Hepatic and splenic evaluation by ultrasonography and elastography of fibrosis and portal hypertension in *Schistosomiasis mansoni*

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ABSTRACT
Schistosomiasis is a neglected tropical disease and an important public health problem, mainly due to its magnitude and transcendence. Although most cases are characterized as a mild infection, due to its morbidity, the untreated disease can cause economic burden and incapacitation. Periportal fibrosis (PPF) is the most common complication of schistosomiasis mansoni chronic infection and a large number of deaths are mainly caused by the rupture of esophageal varices resulting from portal hypertension (non-cirrhotic). Regarding the diagnosis and assessment of PPF and portal hypertension, different methods are applied. Although wedge liver biopsy is considered the gold standard, it is not justified in non-surgical patients, whereas percutaneous liver biopsy, even considered informative, does not have sufficient sensitivity. Thus, imaging techniques such as ultrasonography, computed tomography, magnetic resonance imaging and elastography have been applied, not only to support the diagnosis of schistosomiasis, but also to assess signs of portal hypertension. In the present chapter, an evaluation of the non-invasive imaging methods currently available for the evaluation of PPF and portal hypertension in schistosomiasis was carried out. The objectivity of elastography compared to ultrasonography is emphasized, because even though ultrasound is more frequently performed, it still has the limitation of being operator-dependent. Transient elastography (TE) has been applied more and it has shown good results in differentiating clinical forms and PPF stages, in addition to presenting potential in predicting esophageal varices. On the other hand, point shear wave elastography (pSWE) has shown more promising results in the analysis of spleen stiffness, when compared to liver stiffness. Therefore, there is a need for further studies applying liver and spleen elastography in the evaluation of PPF and portal hypertension in these patients.

Keywords: *Schistosoma mansoni*, Liver fibrosis, Elastography, Ultrasonography, Portal hypertension.

1 INTRODUCTION

Schistosomiasis is characterized as a neglected tropical disease (NTD), which affects about 230 million people in low- and middle-income countries (UZOEGBO; JACKSON; Bloch, 2022). It is therefore considered one of the indicators of poverty, as it is often associated with the lack of adequate

sanitation systems, poor hygiene conditions and because it is present in the poorest countries of the world (KARUNAMOORTHI; ALMALKI; GHAILAN, 2018; QADEER et al., 2022).

Thus, the WHO roadmap for NTDs (2021-2030) aims at the global elimination of schistosomiasis as a public health problem. Control strategies include preventive chemotherapy with praziquantel, use of standardized and sensitive diagnostic methods, as well as improvements in sanitary and hygiene conditions (WHO, 2020; WHO, 2022).

In this context, the World Health Organization (WHO) estimates that at least 251.4 million people needed preventive treatment for schistosomiasis in 2021. However, during the Covid-19 pandemic and with efforts to mitigate its impacts, there has been a reduction in the provision of NTD interventions, and consequently in treatment coverage for schistosomiasis (WHO, 2023).

In Brazil, schistosomiasis is still an important public health problem, due to its magnitude and transcendence, although the percentage of positivity for *Schistosoma mansoni* in endemic areas has remained below 4% since 2015, with 2.90% in 2018 and 3.22% in 2019 (BRASIL, 2021). Thus, it is currently observed in the Brazilian population many carriers with low parasite load, which persists among most individuals as a result of consecutive cycles of treatment and frequent exposure to the infectious agent (SILVA-MORAES et al., 2019).

However, although most cases are characterized as low-intensity infection, due to its morbidity, the untreated disease causes economic effects and disability (UZOEGBO; JACKSON; Bloch, 2022). In Brazil, there is also a high prevalence of schistosomiasis in urgent care and hospital admissions, especially in the Northeast region, and among males and in the economically active age group of the population (SILVA et al., 2022). Currently, about 20 million people suffer from complications of chronic *S. mansoni* infection. Of these, up to 42% have periportal fibrosis (PPF), considered the most frequent complication. In addition, annually, about 200 thousand deaths are attributed, mainly, to the rupture of esophageal varices resulting from portal hypertension, even with the best hospital care available (ANDRADE, 2009; GUNDA et al., 2020).

Regarding the diagnosis and monitoring of PPF and portal hypertension, these require different methods. Regarding invasive methods, wedge liver biopsy, despite being considered the gold standard, is not justified in non-surgical patients, while percutaneous liver biopsy, although it may be informative, does not present sufficient sensitivity (ROCKEY et al., 2009; SILVA et al., 2010). Imaging techniques such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and elastography, on the other hand, are used not only to aid in the diagnosis of schistosomiasis, but also to quantify PPF and evaluate signs of portal hypertension resulting from schistosomiasis (DOMINGUES; OF MEDEIROS; Lopes, 2011; OLVEDA et al., 2014a; SANTOS et al., 2018; VEIGA et al., 2017).

Therefore, a combination of a comprehensive anamnesis, a complete physical examination, along with biomarkers for liver fibrosis and the use of imaging methods seems to offer the best approach to evaluate these patients (DOMINGUES; OF MEDEIROS; Lopes, 2011; Lambertucci, 2014; SANTOS et al., 2022).

In the present chapter, the different noninvasive imaging methods currently available for the evaluation of PPF and portal hypertension in schistosomiasis mansoni will be evaluated, with emphasis on US and elastography, as well as their applications, advantages and limitations in clinical practice.

2 PERIPORTAL FIBROSIS

PPF is considered a chronic process and usually a complication of schistosomiasis. This fibrosis stems from an excessive healing response to the presence of *S. mansoni eggs in* the portal venules, resulting in embolization and inflammatory reaction in these areas (ANDRIANAH et al., 2020).

