the means of three or more independent groups. Chi-squared test to compare the percentage of two or more groups. Drawing the ROC and AUROC[13]. Assessing the correlation of normally distributed continuous variables using Pearson correlation, calculating Pearson correlation coefficient or r and 95% confidence interval. Assessing the correlation between a continuous variable and an ordinal variable or Spearman's rank correlation, calculating correlation coefficient Spearman rho (ρ) and 95% confidence interval. A p-value less than 0.05 (typically ≤ 0.05) is statistically significant.

The gold standard used in our study to determine fibrosis stages was the combination of APRI and Fibroscan.

III. RESULT

3.1. Baseline characteristics of the study population

Table 3.1. Characteristics of the study population

Age	Youngest: 23 Oldest: 77	Mean age: 51.65± 13.3
Sex	Male	62.7%
	Female	37.3%
Characteristics of B-mode liver ultrasound images	coarsened hepatic echotexture	44.6%
	Normal liver	55.4%
Clinical symptoms	Indigeston	41%
	Right subcostal pain	2%
	Anorexia	9.5%
	Fatigue	28%

3.2. Fibrosis characteristics assessed by the combination of APRI and Fibroscan

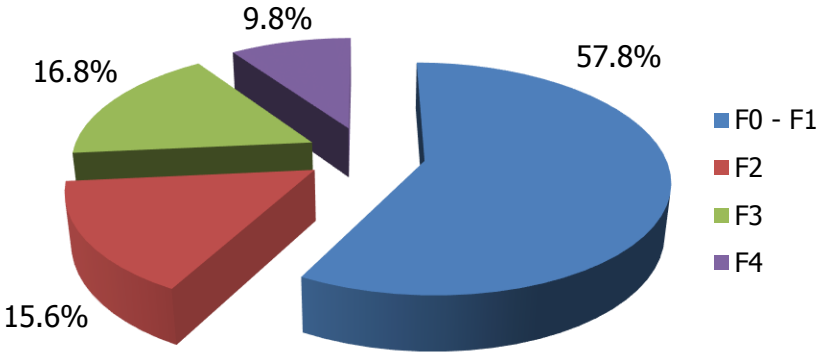


Figure 3.1: Fibrosis stages

Note: No fibrosis (F0) and minimal scarring (F1) stage are the highest with 57.8%

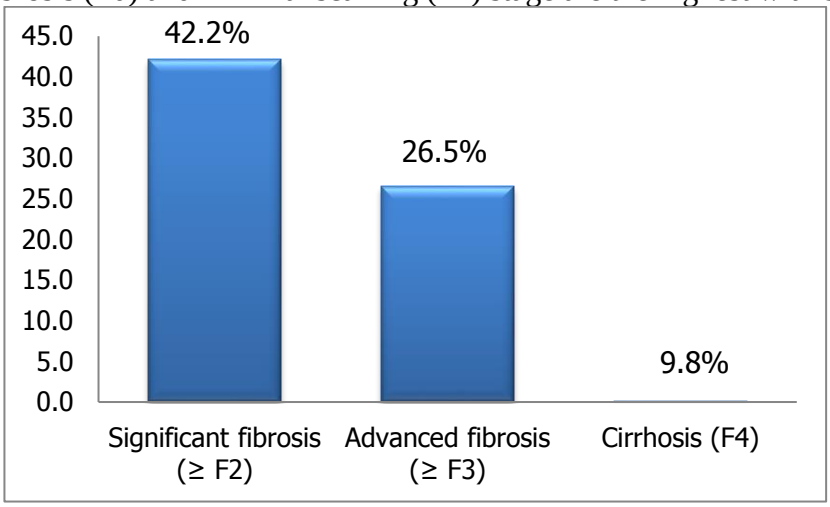


Figure 3.2: Fibrosis stages

Note: Significant fibrosis stage (≥ F2) is the highest with 42.2%

3.3. Cut-off values, sensitivity, specificity, predictive values and accuracy of gpri, fib-4 and ElastPQ

3.3.1. Values of GPRI , FIB-4, ELASTPQ

Table 3.2: AUROC of GPRI, FIB-4 and ElastPQ

	Fibrosis stage	AUROC	SD	95% CI
GPRI	Significant fibrosis (≥F2)	0.75	0.05	0.65 - 0.86
	Advanced fibrosis (≥F3)	0.76	0.06	0.64 - 0.87
FIB-4	Significant fibrosis (≥F2)	0.64	0.06	0.52 - 0.77
	Advanced fibrosis (≥F3)	0.65	0.08	0.49 - 0.80
ElastPQ	Significant fibrosis (≥F2)	0.84	0.045	0.75 - 0.93
	Advanced fibrosis (≥F3)	0.83	0.063	0.70 - 0.95

