HEALTH AND SOCIETY
PORTAL JOURNAL

Original Article

APRI index as marker of liver fibrosis in patients with Mansonic Schistosomiasis

Índice APRI como marcador de fibrose hepática em pacientes com Esquistossomose Mansônica

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https://doi.org/10.28998/rpss.e02106013

Received in: 12/08//2020
Accepted in: 06/04/2020
Available in: 07/15/2021

Corresponding Author:
Rozangela Maria de A. F. Wyzomirska
Email: rozangelaw@yahoo.com.br

Rozangela Maria de Almeida Fernandes Wyzomirska[1,2] Orcid Id nº https://orcid.org/0000-0003-0066-8927
Celina Maria da Costa Lacet[2] Orcid Id nº https://orcid.org/0000-0002-4846-8206
Lucyo Wagner Torres de Carvalho[2] Orcid Id nº https://orcid.org/0000-0002-7990-0209
Heloisa Helena Motta Bandini[2] Orcid Id nº https://orcid.org/0000-0002-7320-2637

[1] Federal University of Alagoas, Maceió, AL, Brazil.
[2] State University of Health Science of Alagoas, Maceió, AL, Brasil.

Abstract

Schistosomiasis mansoni can evolve with periportal fibrosis and the detection of fibrosis has been studied. To evaluate the APRI index in patients with Schistosomiasis mansoni. A total of 84 patients with different forms of the disease were evaluated, undergoing ultrasonography, enzyme determination, and calculation of the APRI index. The data obtained were submitted to statistical analysis as needed. The mean APRI values in the HSS form was 1.27 ± 0.93; in the HIS, it was 1.27 ± 0.93 and in the IS it was 0.25 ± 0.04, with a significant difference (p<0.0001) being observed as the fibrosis progressed. A significant increase in periportal thickening was observed on ultrasound in the HSS form of the disease compared to the others (p<0.001). The correlation between ultrasound and APRI is suggestive that there is a significant concordance between the two. The APRI cut-off point of 1.7 showed sensitivity and specificity of 100%. The APRI performed well in identifying liver fibrosis in Schistosomiasis mansoni. An APRI calculation equal to or greater than 1.7 indicates severe fibrosis, while a threshold below 0.35 reliably indicates no fibrosis. It is safe to use the APRI to identify the existence of liver fibrosis. For stratification of the degree of fibrosis, an APRI result above 1.7 confirms the presence of severe fibrosis.
Keywords: Schistosomiasis; APRI; Hepatic Fibrosis.

Resumo

A Esquistossomose Mansônica pode evoluir com fibrose periportal e a detecção da fibrose vem sendo estudada. Avaliar o índice APRI em pacientes portadores de Esquistossomose Mansônica. Foram avaliados 84 pacientes com formas diferentes da doença submetidos a exames de ultrassonografia, determinação de enzimas e cálculo do índice APRI. Os dados obtidos foram submetidos à análise estatística conforme a necessidade. A média de valores do APRI na forma EHE foi de 1,27 ± 0,93; na EHI, de 1,27 ± 0,93 e na EI foi de 0,25 ± 0,04, sendo observada uma diferença significativa (p<0,0001) à medida que a fibrose avançava. Foi observado um aumento significativo do espessamento periportal ao ultrassom na forma EHE da doença em relação às demais (p<0,001). A correlação entre o ultrassom e o APRI é sugestiva de haver uma concordância significativa entre os dois. O ponto de corte de 1,7 do APRI mostrou sensibilidade e especificidade de 100%. O APRI apresentou boa performance na identificação de fibrose hepática na Esquistossomose Mansônica. Um cálculo de APRI igual ou maior que 1,7 indica uma fibrose severa, enquanto um limiar abaixo de 0,35 indica, com segurança, que não existe fibrose. É seguro usar o APRI para identificar a existência de fibrose hepática. Para a estratificação do grau de fibrose, um resultado do APRI acima de 1,7 confirma a presença de fibrose severa.
Palavras-chave: Esquistossomose; APRI; Fibrose Hepática.