Thus, PPF is characterized as one of the drivers of schistosomiasis morbidity and mortality. However, liver fibrosis occurs and progresses differently in individuals with schistosomiasis, although they present the same parasite load and biosocial characteristics, such as age, sex and time of residence in an endemic site, suggesting, therefore, that intrinsic factors still little studied related to the host and independent of the parasite may play a decisive role in the regulation of liver fibrosis in schistosomiasis. The regulation of the progression of liver fibrosis in hepatosplenic schistosomiasis (HEE) is probably multifactorial and requires further studies incorporating this concept (DE CARVALHO, 2023; KAMDEM et al., 2018).

In addition, in patients with HEE, PPF can result from a moderate to advanced form, also called Symmers' fibrosis, and described as *pipe-stem-shaped*. On ultrasound, this fibrosis is associated with splenomegaly, with or without hepatomegaly. In endemic areas, it is possible to find patients with advanced PPF without splenomegaly, also known as the hepatic form of the disease. On the other hand, some individuals without PPF and with splenomegaly due to other causes can also be found, and without the help of US these patients would be misdiagnosed, based on clinical examination, as EHE (SANTOS et al., 2022).

Therefore, Symmers fibrosis is the most relevant feature of liver alteration in schistosomiasis mansoni and is represented by a process of fibrosis along the portal branches and within the portal spaces (ANDRADE, 2004). At the onset of the disease, granulomas around the parasite's eggs can be seen in abundance in these spaces, which disappear when the disease becomes chronic and fibrosis remains. As a consequence, there are also obstructive vascular lesions secondary to granulomas, thrombosis, phlebosclerosis and fibrous thickening of the intima (ANDRADE, 2004; LAMBERTUCCI, 2014).

In short, the main hepatic alteration caused by granulomas results from physical obstruction and tissue compression, while splenomegaly results from both chronic passive congestion and reactive hyperplasia of the reticuloendothelial system due to the very immune stimulus resulting from eggs and worms (DE CARVALHO, 2023; LAMBERTUCCI, 2014). The main clinical manifestation of HES is portal hypertension (non-cirrhosis) and portosystemic collateral circulation, notably esophageal varices (ANDRADE, 2009; COUTINHO, 1968).

In schistosomiasis, the hepatic parenchyma maintains its usual acinar structure, which is reflected in patients with preserved liver function, despite the signs of portal hypertension, but without the stigmas of chronic liver disease, unlike cirrhosis. However, in some cases, compensated HES can progress to decompensated HEE, with the presence of ascites, muscle loss and liver failure (ANDRADE, 2009). These cases of progression from schistosomiasis to liver cirrhosis, with impaired capacity for hepatocyte synthesis, are sometimes observed in clinical practice in patients who have recurrent episodes of digestive bleeding and frequent necrosis of hepatocytes (DE CARVALHO, 2023; SANTOS et al., 2022). In some cases, the appearance of venous fistulas can divert blood flow from the portal circulation to the systemic circulation (hepatofugal flow), providing chronic hepatocyte ischemia and cirrhothinization of the liver (HASHIM; Berzigotti, 2021; SILVA-NETO et al., 2021).

3 PORTAL HYPERTENSION

Portal hypertension is the main complication of liver fibrosis and is defined by an elevation of the venous pressure gradient above 5 mmHg. In HEE, periportal fibrosis by retention of *S. mansoni* eggs in the portal space and granulomatous thrombophlebitis can lead to progressive obstruction of presinusoidal blood flow at the level of terminal portal venules, and consequently to an increase in resistance in the vessels, causing portal hypertension (MASI et al., 2020).

Non-cirrhotic portal hypertension is one of the most important consequences in the natural history of schistosomiasis, since it can lead to its most serious complications such as: esophageal varices, which can cause hemorrhagic events, triggering ascites and encephalopathy, or even death. Additionally, the great splenomegaly, by immune stimulation, can increase blood flow through the splenic vein and further increase the pressure in the portal vein (DE CARVALHO, 2023; COUTINHO, 1968).

In this context, esophageal varices arise as complications associated with portal hypertension and may begin at the most distal end of the esophagus, at first thin and straight, gradually becoming more caliber, bluish, tortuous, reaching the proximal part of the esophagus. The time of formation of varicose veins depends mainly on the severity of portal hypertension, the degree of PPF and individual predispositions. The caliber of varicose veins is directly related to the risk of bleeding (BORGHERESI et al., 2021).

The gold standard for assessing the presence and severity of portal hypertension remains the pressure gradient of the free and occluded hepatic vein, however, this is valid only in cirrhotic because it does not work in cases of presinusoidal portal hypertension, as occurs in schistosomiasis. However, the recent development of non-invasive techniques through elastography offer promising alternatives in the evaluation of portal hypertension and its complications (ROCCARINA et al., 2018).