Note: ElastPQ tool had a high accuracy in diagnosing significant fibrosis and advanced fibrosis (AUROC was 0.84 and 0.83, respectively)

Table 3.3: Comparing sensitivity, specificity, PPV and NPV of ElastPQ, GPRI, FIB-4 in assessing liver fibrosis

	Fibrosis stage	Cut-off values	Sens (%)	Spec (%)	PPV (%)	NPV (%)
GPRI	Significant (≥ F2)	0.38	80	58	58	80
	Advanced (≥ F3)	0.59	86	52	38	91
FIB- 4	Significant (≥ F2)	2.34	53	92	75	65
	Advanced (≥ F3)	2.65	47	90	63	84
ElastPQ	Significant (≥ F2)	6.07	86	71	68	87
	Advanced (≥ F3)	9.43	67	97	87	90

AUROC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value; Sens: sensitivity; Spec: specificity.

Note: GPRI and liver elastography using ElastPQ had high sensitivity, 80% and 86% respectively in assessing significant fibrosis (≥ F2); regarding the specificity, FIB-4 and ElastPQ had very high specificity in assessing significant fibrosis and advanced fibrosis (>90%).

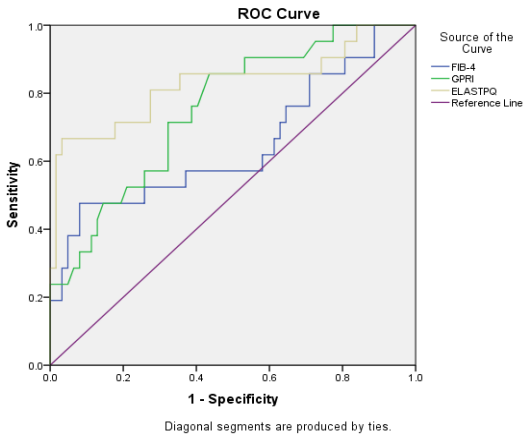


Figure 3.3. Receiver operating characteristic curves of combination transient elastography (TE) and APRI -based fibrosis markers for differentiating advanced liver fibrosis (≥ F3). Values were based on the liver stiffness or scores measured with Fibrosis-4 (FIB-4), Gamma-glutamyl transpeptidase to platelet ratio index (GPRI), ultrasound shear wave elastography point quantification (ElastPQ).

3.4. Evaluating the correlation between gpri, fib-4 , elastpq and fibrosis stages

3.4.1. GPRI

Table 3.4: The average, highest and lowest value of GPRI, FIB-4, ElastPQ in this study

	Average	Lowest	Highest
GPRI	1.15 ± 2.46	0.14	21.34
FIB-4	1,85 ± 1.64	0.4	13.44
ElastPQ	7.8 ± 5.09 kPa	2.97	27.34

