

Schistosomiasis Mansoni in Low Transmission Areas. Abdominal Ultrasound

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In endemic areas with low prevalence and low intensity of infection, the diagnosis of hepatic pathology due to the Schistosoma mansoni infection is very difficult. In order to establish the hepatic morbidity, a double-blind study was achieved in Venezuelan endemic areas, with one group of patients with schistosomiasis and the other one of non-infected people, that were evaluated clinically and by abdominal ultrasound using the Cairo classification. Schistosomiasis diagnosis was established based on parasitologic and serological tests. The increase of the hepatic size at midclavicular and midsternal lines (in hepatometry) and the hard liver consistency were the clinical parameters able to differentiate infected persons from non infected ones, as well as the presence of left lobe hepatomegaly detected by abdominal ultrasound. The periportal thickening, especially the mild form, was frequent in all age groups in both infected and uninfected patients. There was not correlation between the intensity of infection and ultrasound under the current circumstances. Our data suggest that in Venezuela, a low endemic area of transmission of schistosomiasis, the hepatic morbidity is mild and uncommon. The Cairo classification seems to overestimate the prevalence of periportal pathology. The specificity of the method must be improved, especially for the recognition of precocious pathology. Other causes of hepatopathies must be investigated.

Key word: ultrasound - schistosomiasis - low transmission - Venezuela

The diagnosis of schistosomiasis in Venezuela is very difficult due to the low prevalence, low intensity of the infection and to the unspecificity of clinical signs usually associated with this disease (Ruiz et al. 1999). For this reason, the Venezuelan Schistosomiasis Research Group has recommended the employment of immunological techniques for the diagnosis of schistosomiasis (Alarcón de Noya et al. 1992).

Moreover, the prevalence of hepatic morbidity in schistosomiasis is difficult to determine because some of the methods that could be used for diagnosis such as the biopsy, or those that evaluate the hemodynamic alterations of the liver, are dangerous and invasive procedures that can not be performed on patients under field conditions.

Periportal fibrosis is one of the most characteristic alteration in the liver of infected patients with schistosomiasis (Prata 1987) and it is considered, the most frequent cause of hepatic fibrosis worldwide (Warren 1984). Abdominal ultrasound has shown to be an alternative method for diagnosis, when the liver biopsy is contraindicated or

impracticable (El-Rooby 1985). This method is relatively inexpensive, rapid, portable, causes no biological hazards to the patients and its sensitivity and specificity in the recognition of periportal fibrosis, is comparable with the one reported for hepatic biopsy (Abdel-Wahab et al. 1989, Cerri et al. 1984, Homeida et al. 1988), percutaneous transhepatic portography, angiography (Hatz et al. 1992a), and clinical examination (Kardorff et al. 1997). It reflects the dynamic changes produced by portal hypertension, since it measures the portal vein diameter and the presence of systemic collateral blood vessels that are correlated with esophageal varices (Abdel-Latif et al. 1981, Davidson et al. 1991, Abdel-Wahab et al. 1993, Richter et al. 1998). However, this tool requires well-trained physicians, and its standardization is still a matter of debate after two WHO workshops (Cairo Working Group 1992, Niamey Working Group 2000).

Some studies have reported that ultrasound could improve the accuracy of clinical examination in endemic areas of schistosomiasis (Lambertucci et al. 2000). Moreover, it has been shown that ultrasound could be an excellent indicator for diagnosis, and very useful for planning and monitoring control programs in areas of different endemicity (Hatz et al. 1990, 1992b, Lambertucci et al. 2000).

Almost all investigations on abdominal ultrasound have been done in hospitalized patients or in endemic areas with high schistosomiasis prevalence and intensity of infection. The aim of this work was to evaluate the use of abdominal ultrasound using the Cairo classification for the schistosomiasis hepatic fibrosis diagnosis in Venezuela, a low transmission endemic area with low prevalence and morbidity.

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MATERIALS AND METHODS

Study area and population - This transverse and double blind study was carried out between 1998 and 2001 in three villages situated in the Venezuelan endemic area for schistosomiasis: Caraballeda, La Curía and Belén. Participants were considered cases of schistosomiasis according to a recent proposal of our group (Ruiz et al. 1999) and described below. Simultaneously, we selected a group of non infected persons from endemic areas to match them according to sex and age with the infected ones. These persons did not have antecedents of schistosomiasis and all the laboratorial tests for this disease were negatives.