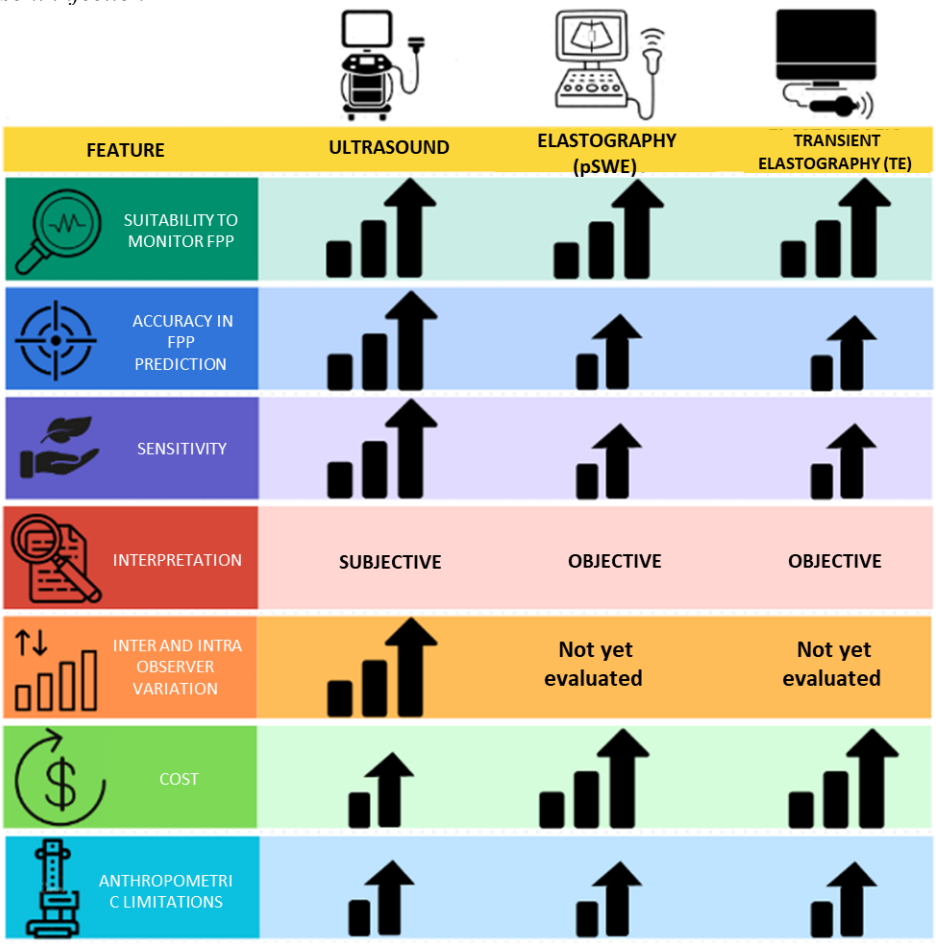
4 NONINVASIVE IMAGING METHODS FOR EVALUATION OF LIVER FIBROSIS AND PORTAL HYPERTENSION

Early detection of serious complications is of great importance in the monitoring of schistosomiasis. Thus, the use of diagnostic imaging techniques such as US, CT and MRI stand out, as each of them has a relevant role in the diagnosis and evaluation of schistosomal disease morbidity (SAH et al., 2015; WEIFENG et al., 2018).

US has been extensively used in the diagnosis of PPF and is considered the main imaging modality for the diagnosis of HES, detection of organomegaly and alteration of liver texture due to fibrosis. However, other imaging techniques, such as elastography and MRI, allow the quantification of liver fibrosis and consequent evaluation of vascular and hemodynamic changes, constituting valuable markers of staging, prognosis and response to treatment (HASHIM; Berzigotti, 2021; MASI et al., 2020). Doppler ultrasonography also enables the evaluation of portal hypertension through some of its clinical determinants: portal vein dilation, splenomegaly, presence of collateral circulation, portal vein thrombosis, portal flow measurement (HASHIM; BERZIGOTTI, 2021).

It is noteworthy that, although CT can detect low-density periportal areas with the use of contrast, and MRI is more sensitive than US, these techniques are not routinely used in the diagnosis of schistosomiasis in endemic sites, mainly due to the use of contrast, the associated risks and costs (BEZERRA et al., 2007; WEERAKOON et al., 2015). Thus, we chose in this chapter to restrict the discussion on imaging methods for the evaluation of PPF and portal hypertension, according to the reality observed in these areas, with emphasis on US, the most accessible technique, and hepatic and splenic elastography. Figure 1 summarizes the main characteristics of these imaging methods.

Figure 1. Advantages and limitations of imaging methods for the evaluation of periportal fibrosis in patients with *Schistosoma mansoni infection*.