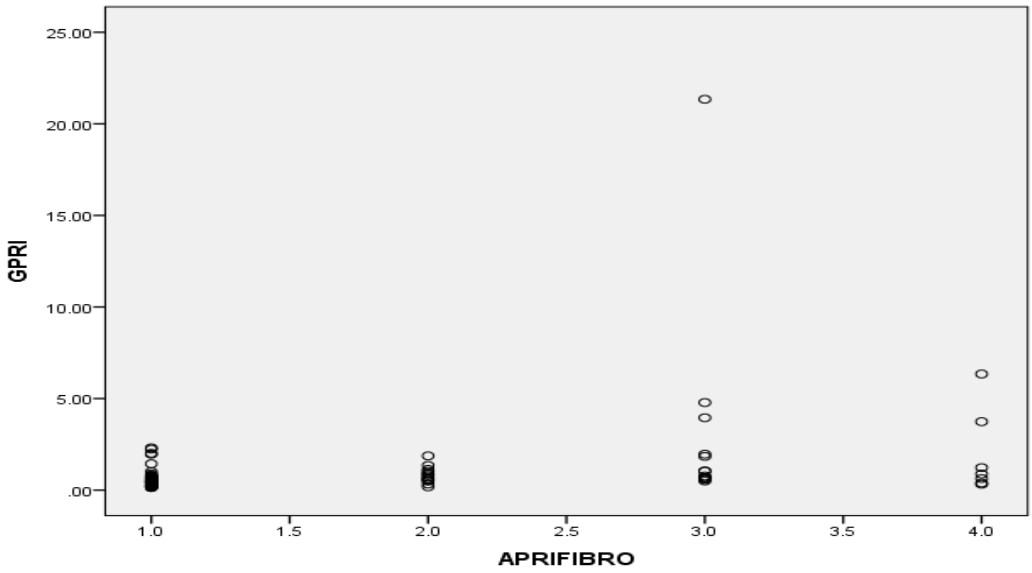


Figure 3.4: Plot showing the correlation between GPRI and fibrosis stage

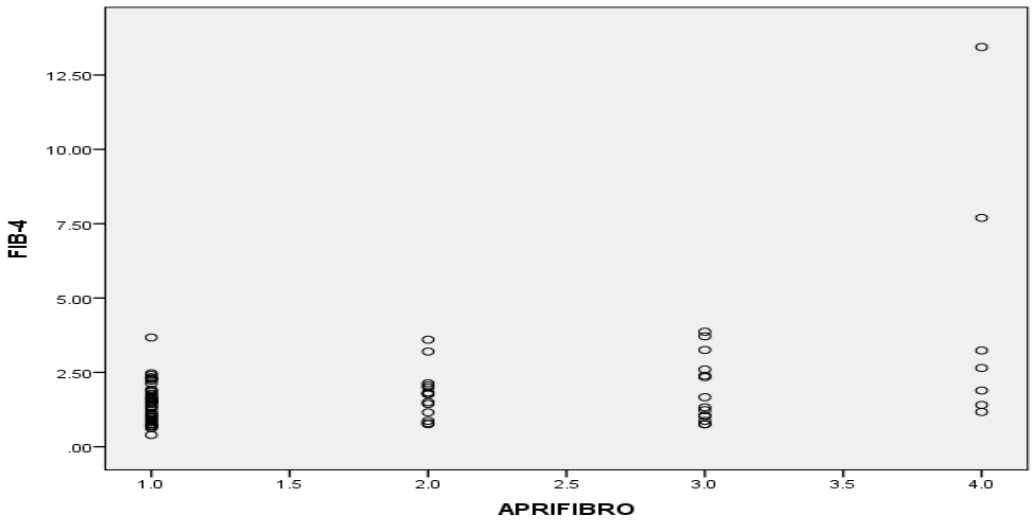


Figure 3.5: Plot showing the correlation between FIB-4 and fibrosis stage

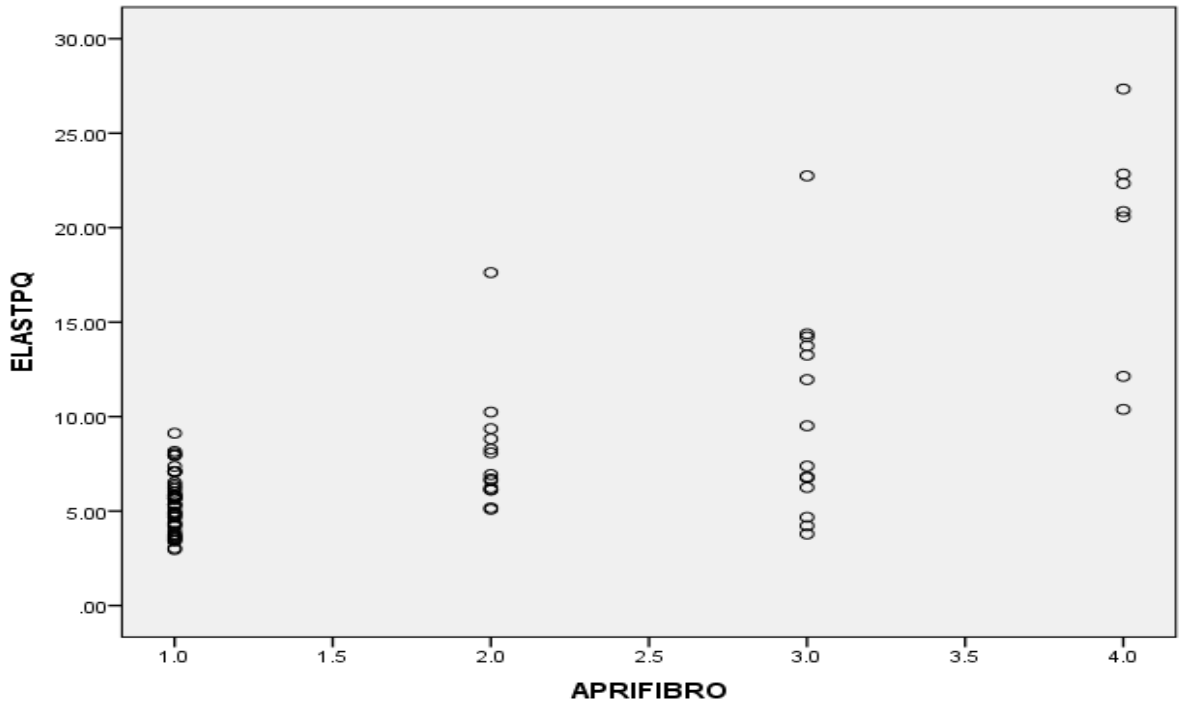


Figure 3.6: Plot showing the correlation between ElastPQ and fibrosis stage

Table 3.5: Correlation between GPRI, FIB-4, ElastPQ and fibrosis stages

	Liver fibrosis	
	Spearman rho hay r	P
GPRI	0.44	<0.0001
FIB-4	0.3	0.012
ElastPQ	0.62	< 0.001

Note: All 3 tools GPRI, FIB-4 and ElastPQ had significant positive correlation with fibrosis stage ($p < 0.001$). Among them, liver elastography using ElastPQ had the strongest correlation ($r = 0.62$, $p < 0.001$)

IV. DISCUSSION

4.1.Cut-off values, sensitivity, specificity, predictive values and accuracy of GPRI, FIB-4 and ELASTPQ in diagnosing liver fibrosis

4.1.1.Values of GPRI

In our study, AUROC of GPRI for diagnosing significant fibrosis (≥ F2) was 0.75; this result was in good agreement with that reported by Lemonie M (2015) [6] (AUROC=0.73) and Zhang Q (2016) [16] (AUROC=0.72). Similarly, AUROC of GPRI for the diagnosis of advanced fibrosis (≥ F3) in our study was 0.76, which was lower than that from the study of Lemoine M (AUROC=0.93) and Zhang Q (AUROC= 0.83). For diagnosing significant fibrosis (≥ F2), GPRI in our study had a cut-off value of 0.38, which was consistent with that of other