Resumen

La esquistosomiasis mansónica puede evolucionar con fibrosis periportal y la detección de fibrosis viene siendo estudiada. Evaluar el índice APRI en pacientes con Esquistosomiasis mansónica. Se evaluaron 84 pacientes con diferentes formas de la enfermedad a los que se les realizó ecografía, determinación de enzimas y cálculo del índice APRI. Los datos obtenidos se sometieron a análisis estadístico según fue necesario. La media de los valores de APRI en la forma EHE fue de 1,27 ± 0,93; en EHI fue de 1,27 ± 0,93 y en IE de 0,25 ± 0,04, observándose una diferencia significativa (p <0,0001) a medida que avanzaba la fibrosis. Se observó un aumento significativo en el engrosamiento periportal ecográfico en la forma EHE de la enfermedad en comparación con las demás (p <0,001). La correlación entre ultrasonido y APRI sugiere que existe un acuerdo significativo entre los dos. El punto de corte APRI de 1,7 mostró una sensibilidad y especificidad del 100%. APRI tuvo un buen desempeño en la identificación de fibrosis hepática en la esquistosomiasis mansónica. Un cálculo de APRI igual o superior a 1,7 indica fibrosis grave, mientras que un umbral inferior a 0,35 indica de forma fiable que no hay fibrosis. Es seguro utilizar APRI para identificar la fibrosis hepática. Para la estratificación del grado de fibrosis, un resultado APRI superior a 1,7 confirma la presencia de fibrosis grave.
Palabras clave: Esquistosomiasis; APRI; Fibrosis hepática.

INTRODUCTION

Schistosomiasis mansoni is a parasitic disease caused by a trematode worm of the genus Schistosoma, affecting more than 240 million people worldwide who have required preventive treatment for the worm. Approximately 1.5 million people are infected by the parasite in Brazil (1).

The clinical manifestations correspond to the stage of parasite development in the host, and may evolve to the chronic form, hepatosplenic, which is characterized by hepatic fibrosis, splenomegaly, portal hypertension, appearance of esophageal varices, and hypersplenism. In the case of schistosomiasis, fibrosis is installed in the periportal region, due to the presence of S. mansoni eggs in the periportal vessels, with consequent granulomatous inflammatory reaction and production of fibrotic tissue (2). Accurate assessment of the presence of fibrosis, as well as its possible reversibility, has made the detection and monitoring of fibrosis an important factor in medical management decisions (3).

Upper abdominal ultrasound (US) has become a useful diagnostic tool to diagnose and quantify periportal fibrosis (PPF), especially in areas where schistosomiasis is endemic (4). However, this method is not readily available in all endemic areas because it requires equipment and a qualified examiner. Liver biopsy is still the gold standard for assessing the degree of liver fibrosis, and it also provides information on inflammation, necrosis, steatosis, and hepatic iron or copper deposits. However, it has limitations and risks (5). The accuracy of histological examination is also another aspect that can be compromised by significant inter-examiner variability (6). Finally, needle biopsy is not sensitive enough to diagnose PPF.7

In light of these facts, a large number of noninvasive methods for the detection of liver fibrosis have been studied. Wai et al., (8) studying the relationship between serum aspartate aminotransferase (AST) levels and platelet count, proposed the AST to platelet ratio index (APRI) as the marker of liver fibrosis in cirrhosis in patients with HCV hepatopathy. Wyszomirska et al. (9) observed elevated serum levels of type IV collagen and laminin in all clinical forms of schistosomiasis. In another study, Wyszomirska et al.(10) found high serum levels of type IV collagen and TMP1 in patients with the hepatosplenic form of schistosomiasis, with a significant decrease after splenectomy. More recently, studies have shown satisfactory results with the use of APRI, FIB-4 and imaging methods for the detection of fibrosis in patients with liver cirrhosis, and can be used separately or combined in algorithms for improved diagnostic accuracy (11).

In schistosomiasis, studies are scarce. Souza et al. (12) reported that a platelet count of 130 x 109/ mm3 was the most efficient marker in differentiating between the clinical forms of schistosomiasis and its accuracy is higher in schistosomal patients who do not use alcoholic beverages. Domingues et al., (13) when evaluating several non-invasive markers, found these markers promising, but could not find an ideal marker to replace ultrasound findings in the evaluation of PPF in schistosomiasis. They then suggested that these markers could be used in field work, in endemic regions, to select patients with more advanced lesions that would require more attention. Finally, Nascimento et al., (14) in another study that tried to evaluate the correlation between three non-invasive methods for liver fibrosis in two groups of patients with viral hepatitis and schistosomiasis, suggested that non-invasive methods for diagnosis and monitoring of liver fibrosis have a high degree of acceptance, especially in patients with HCV.

The objective of this study was to evaluate the use of the APRI index as a marker of hepatic fibrosis in patients with intestinal, hepatointestinal and hepatosplenic forms of Schistosomiasis, as well as to define an APRI cut-off point in this group.