Stool evaluation and serologic tests - Stool samples were collected and examined for the presence of *S. mansoni* eggs by the Kato Katz technique (Katz et al. 1972). For the serological diagnosis of schistosomiasis different immunological tests were performed: Enzyme Linked Immuno Absorbent Assay with Sodium Metaperiodate (SMP-ELISA) (Alarcón de Noya et al. 2000), Circumoval Precipitin Test (COPT) (Spencer et al. 1991) and Alkaline Phosphatase Immunoassay (APIA) (Pujol & Cesari 1990).

Clinical evaluation - This evaluation included a medical history, epidemiological data, current symptoms and a physical examination. Informed consent was obtained from each patient or representing in the case of children, and only volunteers were admitted in this study. Experienced observers carried out an abdominal ultrasound employing a portable Toshiba equipment with curved 3.75 MHz transducer. The echographers make first diagnostic impression and cataloged as normal, periportal fibrosis, hepatomegaly and hepatic steatosis according the observations during the exam. Thereafter, the ecographical evaluation was made following the standardized Cairo classification (Cairo Working Group 1992), and measures were done for final ultrasound diagnosis. All schistosomiasis patients were treated with praziquantel, 40 mg/kg in single oral dose.

Definitions - We consider "cases" of schistosomiasis (Ruiz et al. 1999) those people with one of the following criteria: (1) eggs of *S. mansoni* in stools; these patients have positive COPT, SMP-ELISA, and APIA (Criterion I); (2) persons without *S. mansoni* eggs in stools but with positive COPT, who have not received previous anti-*S.*

mansoni chemotherapy in the last 12 months (Criterion II); (3) persons without *S. mansoni* eggs in stools, with negative COPT, but with both SMP-ELISA and APIA (immunoassay tests) positive simultaneously and without previous chemotherapy against schistosomiasis (Criterion III).

Hepatomegaly was considered when the liver surpassed the costal margin in persons older than 5 years-old. The right lobe was measured at the anterior axilar line and the left lobe at the line passing by the xyphoid appendix. In those persons with palpable liver below the costal margin, it was determined: liver consistence (soft, firm or hard), hepatic surface (smooth or nodular), left lobe prominence (when it was proportionally larger than the right lobe) (Prata & Bina 1968). Another hepatomegaly criteria was hepatometry with anterior axilar line (AAL) > 9 cm, midclavicular line (MCL) > 12 cm and midsternal line (MSL) > 9 cm. Splenomegaly was diagnosed when spleen surpassed the costal margin (Prata 1970).

The following findings were considered as indicators of periportal fibrosis: (1) hepatic left lobe in longitudinal section larger than 70 mm; (2) portal vein diameter superior to 12 mm; (3) mean diameter of three peripheral portal vein branches superior to 3 mm. Periportal thickening in turn, was classified in Grade I: 3-5 mm (mild), Grade II: > 5-7 mm (moderate) and Grade III: > 7mm (severe); (4) mesenteric vein diameter above 11 mm; (5) splenic vein superior to 12 mm; (6) longitudinal diameter of spleen superior to 120 mm; (7) gallbladder wall superior to 5 mm; (8) presence of collateral vessels or ascitis.

Statistical analysis - The Chi-square test was used to evaluate differences between proportions ($p < 0.05$).

RESULTS

In total, 175 *S. mansoni* infected patients and 87 non-infected were evaluated. Out of the 175 cases of schistosomiasis, 96 (54.9%) persons were diagnosed by stool examination and 79 (45.1%) individuals by serology. The median of eliminated *S. mansoni* eggs was 122 per/g of feces (range: 24-1928). According to the elimination of eggs, 65 (67.7%) of them had mild infection, 28 (29.2%) moderate, and 3 (3.1%) severe.