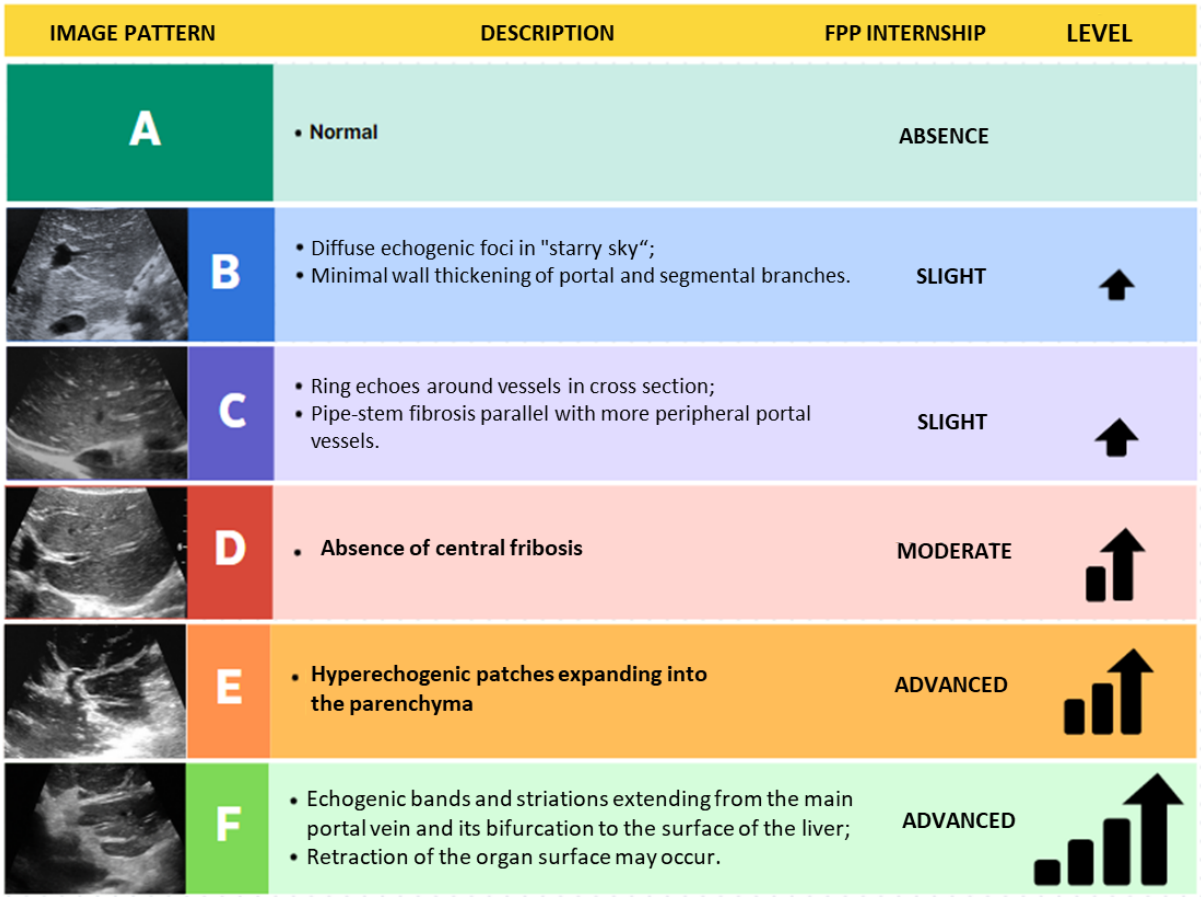
Source: The Authors (2023). Legend: PPF: periportal fibrosis; pSWE: *point shear wave elastography*; TE: transient elastography.

4.1 ULTRASOUND

Due to its practicality and reliability, US has been routinely used in the diagnosis and evaluation of patients with schistosomiasis mansoni, and has become the most well-established tool to assess PPF. This method can be applied both to demonstrate the classic characteristics of schistosomal liver injury, and to classify the patterns of PPF and the clinical form of the disease, based on the criteria of the protocol published by the WHO (WHO, 2000).

US is a simple, inexpensive and safe tool with greater sensitivity in the diagnosis of advanced PPF (Symmers fibrosis), when compared to the milder stages. Since the advent of the WHO protocol, and later the Niamey-Belo-Horizonte Protocol (2001), US has become the gold standard in the diagnosis of PPF and in the classification of its intensity (absent, mild, moderate or advanced). This evaluation is based mainly on the appearance of the hepatic parenchyma and the distribution of fibrosis from the comparison with six image patterns (A to F) (Figure 2). Other protocols previously used, such as Cairo and Managil, were abandoned due to failures in the classification of mild forms of the disease (FRIIS et al., 1996; NOOMAN et al., 1995).

Figure 2. Classification and description of periportal fibrosis imaging patterns, according to the World Health Organization.



Source: The Authors (2023). Liver ultrasound images were obtained from patients with periportal fibrosis due to schistosomiasis mansoni infection using a Siemens device and based on the Niamey standard, Pernambuco, Brazil, 2020.

The high-frequency surface probe allows the characterization of PPF and reveals a band-shaped hyperechoic periportal thickening. During the more advanced stages of PPF, pseudonodules and large patches of fibrosis secondary to extensive scarring and retraction may be observed. Other ultrasound features of HES include hypertrophy of the left hepatic lobe with atrophy of the right lobe, thickening of the gallbladder wall, and splenic nodules. In addition, US also facilitates the evaluation of consequent portal hypertension, by enabling the evaluation of portal vein dilation, splenomegaly and, occasionally, portal vein thrombosis, and also the exclusion of other intra-abdominal diseases (ANDRIANAH et al., 2020; HASHIM; BERZIGOTI, 2021).

Santos et al. (2018) demonstrated moderate to substantial reproducibility in the classification of 358 adult patients with PPF and using imaging standards according to the WHO protocol (SANTOS et al., 2018). In field studies, the use of these standards is reported as simpler and more reproducible than the application of other measures, such as the thickness of the portal branch wall and the diameter of the portal vein, which are also recommended in the WHO protocol (BERHE et al., 2006; KING et al., 2003).

Andrianah et al. (2020) analyzed the stages of PPF in 29 patients with positive serology for schistosomiasis and complications of portal hypertension, such as upper and/or lower gastrointestinal

hemorrhage and splenomegaly, by means of US and according to the degrees of periportal thickness resulting from high echogenicity. The authors identified that stage III was the most frequent in these patients (81.3%), characterized by the presence of hyperechoic periportal bands with thickness greater than 7mm and late diagnosis, followed by stage II (11.5%) and stage I (7.2%). Other findings were splenomegaly in 83.2% of cases, hepatomegaly in 48.9%, portosystemic shunt in 80.7% and ascites in 72.3%, highlighting the importance of US in the classification of PPF, in the investigation of complications such as portal hypertension and in the follow-up of these patients (ANDRIANAH et al., 2020).

In addition, more advanced portable US equipment, such as color Doppler ultrasound, allows a prediction of the prognosis of the disease from the characterization of portal vein perfusion, and thus decisions can be made about the best treatment options for complications of portal hypertension, such as portal vein thrombosis (OLVEDA et al., 2014b). It is also evident that other advances have increased US portability and decreased costs, such as tablet-based ultrasound systems with image visualization through an application, making it more feasible to incorporate this technology into a control program in endemic rural areas, as well as the identification of other diseases and referral of the population to specialized care (STRAILY et al., 2021).