authors such as Lemoine M [6] (cut-off =0.32) and Zhang Q [16] (cut-off =0.46).

The difference might be attributable to the fact that the prevalence of moderate or higher fibrosis stages in our study population was lower than that reported by these 2 authors. At this cut-off value, sensitivity and specificity of GPRI in our study were 80% and 58% respectively, which were comparable to those reported by Lemoine M (83% and 69%, respectively) and high than those of Zhang Q (59% and 78%, respectively).

Likewise, for diagnosing advanced fibrosis (≥ F3), GPRI in our study had a cut-off value of 0.59, which was higher than that of Lemoine M [6] (cut-off =0.32) and Zhang Q [16] (cut-off =0.53).

This difference might be due to the fact that the prevalence of advanced fibrosis in the studies of these authors was higher than that in our study. In addition, at the cut-off value in our study, sensitivity and specificity of GPRI for diagnosing advanced fibrosis were 86% and 52% respectively, which were concordant to those in the study of Lemoine M [6] (86% and 64%, respectively) and higher than those reported by Zhang Q [16](76% and 81%, respectively). Thus, GPRI had a relatively high accuracy in screening advanced fibrosis in naive treatment CHB patients. It has a significant implication in applying GPRI in clinical practice since this is a very simple indicator, easy to use and inexpensive.