METHODS

A historical cohort study was carried out, in which 84 patients with Schistosomiasis mansoni were evaluated, 18 of the intestinal form - IS (ten males and eight females, mean age 27.71 + 6.56 years), 17 of the hepatointestinal form - HIS (six males and 11 females, with mean age of 41.82 + 16.13 years) and 49 of the hepatosplenic form - HSS (27 males and 22 females, mean age 44.40 ± 13.64 years), treated at the Liver Disease Outpatient Clinic of Hospital Universitário Professor Alberto Antunes, Universidade Federal de Alagoas (UFAL). The diagnosis of Schistosomiasis mansoni was established by means of Schistosoma mansoni egg research in stool sample by the Kato Katz method or rectal biopsy or ultrasonography. Exclusion criteria were alcoholism, chronic active hepatitis, immunodeficiency syndrome, pregnancy, and other liver diseases. This study was part of a demonstration project in a region endemic for Schistosomiasis mansoni in the state of Alagoas, Brazil, composed of several stages, and was approved by the UFAL Ethics Committee No. 024215/2008-22 and carried out in accordance with the Declaration of Helsinki.

Laboratory examinations

Tests were analyzed for aminotransferases (AST and ALT), Gamma Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), Total Bilirubin (TB), Direct Bilirubin (DB), platelet and leukocyte counts, as well as viral markers for HBV (AgHBs, anti-HBs, anti-HBc) and HCV (anti-HCV).

AST and platelet count were used to determine APRI = [AST/(upper limit of normal)/platelet 109/l]×100.

Ultrasound

All patients were submitted to US by the same examiner, and the following parameters were considered normal: right hepatic lobe <140 mm; left hepatic lobe <70 mm; spleen <120 mm; portal vein caliber <12 mm; splenic vein caliber < 5 mm and absent ascites; normal periportal thickening up to 3 mm; grade I between 3-5 mm; grade II between 5-7 mm and grade III above 7 mm.15

Statistical Analysis

The quantitative variables were presented as maximum values, minimum values, mean ± standard deviation (SD) of the variables.

The data obtained was submitted to the Lilliefors test to verify the assumption of normality and then to Levene's Test to verify the assumption of homogeneity of variances of the residuals, these assumptions being parametric.

When the assumptions were met, the data obtained were subjected to analysis of variance, Student's t test and Tukey's test ($p<0.05$). If the assumptions were not met, the Kruskal Wallis, Mann-Whitney, and Dunn's tests were used for multiple comparisons ($p<0.05$). For the observation of correlations, Pearson's coefficient was used.

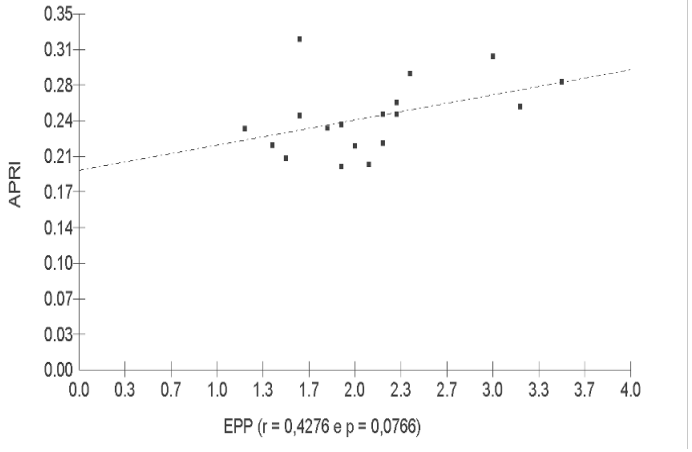
The cut-off point was defined, with sensitivity and specificity, using all values, and a cut-off was made for results with values higher than 1.5 in the HSS form and lower than 0.5 in the HIS and IS forms. Finally, the results with values between 9.5 and 1.5 for the three forms studied (HSS, HIS, and IS) were clipped.

RESULTS

Table 1 shows the results of laboratory tests, ultrasound measurements of periportal thickening, and APRI values according to the groups studied. The laboratory test results showed a significant reduction in platelet count ($p<0.0001$), WBC count ($p<0.0001$), as well as AST ($p<0.0001$), ALT ($p<0.0035$) and BD ($p<0.0001$) between the HSS and HIS/IS forms. The results of the APRI index calculation and periportal thickening showed similar results, with a statistically significant difference ($p<0.0001$) between the HSS form and the others as liver fibrosis progressed.