Regarding the limitations of the technique, it is noteworthy that as US is an operator-dependent technique, the previous experience of the examiner is very important in the evaluation of imaging patterns and, therefore, in obtaining more consistent results. Imaging patterns B, C, and D, for example, can also be found in other diseases, such as congenital liver fibrosis, viral and autoimmune hepatitis, primary sclerosing cholangitis, and cirrhosis of the liver. Consequently, a more rigorous observer analysis is necessary to find other signs that lead to a differential diagnosis of liver fibrosis by *S. mansoni* (PINTO-SILVA et al., 2010).

In clinical practice, it is also observed that the Niamey protocol is not widely applied by all physicians who usually perform US, but only by the few who are trained and interested in research projects. It is important to emphasize the need for the evaluation of PPF by US in rural endemic areas to be performed by well-trained physicians or professionals attentive to the differential diagnosis with other liver diseases, resulting in a more efficient application of this protocol.

4.2 HEPATIC AND SPLENIC ELASTOGRAPHY

In general, focal and diffuse liver diseases are associated with structural tissue changes, leading to changes in the biomechanical properties of the liver, which can be quantified by tissue elastography. Elastography techniques can be divided into two main categories, magnetic resonance imaging-based elastography techniques and US-based elastography techniques (TARU et al., 2023). Due to the high

cost and infeasibility of MRI in endemic rural areas, US-based elastography techniques are the most widely used.

Elastography techniques have shown value in the evaluation of HES and portal hypertension, although the evidence remains limited due to the small number of patients evaluated in most studies. Hashim & Berzigotti (2021), highlighted the need for longitudinal studies with larger sample sizes to establish robust criteria to accurately assess the performance of these techniques in predicting regression and progression of the stage of PPF, in addition to identifying their cost-effectiveness in community screening (HASHIM; BERZIGOTTI, 2021).

Elastography-based techniques, such as transient elastography (TE) and point shear wave elastography (pSWE) using acoustic radiation force imaging (ARFI), have received substantial attention regarding the non-invasive evaluation of tissue mechanical properties. These techniques have emerged as complementary to US imaging in the study of liver fibrosis in many liver diseases (COSGROVE et al., 2017; DIETRICH et al., 2017), including schistosomiasis mansoni (LIMA; LACET; PARISE, 2020; PEREIRA et al., 2021; SANTOS et al., 2018; SINKALA et al., 2020; VEIGA et al., 2017, 2021).

Due to changes in the elasticity of the soft tissues of the affected organs, including the liver and spleen, using these techniques, qualitative and quantitative information is obtained that can be used for diagnostic and prognostic purposes (SIGRIST et al., 2017). In this context, the noninvasive evaluation of portal hypertension has become an issue of great interest in recent years. Recently, splenic stiffness has been identified as a potential substitute for the marker of portal hypertension in cirrhotic patients (VEIGA; WALNUT; FERNANDES, 2020). In fact, recent studies have shown that measurement of spleen stiffness by ET and pSWE correlates with liver stiffness and portal hypertension in patients with HES (PEREIRA et al., 2021; VEIGA et al., 2017). Table 1 summarizes the studies that used elastography in the evaluation of PPF and splenic stiffness in patients with *S. mansoni* and Figure 3 summarizes the cutoff points reported in the literature for these methods.

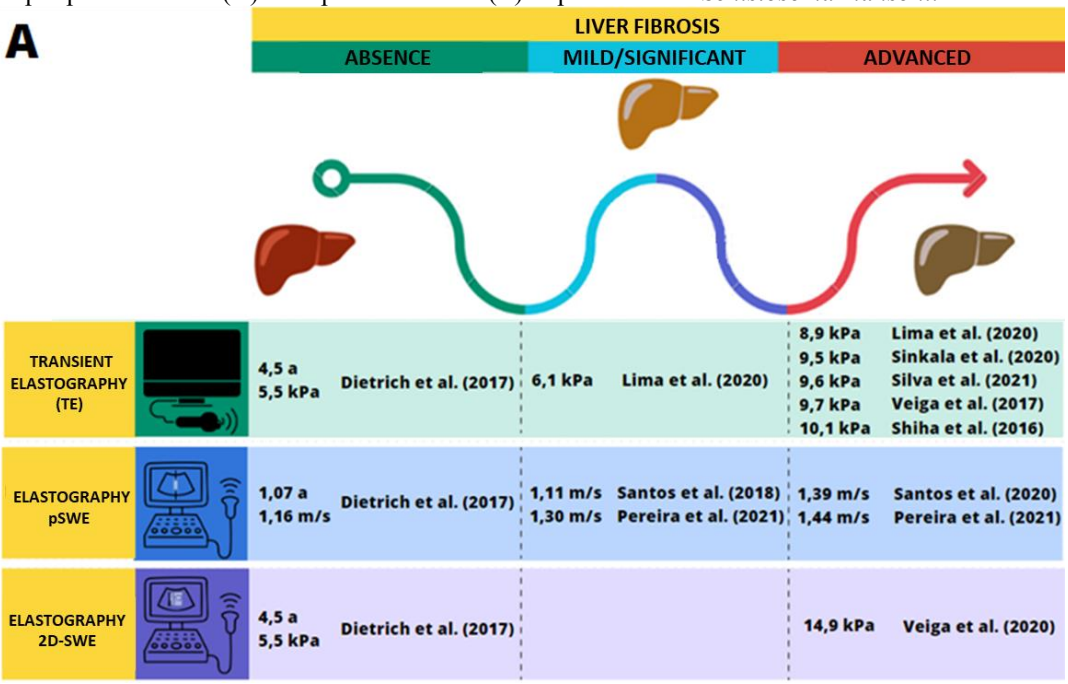
Table 1. Studies described in the literature that used elastography in the evaluation of periportal fibrosis and splenic rigidity in patients with *Schistosoma mansoni.*