Table I shows clinical findings in infected and non-infected patients. By hepatic percussion the midclavicular and midsternal line values (> 12 cm and > 9 cm respec-

TABLE I
Clinical findings in infected and uninfected persons in the Venezuelan schistosomiasis area, 1998-2001

Clinical findings	Infected (n = 175)	Uninfected (n = 87)	χ^2	p
Palpable liver	94 (53.7%)	43 (49.4%)	0.43	0.5127
Hepatic size				
Axillar line > 9 cm	141 (80.6%)	65 (74.7%)	1.19	0.2760
Midclavicular line > 12 cm	58 (33.1%)	15 (17.2%)	7.31 ^a	0.0069
Midsternal line > 9 cm	64 (36.6%)	20 (23%)	4.92 ^a	0.0026
Hard liver	30 (17.1%)	7 (8%)	3.97 ^a	0.0465
Prominent left lobe	32 (18.3%)	12 (14%)	0.84	0.3596
Nodular liver	5 (2.9%)	3 (3.4%)	0.07	0.7934
Splenomegaly	6 (3.4%)	1 (1.1%)	1.16	0.2813

a: statistically significant

tively) as well as hard liver, were significantly associated with schistosomiasis. There were not statistically significant differences between the rest of the variables.

The association between ultrasound findings and infection is shown in Table II. It was found that left lobe was hypertrophied in 160 of infected patients (91.4%) and in 72 of uninfected (82.8%), with a statistical difference between both groups. Periportal thickening was found in 159 infected persons (90.9%) and in 73 (83.9%) non-infected, this difference was important but it was not statistically significant. Other features such as splenomegaly, portal and mesenteric vein dilatation, are also shown in Table II.

When comparisons were made according to ultrasonographical findings and age, it was found that the frequency of left lobe hepatomegaly in infected and non-infected people was similar in all age groups (data not shown). This frequency was 100% among infected persons older than 50 years. There were not statistically significant differences among these groups (data not shown). The presence of periportal thickening among the infected and non-infected persons was similar in all ranges of age, also, without statistically significant differences. Typical ultrasound findings, left lobe hepatomegaly, splenomegaly, portal vein dilatation, periportal thickening, in Venezuelan schistosomiasis patients are shown in Fig. 1. The

TABLE II
Ultrasound findings in schistosomiasis patients and uninfected persons, Venezuela, 1998-2001

Ultrasound findings	Infected (n = 175)	Uninfected (n = 87)	χ^2	P
Left lobe > 70 mm	160 (91.4%)	72 (82.8%)	4.31 ^a	0.0379
Portal vein > 12 mm	6 (3.4%)	1 (1.1%)	1.17	0.2785
Mesenteric vein > 11 mm	9 (5.1%)	1 (1.1%)	2.52	0.1121
Spleen > 120 mm	8 (4.6%)	1 (1.1%)	2.05	0.1521
Periportal thickness (PT)	159 (90.9%)	73 (83.9%)	2.77	0.0962
PT 3-5 mm	128	64	—	—
PT > 5-7 mm	30	8	—	—
PT > 7 mm	1	1	—	—