When Pearson's Correlation Test was performed between APRI calculation results and PPE measurements at US, in HSS form, no significant difference ($p=0.8011$) was observed between the parameters, suggesting a significant agreement between the two methods, as can be seen in figure 1.

Figure 1 - Correlation between APRI and PPE values in patients with the HSS form of SM.



Cut-off point, sensitivity and specificity

When considering the APRI values found in the HSS, HIS, and IS forms, for the cutoff point of 0.45, a sensitivity of 90% and a specificity of 97% were observed (Figure 2).

When considering APRI values higher than 1.5 in the hepatosplenic group and lower than 0.5 in the intestinal and hepatointestinal groups, for the cutoff point of 1.7, a sensitivity of 100% and specificity of 100% were observed (Figure 3). Using the same criteria and eliminating intermediate values, for the cutoff point of 0.35, a sensitivity of 88% and specificity of 89% were observed (Figure 4).

Table 1 - Results of laboratory tests in patients with SM.

Parameters	HSS		HIS		IS		P
	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	
Platelets +	108408 ± 6750 a	49	209529 ± 54591 b	17	235889± 47167 b	18	<0.0001
Leukocytes #	3176 ± 1413 a	46	6376 ± 1728 b	17	7321 ± 2924 b	18	<0.0001
AST #	40.41 ± 21.61 a	49	26.47 ± 10.40 b	17	23.67 ± 6.83 b	18	<0.0001
ALT #	35.41 ± 19.67 a	49	26.88 ± 11.30 ab	17	22.00 ± 9.68 b	18	0.0035
FA #	129.26 ± 137.21 a	49	138.94 ± 75.20 a	17	103.69 ± 49.29 a	16	0.2689
GGT #	57.98 ± 50.56 a	48	86.67 ± 78.39 a	15	52.86 ± 29.28 a	14	0.4259
TB#	0.98 ± 0.64 a	48	0.96 ± 0.50 a	17	0.80 ± 0.37 a	18	0.1282
DB #	0.39 ± 0.32 a	49	0.84 ± 0.28 b	14	0.54 ± 0.19 b	15	<0.0001
APRI#	1.27 ± 0.93 a	49	0.32 ± 0.11 b	17	0.25 ± 0.04 b	18	<0.0001
PPE (US)#	4.47 ± 1.19 a	48	2.73 ± 0.88 b	17	2.12 ± 0.62 b	18	<0.0001

+ Means followed by the same letter in the rows do not differ by Tukey's test ($p<0.05$). # Means followed by the same letter in the rows do not differ using Dunn's test ($p<0.05$). Means± SD followed by the same letter in the rows do not differ statistically.

Figure 1 - Correlation between APRI and PPE values in patients with the HSS form of SM.

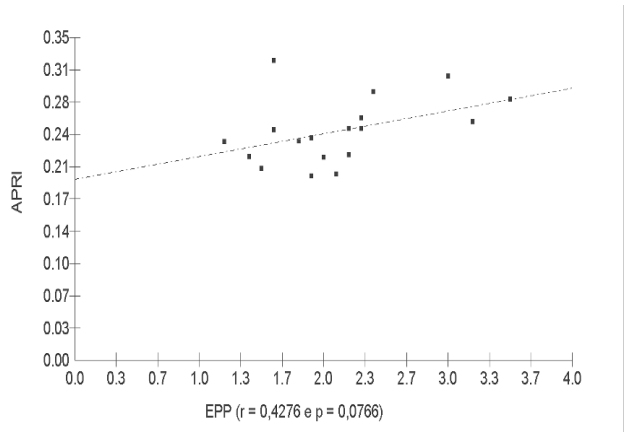


Figure 2 – Cut-off point for APRI values in patients with SM in groups IS, HIS, and HSS.

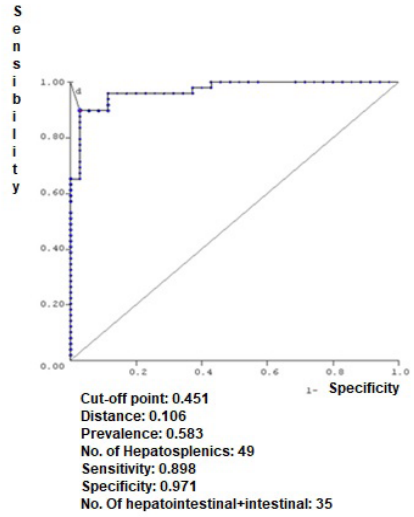


Figure 3 – Cut-off point for APRI values in SM patients using APRI values above 1.5 in the HSS form and below 0.35 in the HIS and IS forms.