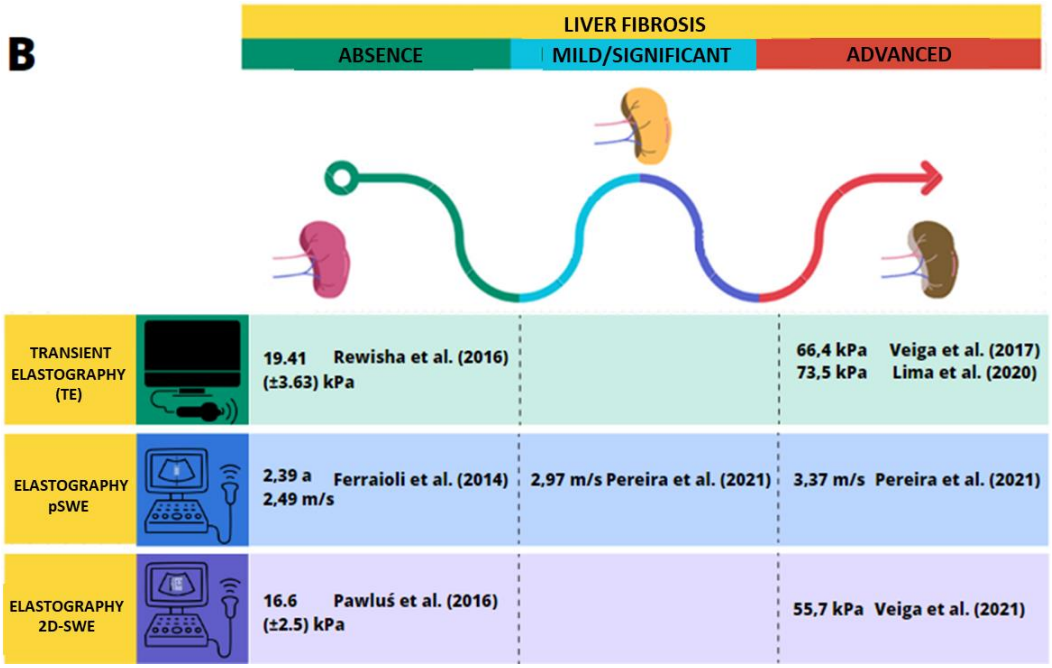
Authors	Location (Country)	Study design	Objective of the study	Number of patients	Variables	Findings
Transient elastography (ET)						
Shiha et al. (2016)	Sherbin (Egypt)	Transverse	To evaluate the accuracy of ET in the diagnosis of PPF.	Schistosomiasis: 30	Hepatic stiffness	Low accuracy in the detection of splenomegaly (36.7%) and varicose veins (37.9%)
Veiga et al. (2017)	Rio de Janeiro (Brazil)	Multicenter transverse	To describe the parameters of hepatic and splenic stiffness by ET in patients with HES and correlate with USG.	EHE: 30; HCV cirrhosis: 30; Controls: 17.	Hepatic and splenic stiffness	Association of liver stiffness with the differentiation between cirrhosis and HES, and splenic stiffness as a potential marker of portal hypertension.
Nascimento et al. (2018)	Sergipe (Brazil)	Transverse	To evaluate the correlation between APRI, FIB-4 and ET.	Chronic schistosomiasis: 17; HCV: 45.	Hepatic stiffness	Positive correlation between APRI and FIB-4 and between FIB-4 and ET in patients with schistosomiasis.
Sinkala et al. (2020)	Lusaka (Zambia)	Nested control case	To evaluate liver stiffness in patients with HEE.	EHE: 48; Controls: 22	Hepatic stiffness	Increased liver stiffness in patients with HES and positive correlation of ET with inflammatory markers.
Lima et al. (2020)	Alagoas (Brazil)	Case-control	To correlate the measurements of liver stiffness obtained by ET with the stage of fibrosis of USG.	Schistosomiasis: 117	Hepatic stiffness	Positive and direct correlation between ET and the clinical form and with the presence of fibrosis and significant fibrosis.
Silva et al. (2021)	Minas Gerais (Brazil)	Transverse	To investigate the role of ET in differentiating between HES and cirrhosis and the factors associated with hepatic and splenic stiffness in HES.	EHE: 29; Cirrhosis by NASH: 23	Hepatic and splenic stiffness	Higher levels of hepatic stiffness, splenic in the group with HES and association with varicose veins and DVT.
Nardelli et al. (2022)	Rio de Janeiro and Minas Gerais (Brazil)	Multicenter transverse	To investigate noninvasive methods in the prediction of esophageal varices in patients with HES.	EHE: 51	Hepatic and splenic stiffness	Variables related to the spleen were shown to be predictors of esophageal varices in patients with HES and non-cirrhotic portal hypertension.
pSWE						
Santos et al. (2018)	Pernam-buco (Brazil)	Transverse	Evaluate the performance of pSWE in predicting significant FPP and determine the best cutoff point.	Chronic schistosomiasis: 358	Hepatic stiffness	pSWE was able to accurately differentiate between light FPP and significant FPP.