4.1.2.Values of FIB-4

In our study, AUROC for diagnosing significant cirrhosis (≥ F2) was 0.64 and advanced cirrhosis (≥ F3) was 0.65. These results were in good agreement with those in the study of Lemoine M (2015) (0.66 and 0.68 respectively) but lower than those in the study of Zhang Q (2016) [16] (0.74 and 0.8 respectively); Li Y (2016) [7] (0.7 and 0.73 respectively). In diagnosing significant fibrosis (≥ F2), FIB-4 in our study had a cut-off value of 2.34 which was higher than that of Zhang Q (cut-off value=0.86) [16], Lemoine M (cut-off value=1.45) [6], Li Y (cut-off value=1.1) [7]. This difference might be attributed to the fact that the average age and AST level in our study were higher than those in the studies of these authors. Furthermore, at this cut-off value, the FIB-4 in our study had the sensitivity and specificity of 63% and 92% respectively. This sensitivity was comparable to that of Lemoine M [6] (63%), Li Y [7] (61%) and lower than Zhang Q [16](72%) but the specificity was higher than that of these authors. It indicated that FIB-4 had a relatively high accuracy (high specificity) for diagnosing significant fibrosis in CHB patients.

Furthermore, for diagnosing advanced cirrhosis (≥ F3), our study on 83 CHB patients showed that: at cut-off value of 2.65, FIB-4 had a sensitivity of 47% and a high specificity (90%). This cut-off value was higher than that of Li Y (cut-off=1.3) [7], Zhang Q (cut-off=1.19) [16] but lower than that of Lemoine M (cut-off=3.25) [6]. This difference was attributable to the variation between the average age and AST level in our study and those reported by these authors.

Despite the fact that the sensitivity of FIB-4 in our study was not high even for diagnosing advanced fibrosis but the specificity of FIB-4 was higher than that of Lemoine M (2015) [6], Zhang Q (2016) [16] and Li Y (2016) [7]. It indicated that this index was very good in assessing accurately fibrosis stage in CHB patients (high

specificity) and thus included in WHO treatment guideline in 2015 [17]. Therefore, FIB-4 with the cut-off value lower < 1.45 helped to exclude advanced fibrosis stage in CHB patients.

4.1.3.Values of ElastPQ

Meta-analyses regarding value of ElastPQ in the recent 5 years displayed similar results. For instance, the study of Ma JJ et al (2013) [8] regarding the performance of liver elastography using ElastPQ in comparison with pathology results on 291 CHB patients showed that ElastPQ had a very high accuracy in diagnosing significant fibrosis (≥ F2) with AUROC of 0.94 and a high accuracy in diagnosing advanced fibrosis (≥ F3) with AUROC of 0.89. In addition, the study of Mare R et al (2017) [9] on 228 CHB patients indicated that ElastPQ had a very high accuracy in diagnosing fibrosis stages (all AUROC were higher than 0.9).

Furthermore, the study of Jang HJ (2019) [3] on 67 CHB patients demonstrated that: ElastPQ had a relatively high accuracy in diagnosing significant and advanced fibrosis with AUROC of 0.75 and 0.79, respectively. In our study, AUROC of elastography using ElastPQ for diagnosing significant fibrosis (≥ F2) and advanced fibrosis (≥ F3) was relatively high (AUROC > 0.8), which was concordant with larger scale studies of Mare R et al (2017) [9], Lee JE(2017) [5] and Ma JJ (2013) [8].

Liver elastography using ElastPQ in assessing fibrosis stage in our study had a cut-off value of 0.67 for diagnosing significant fibrosis (≥ F2) and 9.43 for diagnosing advanced fibrosis (≥ F3). These cut-off values were comparable to those in the studies of Ma JJ (2013) [8] and Mare R (2017) [9], but higher than those reported by Lee JE (2017) [5].

The difference might be attributable to the variation in prevalence of fibrosis stages in these studies; in our study, the prevalence of patients with significant fibrosis (≥ F2) was 42,16%, which varied widely from that in the study of Lee JE (2017) (32.26%), Ma JJ (2013) (66.32%). At different cut-off values, sensitivity, specificity, PPV, NPV in our study were similar to those in studies of JJ (2013) [8] and Mare R (2017) [9]. Especially, the sensitivity in assessing significant fibrosis (≥ F2) in our study was high (86%). In addition, specificity of ElastPQ in assessing advanced fibrosis was very high (97%), it demonstrated a very high accuracy of this tool in evaluating advanced fibrosis in CHB patients.