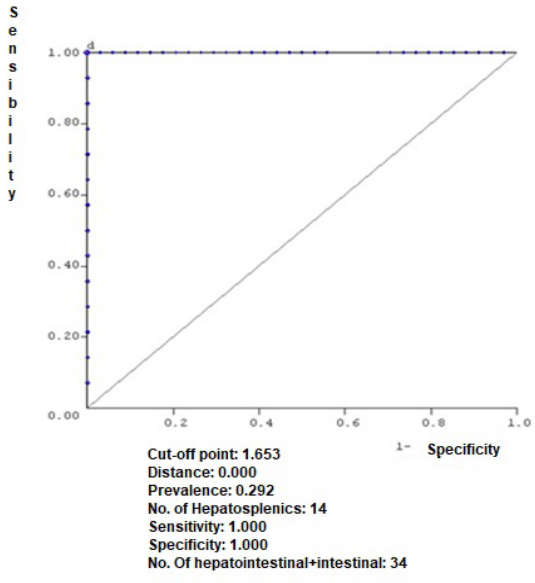
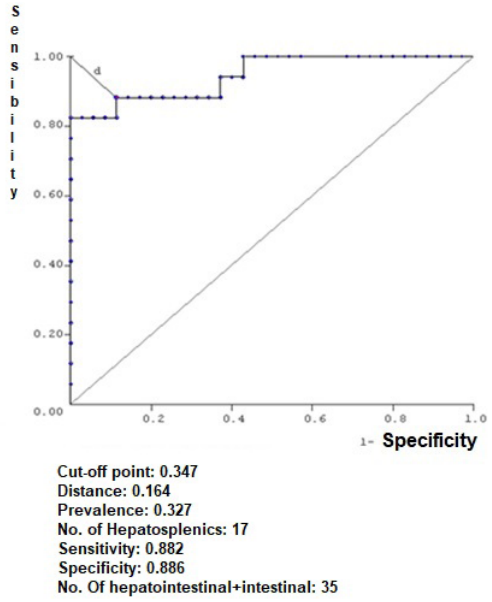


Figure 4 – Cut-off point for APRI values in SM patients using APRI values above 1.5 in the HSS form and below 0.35 in the HIS and IS forms.



DISCUSSION

In this study, it was observed that AST and platelet count values showed significant difference between the HSS and HIS/IS groups. The HSS form is characterized by the presence of PPF, splenomegaly, and portal hypertension of various levels. The findings of this study are compatible with those obtained in previous studies16 in which it was possible to observe a significant reduction in the number of platelets associated with fibrosis progression and increased spleen size.

The results of this study also demonstrated a significant difference ($p<0.0001$) in the measurement of periportal thickening on US as the disease progressed from the simplest form (IS) to the severe form (HSS) of Schistosomiasis mansoni. For more than 25 years, US have been used as a useful tool for the diagnosis and quantification of PPF in schistosomiasis endemic regions (17) However, the method has limitations in that it is not available in all endemic areas, has wide variation among observers, and is totally dependent on qualified examiners (18).

Interest in the field of non-invasive assessment of liver fibrosis has grown explosively in recent decades, particularly in viral hepatitis. Shiha et al.19 published the recommendations of the Asian Society for the Study of the Liver (APASL) Consensus on Liver Fibrosis in which APRI was considered advantageous and easy to apply, requiring no equipment to calculate the value. They then recommended that noninvasive markers could be incorporated into liver fibrosis clinical guidelines and could reduce the number of liver biopsies by about 30%. Other authors have performed systematic reviews on noninvasive markers of liver fibrosis, concluding that the usefulness of noninvasive diagnosis remained limited to pre-screening, allowing the physician to restrict the patient population prior to definitive testing of liver fibrosis by liver biopsy (20). These studies, however, did not authorize the full use of noninvasive markers to replace liver

biopsy.