Pereira et al. (2021)	Pernam-buco (Brazil)	Transverse	To evaluate the morbidity of schistosomiasis by hepatic and splenic pSWE and relate it to USG parameters.	Chronic schistosomiasis: 74	Hepatic and splenic stiffness	Positive and direct correlation between the FPP pattern and the spleen-only pSWE values. Significant correlations between splenic pSWE values, longitudinal and transverse lengths of the spleen, and portal and splenic vein diameters.
2D-SWE						
Veiga et al. (2021)	Rio de Janeiro (Brazil)	Transverse	To analyze the correlation between single and multiple measurements of liver and splenic stiffness and the variability of these measurements among the hepatic lobes.	EHE: 26 patients	Hepatic and splenic stiffness	Higher values of liver stiffness in the left lobe when compared to the right lobe and conclusion that a single measurement would be sufficient to assess splenic and hepatic stiffness in patients with HES.

Source: The Authors (2023). Legend: APRI: Index of the ratio of aspartate aminotransferase to platelets; HEE: Schistosomiasis, Hepatosplenic; NASH: Nonalcoholic steatohepatitis; FIB-4: Fibrosis-4 index; PPF: Periportal Fibrosis; HCV: Hepatitis C Virus; pSWE: Point shear wave elastography; TE: Transient elastography; USG: Ultrasonography.

Figure 3. Cutoff points reported in the literature for transient elastography (ET) and shear wave elastography (SWE) in the evaluation of periportal fibrosis (A) and splenic stiffness (B) in patients with *Schistosoma mansoni.*





Source: The Authors (2023).

With regard to the limitations of the method, we highlight the cost, the difficulty of availability of the equipment in endemic areas. As well, there is a need for a greater number of studies with hepatic elastography and more detailed studies in relation to splenic elastography.

4.2.1 Transient elastography (ET)

Similarly to most liver elastography techniques, ET performs the measurement of shear wave velocity using a transient force, however, it stands out as the only quantitative elastography method that has not been integrated into a standard ultrasound system and uses an external impulse mechanism (DIETRICH et al., 2017; TARU et al., 2023). It is worth mentioning that in the evaluation of schistosomiasis mansoni with ET, in which liver fibrosis is not diffuse, there is the possibility of triggering the wave impulse on top of a periportal fibrosis beam and, consequently, obtaining overestimated values.

The velocity of the shear wave is obtained through 10 valid measurements, with interquartile range (IQR), and interquartile / median ratio (IQR/M) ≤30%. The more rigid the tissue, the higher the values of liver stiffness, calculated in kilopascal (kPa), while lower values indicate a more elastic liver. In the healthy population, a liver stiffness of about 4.5–5.5 kPa is reported (DIETRICH et al., 2017; TARU et al., 2023) and splenic of 19.41 (±3.63) kPa (REWISHA; ELSABAAWY; ALSEBAEY, 2016).

Initial studies in patients with schistosomiasis mansoni, conducted by Shiha et al. (2016), evaluated the use of ET in 30 patients infected with *S. mansoni,* and reported that this method was not useful in the diagnosis of PPF or esophageal varices, but that it would be necessary to confirm these

findings in a larger group of patients, as well as to evaluate the applicability of ET in cases of prehepatic portal hypertension, such as portal vein thrombosis and congenital hepatic fibrosis (SHIHA et al., 2016).

On the other hand, Veiga et al. (2017) when comparing 30 patients with HEE, 30 cirrhotic patients with hepatitis C virus (HCV) infection and 17 controls (negative serology for hepatitis B and C and no history of liver disease), through ultrasound and transient elastography, observed that schistosomal patients had significantly higher liver stiffness (9.7 kPa) than the control group (3.7 kPa), however, lower than the cirrhotic (27 kPa). Therefore, this assessment may be a useful tool to differentiate cirrhosis-related portal hypertension from that of HES. The authors also highlighted that spleen stiffness was associated with the diameter of the right hepatic lobe, spleen and portal and splenic veins, as well as with the resistance index of the splenic artery and congestion of the portal vein. Thus, in view of these findings, they suggested that splenic stiffness could be a potential surrogate marker for the evaluation of portal hypertension in schistosomal patients (VEIGA et al., 2017).

Similarly, Sinkala et al. (2020) when comparing 48 adults with HES and 22 healthy individuals, identified that the former had greater liver stiffness when compared to the control group. The authors also verified positive correlations between inflammatory markers and liver stiffness, suggesting that HES results in changes in both periportal and parenchymal fibrosis and that the evaluation of liver stiffness may be useful in identifying fibrosis in these patients (SINKALA et al., 2020).

The other studies with ET, conducted only in patients with schistosomiasis mansoni, without co-infection with other liver diseases, sought to compare it with indirect noninvasive markers of liver fibrosis, such as the indices of aspartate aminotransferase ratio over platelets (APRI) and fibrosis-4 (FIB-4) (NASCIMENTO et al., 2018) and with the findings of US (LIMA; LACET; PARISE, 2020). Nascimento et al. (2018), when investigating 17 patients with schistosomiasis 45 patients with chronic hepatitis by HCV, reported a positive correlation between the results of APRI and FIB-4 and between FIB-4 and elastography in patients with schistosomiasis, suggesting that noninvasive methods for diagnosis and monitoring of liver fibrosis in this group have good acceptance. Similarly, Lima et al. (2020), when evaluating 117 adult patients from endemic areas with schistosomiasis, using the Niamey protocol, reported that ET was effective in the diagnosis of PPF, being able to identify advanced forms of the disease and predict the risk of clinical complications in endemic regions.

Regarding the measurement of splenic stiffness by ET, some studies have shown that it can predict the presence and size of esophageal varices, as well as clinical complications in compensated cirrhosis (BARANOVA et al., 2011; NIELSEN et al., 2017; OLVEDA et al., 2014a). Consequently, this measure can also be a predictor of bleeding from esophageal varices in HES and used in the prevention of complications of schistosomiasis mansoni (SILVA et al., 2021).