a: statistically significant

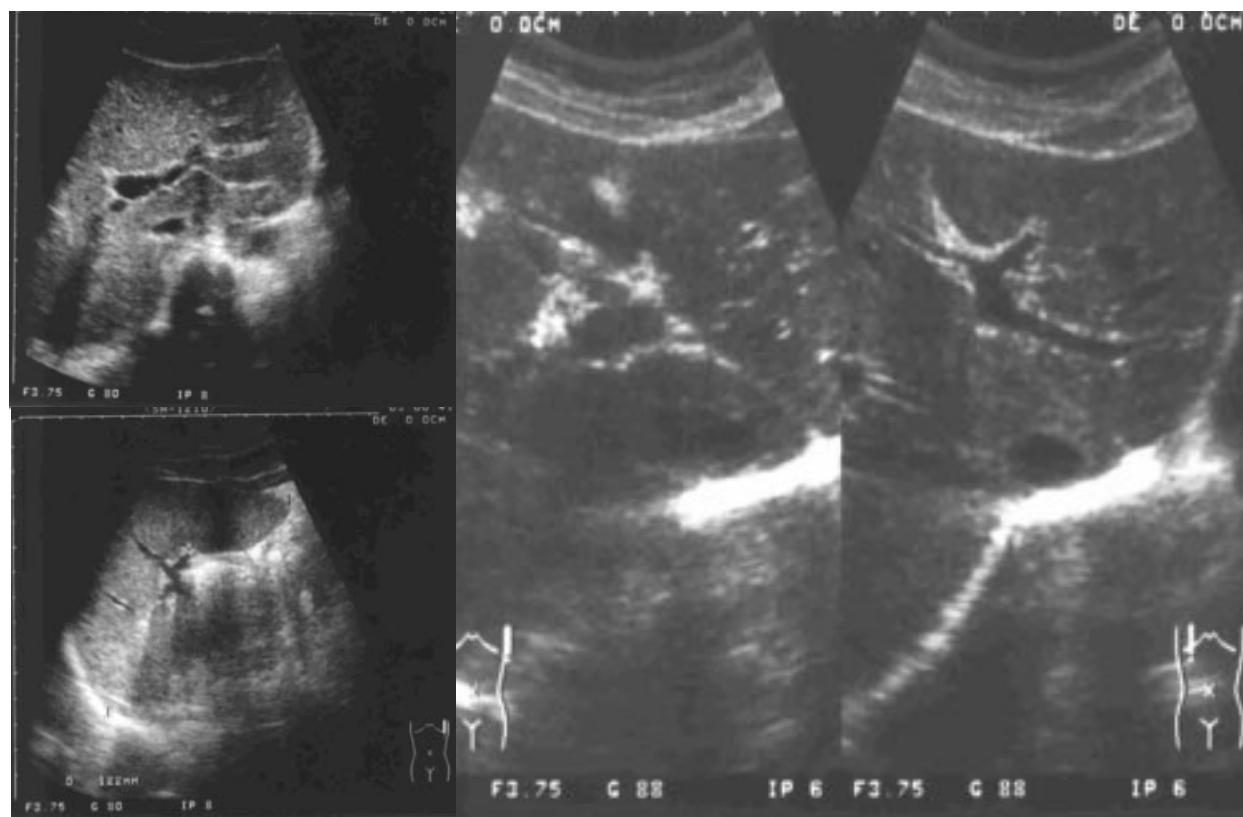


Fig. 1: left lobe hepatomegaly, splenomegaly, portal vein dilatation, periportal fibrosis and hepatomegaly in Venezuelan schistosomiasis patients.

Fig. 2 demonstrates hepatic lesions suggestive of periportal thickening in a non-infected person.

A summary of the results obtained by ultrasound according to the criteria used for diagnosis of schistosomiasis is presented in Table III. In both groups of patients, the left lobe hepatomegaly was a common finding, 90.6% and 92.4% from those diagnosed by coprology or serology respectively (persons with Criteria II or III). Also, the periportal thickening was found in 90 (93.8%) persons with fecal *S. mansoni* eggs and in 69 (87.3%) diagnosed only by serology. The rest of the evaluated parameters were less frequent in both groups. In any case, there was not statistical significant difference when ultrasound findings were compared according to the criteria used for the diagnosis of schistosomiasis.

The association between the intensity of infection and ultrasound findings is shown in Table IV. The Chi-Square test did not detect statistical differences between these variables.

Some relevant antecedents and first ultrasonographic reports in non-infected persons are shown in people with periportal thickening and left lobe hepatomegaly demonstrable after measures (Table V).

DISCUSSION

Usually, hepatomegaly and intensity of infection are employed as the classic morbidity markers in schistosomiasis (Arap-Siongok et al. 1976, Barreto & Loureiro 1984, Gryseels 1992). In our study, hepatomegaly below the costal margin was detected in similar percentages in in-