Regarding the results of the APRI index calculation, a significant difference (p<0.0001) was found between the HSS form and the others as liver fibrosis progressed. The mean APRI values found in the HSS form was 1.27 ± 0.93; in the HIS form, 1.27 ± 0.93, and in the IS form, 0.25 ± 0.04. These results are in agreement with Lambertucci et al..21 who concluded in their study that APRI and platelet count are promising, low cost markers to detect hepatic fibrosis in schistosomiasis, and can contribute to define the degree of liver involvement. They found mean APRI values of 1.72 ± 1.20 in the hepatosplenic group and 0.34 ± 0.22 for the intestinal group. Hou et al., (22) in evaluating the diagnostic value of non-invasive markers for diagnosing liver fibrosis in patients with advanced schistosomiasis japonica, concluded that AST and APRI levels were reliable and sensitive markers for differentiating significant liver fibrosis in patients with advanced schistosomiasis japonica. Weerakoon et al.,23 in an extensive review on advances in the diagnosis of human schistosomiasis, recognized that different indices, based on routine investigative findings, are relevant in the evaluation of liver disease, APRI being one of these tools considered, stressing, however, that non-invasive markers are not disease-specific and therefore need to be evaluated in combination with other clinical and investigative parameters in clinical practice. The results of the study by Derbala et al. (24) also suggested that non-invasive biochemical markers such as APRI are sensitive and specific in diagnosing the degree of fibrosis and cirrhosis in patients with HCV and schistosomiasis coinfection when compared to biopsy.

In this study, when considering all APRI values in the groups studied, for the cutoff point of 0.45, a sensitivity of 90% and a specificity of 97% were observed, and this threshold may indicate, early on, the presence of fibrosis. When considering APRI values higher than 1.5 in the HSS group (intense fibrosis) and lower than 0.5 in the IS and HIS (no fibrosis and mild fibrosis), for the cutoff point of 1.7, the sensitivity of 100% and the specificity of 100% were observed, confirming that the threshold of 1.7 is safe for the detection of fibrosis. Using the same criteria and eliminating intermediate values, for the cutoff point of 0.35, a sensitivity of 90% and a specificity of 89% were observed. Thus, it is demonstrated that an APRI threshold equal to or greater than 1.7 certainly indicates severe fibrosis, while a threshold below 0.35 provides a high accuracy to affirm the absence of fibrosis. To evaluate mild to moderate fibrosis, APRI values between 0.5 and 1.5. These results are superior to those found by Shaheen & Myers, (25) who, in a meta-analysis comprising more than 8,700 patients, but in carriers of hepatitis C virus, concluded that, for APRI values of 0.7, the sensitivity was 77% and the specificity 72%, whereas, for APRI threshold of 1.0, the sensitivity and specificity were 61 and 64%, respectively. In cases with liver cirrhosis, the sensitivity and specificity of an APRI threshold of 1.0 were 76% and 72%, which is considered a moderate result for the accuracy of APRI for the diagnosis of fibrosis. Lambertucci et al., (21) found thresholds of 0.96, with a 95% confidence interval, in schistosomal groups. For significant fibrosis, an APRI threshold of 0.44 showed 96% sensitivity and 85% specificity, close to the result found in this study, for a threshold of 0.35.

The results also demonstrated that when the Pearson's Correlation Test was performed between the results of APRI calculation and the measurements of PPF at US, in the HSS form, no significant difference (r=0.8011 and p=0.0766) was observed between the parameters, demonstrating that there is a significant agreement between the two methods. This fact may bring a greater confidence in the use of APRI for the detection of hepatic fibrosis in schistosomal patients, especially in places where it is not possible to perform US. Domingues et al.,(13) in a study comparing some biological markers with US findings in patients with schistosomiasis mansoni, concluded that APRI and GGT seemed to be good markers, but considered that no ideal marker had been found to replace US findings in the evaluation of PPF in schistosomiasis. The results of this study demonstrate that APRI can, within the limits of what is commented in the text, be used in field work to select those patients with more advanced lesions and who will need more attention.

CONCLUSION

In conclusion, the results of the present study demonstrate that US and APRI present a good performance in the identification of hepatic fibrosis in Schistosomiasis mansoni. Thus, the APRI, at a threshold of 0.45, may be used as a screening test for those patients who intend to identify early signs of hepatic fibrosis, especially in areas where US is difficult to be performed. Additionally, an APRI threshold equal to or greater than 1.7 certainly indicates severe fibrosis, with sensitivity and specificity of 100%, while at a threshold below 0.35, there is a high accuracy to affirm the absence of fibrosis.

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Citation

Wyzomirska RMA, Lacel CMC, Carvalho LWT. APRI index as marker of liver fibrosis in patients with Mansonic Schitosomiasis. Rev. Port. Saúde e Sociedade. 2021;6(único):e02106013. Doi:10.28998/rpss.e02106013.