4.1.4.Comparing sensitivity, specificity, PPV, NPV of GPRI, FIB-4 and ElastPQ in assessing liver fibrosis.

When comparing sensitivity and specificity of noninvasive methods, we found that GPRI and liver elastography using ElastPQ had high sensitivity, 80% and 86% respectively in assessing significant fibrosis (≥ F2); regarding the specificity, FIB-4 and ElastPQ had very high specificity in assessing significant fibrosis and advanced fibrosis (>90%). It demonstrated the value of liver elastography using ElastPQ in diagnosing fibrosis stage in CHB patients. Furthermore, both NPV of GPRI and ElastPQ were very high, especially in assessing advanced fibrosis (>90%). Therefore, these noninvasive methods were very valuable in excluding significant and advanced fibrosis in CHB patients.

4.2.Correlation between GPRI, FIB-4 and ELASTPQ and liver fibrosis stage

4.3.1. GPRI

Li Y et al (2016) [7] conducted a study about the performance of noninvasive

methods in assessing liver fibrosis stage on 372 CHB patients. It showed that the average of GPRI was 0.67 which was lower than in our study (average GPRI value=1.15). Spearman correlation coefficient of GPRI and fibrosis stage was 0.475 with p < 0.001 which was in good agreement with our study (Spearman rho = 0.44). In a meta-analysis (2019) [10] including 10 studies on 5882 CHB patients, Ming-Jian L evaluated the GPRI in assessing liver fibrosis. The study demonstrated that GPRI had a very strong correlation with significant fibrosis (Spearman rho = 0.73, p = 0.016), but insignificant correlation with advanced fibrosis (≥ F3) (Spearman rho = 0.65, p = 0.058).

4.3.3. FIB-4

In a study in 2016, Zhang Q evaluated the FIB-4 in assessing liver fibrosis in 312 CHB patients. In this study, the average FIB-4 score was 1.52, which was lower than that in our study (average FIB-4 score=1.85). Meanwhile, Spearman correlation coefficient between FIB-4 and liver fibrosis stage in our study was 0.3, lower than that reported by Zhang Q (rho = 0.508, p < 0.001)[16].

4.3.4. ElastPQ

In the study of Jang HJ et al (2019) [3] on 67 CHB patients, the average ElastPQ stiffness value was 6.3, which was lower than in our study (average ElastPQ stiffness value=7.8). In a study in 2017, Lee JE evaluated the performance of liver elastography using ElastPQ for assessing liver fibrosis in 106 CHB patients. It demonstrated that the average ElastPQ stiffness value was 5.08, lower than in our study (average ElastPQ stiffness value=7.8). In the study of Lee JE [5], Spearman correlation coefficient between ElastPQ and liver fibrosis stage was 0.68, which was similar to that of our study (rho = 0.62). This was a very strong positive correlation and it demonstrated a very high accuracy of this technique in diagnosing liver fibrosis.

V. CONCLUSION

All 3 tools GPRI, FIB-4 and ElastPQ had significant positive correlation with fibrosis stage. Among them, liver elastography using ElastPQ had the strongest correlation. GPRI, FIB-4 had a high accuracy in diagnosing fibrosis stags and were based on appropriate biochemical blood tests and had a reasonable cost, so they should be applied in clinical practice along with APRI which was recommended in WHO guideline in 2015. For easily assessing fibrosis, we could use ElastPQ cut-off value of 6.07 kPa for diagnosing significant fibrosis (≥ F2) and 9.43 kPa for advanced fibrosis (≥ F3) along with already widely used Fibroscan.

VI. LIMITATIONS OF THE STUDY

- In our study, we did not use liver biopsy as the gold standard, but we used the combination of APRI and Fibroscan to determine liver fibrosis stage. Consequently, the accuracy was lower comparing with that of pathology result.
- We conducted the study mainly on Gastroenterology clinics and the majority of patients had mild or no fibrosis. As a result, we could not assess many cirrhotic patients with chronic hepatitis B, so it could not have a balance of different fibrosis stages.

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