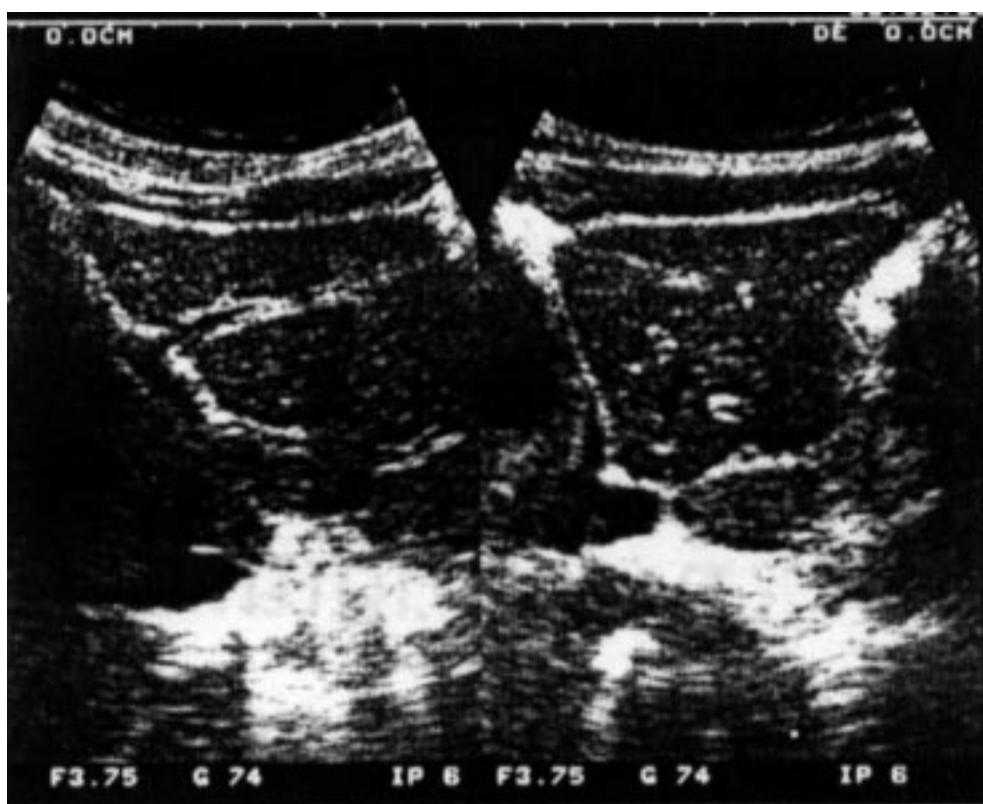


Fig. 2: periportal thickening in an uninfected individual from the Venezuelan schistosomiasis endemic area.

TABLE III

Ultrasound findings according to schistosomiasis diagnosis criteria, Venezuela, 1998-2001

Ultrasound findings	Coprology (n = 96)	Serology (n = 79)	χ^2	p
Left lobe > 70 mm	87 (90.6%)	73 (92.4%)	< 0.1	0.08810
Portal vein > 12 mm	3 (3.1%)	3 (3.8%)	< 0.1	0.8078
Mesenteric vein > 11 mm	5 (5.2%)	4 (5%)	0.0	0.9655
Spleen > 120 mm	5 (5.2%)	3 (3.8%)	0.2	0.6566
Periportal thickness (PT)	90 (93.8%)	69 (87.3%)	2.1	0.1433
PT 3-5 mm	71	57	—	—
PT > 5-7 mm	18	12	—	—
PT > 7 mm	1	0	—	—

ected and uninfected people. However, it is complicated to compare our results with those obtained in other epidemiological settings, because the diagnosis of clinical hepatomegaly has not been standardized (Cook et al. 1974, Lehman et al. 1976, Kardorff et al. 1997). Moreover, it is possible that not all cases of clinical hepatomegaly found in this work could be explained by schistosomiasis. For that reason, other causes of liver disease should be investigated.

In contrast, the increase of the liver size at midclavicular and midsternal line and liver consistency was statistically superior in schistosomiasis patients when compared to uninfected persons. The values that reflect left lobe hepatomegaly are relevant because they could be used as markers for schistosomiasis, especially in some endemic areas in Venezuela where the recognition of this disease is difficult to assess due to the low intensity of infection (Ruiz et al. 1999). Nevertheless, in the present work, children were evaluated with the same hepatometry parameters used for adults and this could cause loss of invaluable information in the pediatric age, for this reason, it is necessary to establish the normal reference values of hepatometry for children.

This classification does not take into consideration the age or height of the patients (Burchard et al. 1998). It is possible that adjusting a body-height dependent reference value, as proposed by the Niamey Working Group (2000), the ultrasound specificity could be improved.

Nodular liver, left lobe prominence, and splenomegaly had low frequency in Venezuelan patients in comparison

to the same signs reported for Brazilian patients with schistosomiasis (Prata & Bina 1968, Prata 1987). In spite of the small number of infected persons with splenomegaly, our results are similar to those reported by Dietze (1983) in a Brazilian area with high endemicity.

In addition, it was found that using the Cairo Working Group (1992) classification was possible to identify infected from non-infected patients based only on the presence of left lobe hepatomegaly, without differences according to the age. If hepatomegaly is used as an indicator of hepatic morbidity, fibrosis prevalence could be overestimated in adults with left lobe > 70 mm, and underestimated in children with left lobe < 70 mm, since variables like height, weight or corporal surface that could influence liver size, are not considered.

Periportal thickening was another frequent ultrasonographical feature, even in non-infected persons, in the Venezuelan schistosomiasis area. This finding may be explained by data that indicates that the Cairo classification overestimates the prevalence of periportal pathology. Moreover, using this classification it is difficult to establish the differences between periportal thickening grades 0 and I. In consequence, for the diagnosis of early pathology the sensitivity and specificity are lower (Boisier et al. 1995, 1998, Nooman et al. 1995, Thomas et al. 1997, Richter 2000). However, these precocious lesions are the most important to be identified because are more prevalent among the population living in endemic areas. Furthermore, the early diagnosis could be useful for planning selective or mass chemotherapy in endemic locali-

TABLE IV
Ultrasound findings according to egg output, Venezuela, 1998-2001

Ultrasound findings	Mild (n = 65)	Moderate (n = 28)	Severe (n = 3)	χ^2	p
Left lobe > 70 mm	61 (93.9%)	23 (82.1%)	3 (100%)	19.5	1.000
Portal vein > 12 mm	2 (3.1%)	1 (3.6%)	0 (0%)	63.5	0.018
Mesenteric vein > 11 mm	2 (3.1%)	3 (10.7%)	0 (0%)	57.4	0.037
Spleen > 120 mm	3 (4.7%)	2 (7.1%)	0 (0%)	32.4	0.999
Periportal thickness (PT)	61 (93.9%)	26 (92.9%)	3 (100%)	27.3	1.000
PT 3-5 mm	46	22	3	-	-
PT 5-7 mm	14	4	0	-	-
PT > 7 mm	1	0	0	-	-

TABLE V
Relevant antecedents and first ultrasonographical findings in non-infected people with definitive periportal thickening and left lobe hepatomegaly at ultrasound, Venezuela, 1998-2001

		Final ultrasound diagnosis	
		Periportal thickening (n = 74)	Left lobe hepatomegaly (n = 72)
First ultrasonographic report	Normal	57 (77%)	52 (72%)
	Periportal fibrosis	7 (9.5%)	7 (9.7%)
	Hepatomegaly	7 (9.5%)	8 (11.1%)
	Hepatic steatosis	4 (5.4%)	5 (6.9%)
Antecedents	Hepatitis	6 (8.1%)	8 (11.1%)
	Alcoholic intake	28 (37.8%)	27 (37.5%)

Included in the 72 patients with left hepatomegaly there are 60 persons who have periportal thickening simultaneously.

ties (Doehring-Schwedtfeger et al. 1989, Abdel-Wahab et al. 1990) preventing the evolution toward hepatosplenic schistosomiasis (Bina & Prata 1981, 1983).

On the other hand, advanced *S. mansoni* disease shows less problems for the diagnosis by the Cairo classification (Hatz et al. 1992b). However, the low frequency of portal hypertension signs found by ultrasound, suggests that in Venezuela the hepatic morbidity is uncommon.

Due to the presence of ultrasonographical abnormalities and clinical findings in some uninfected persons, we suggest that some other factors must be influencing the hepatic architecture in these groups. Some of the information that must be obtained in the clinical history in order to make a differential diagnosis should include: previous schistosomiasis, alcohol consumption, exposition to pesticides, viral hepatitis, other parasitic diseases with hepatic compromise (visceral larva migrans, visceral leishmaniasis).

It was detected that ultrasound parameters did not correlate with laboratory diagnosis, the criteria either parasitologic or serologic in the case of *S. mansoni* infection. This is consistent with previous studies that showed that in Venezuelan endemic areas, the serologic assays are of greater value for the schistosomiasis diagnosis (Alarcón de Noya et al. 1992).

It was also found no differences in ultrasound findings according to the intensity of infection, but it is important to consider that the universe of individuals with heavy infections was low, and this could influence the obtained results.

As it has been proposed previously for other investigations, the validity of the ultrasound for the evaluation and for monitoring the morbidity of the control programs depends on the predictive potential of the indicators of pathology in a given population (Hatz et al. 1992b). For that reason, the standardization of ultrasound must be carried out, especially when ecosonographic is used in areas where the morbidity is difficult to assess and where control measures have been implemented. Only with a correct diagnosis it is possible to evaluate the impact of those measures.

In summary, we found that the diagnosis of hepatic alterations by ultrasound according to the parameters described above, looks more specific than the quantitative Cairo classification. However, these results must be interpreted with caution because in this work we have not standardized the qualitative presence or absence of fibrosis.

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