With regard to this aspect, Silva et al. (2021) compared 29 patients with HEE and 23 with liver cirrhosis secondary to nonalcoholic steatohepatitis and identified lower levels of liver stiffness, and higher levels of splenic stiffness and the controlled attenuation parameter (CAP) in the group with HES. In addition, high splenic stiffness in patients with HES has been shown to be associated with esophageal varices, portal venous thrombosis, previous bleeding of these varicose veins and metabolic disorders (SILVA et al., 2021).

Similarly, Nardelli et al. (2022) evaluated 51 HES patients using ET and identified some spleen-related variables as predictors of esophageal varices in patients with HES and non-cirrhotic portal hypertension: the measurement of splenic stiffness, the diameter of the splenic vein, the index of the measurement of splenic stiffness in relation to platelets (SSPS), the varicose vein risk index (VRS-modified) and the platelet count index in relation to spleen diameter (SRP) (NARDELLI et al., 2022).

In general, in patients with compensated advanced chronic liver disease, the combination of ET ($\leq$ 20 kPa) with platelet count ($\geq$ 150x109/L) is recommended to rule out the presence of varicose veins requiring treatment (DE FRANCHIS et al., 2022)). Roccarina et al. (2017) suggested that the evaluation of specific cutoff points associated with etiology to rule out clinically significant portal hypertension is an unmet clinical need and that incorporating splenic stiffness measurements into noninvasive algorithms and improved measurement scales may improve the noninvasive diagnosis of portal hypertension in these patients (ROCCARINA et al., 2018).

As limitations of ET, it is noteworthy that some changes in liver tissue, such as edema, inflammation, cholestasis, congestion and infiltrative diseases can interfere in the values of liver stiffness, regardless of fibrosis, therefore, these factors should be considered when evaluating the results. Thus, although the examination can be performed by a technical professional, the clinical interpretation should be performed by a specialist who considers the demographic data, etiology of the disease and the biochemical profile of the patient (BOURSIER et al., 2008; DIETRICH et al., 2017; TARU et al., 2023).

4.2.2 Shear wave elastography (SWE)

In SWE, the shear wave velocity is measured, which can be performed at a specific point (pSWE) or at multiple sequential points (2D-SWE, 3D-SWE), chosen as the region of interest – ROI and which are generated using acoustic radiation force (ARFI). While ET uses an acoustic mechanism of external impulse, in ARFI, this impulse is internal, providing a measure of tissue elasticity in meters per second (m/s) or kPa. Thus, the higher the velocity of the shear wave, the greater the hepatic stiffness. In the healthy population, normal values between 1.07 and 1.16 m/s are reported for hepatic pSWE (DIETRICH et al., 2017), and between 2.39 and 2.49 m/s for splenic (FERRAIOLI et al., 2014). With regard to 2D-SWE, 4.5 to 5.5 kPa for liver stiffness (DIETRICH et al., 2017) and 16.6

(±2.5) kPa for splenic (PAWLUŚ et al., 2016) are considered normal . Similarly to ET, in pSWE 10 valid measurements and an IQR/M ratio ≤ 30% are usually required, while in 2D-SWE, there is a need for at least three measurements (DIETRICH et al., 2017; TARU et al., 2023; Villani et al., 2023). However, if these are obtained in m/s the IQR/M should be ≤ 15% (BARR et al., 2020).

In initial studies evaluating pSWE compared to US standards in patients with schistosomiasis mansoni, Santos et al. (2018), analyzed PPF in 358 patients infected with *S. mansoni and* highlighted that this technique could be useful in the diagnosis of advanced forms of schistosomiasis, since ARFI was able to accurately differentiate between mild PPF and significant FPP (SANTOS et al., 2018).

When assessing the morbidity of schistosomiasis mansoni in 74 patients by means of hepatic and splenic elastography (pSWE) and relating it to US parameters, Pereira et al. (2021) reported that as the pattern of PPF progressed, the values of splenic pSWE increased significantly. In addition, these authors observed significant correlations between splenic pSWE values, longitudinal and transverse lengths of the spleen, and portal and splenic vein diameters, indicating the potential of splenic pSWE in the evaluation of morbidity in these patients. These findings, however, were not observed through hepatic pSWE (PEREIRA et al., 2021).

With regard to 2D-SWE, Veiga et al. (2021) analyzed the correlation between single and multiple measurements of liver and splenic stiffness and variability of these measurements among the hepatic lobes of 26 patients with HEE. The authors identified higher values of stiffness in the left lobe when compared to the right lobe and reported an excellent correlation between the first measurement and the median of four measurements in both the hepatic and spleen lobes, concluding that a single measurement would be sufficient to assess splenic and hepatic stiffness in patients with HES.

Regarding the diagnosis of esophageal varices due to portal hypertension, although no studies evaluating patients with schistosomiasis mansoni using SWE have been reported, Hristov et al. (2023) sought to establish whether liver stiffness measured by 2D-SWE could be used as a predictor for the presence and severity of esophageal varices in 86 cirrhotic patients. The authors reported a sensitivity and specificity of 100% in the differentiation between patients at high risk of esophageal varices (grade 4), when compared to the other grades (1 to 3), and suggested that 2D-SWE could be used as a noninvasive method of evaluation in these patients. For the other grades, upper GI endoscopy remains the method of choice (HRISTOV et al., 2023).

As limitations of SWE, the same interferences related to changes in liver tissue stand out, such as edema, inflammation, cholestasis, congestion and infiltrative diseases. The interpretation of elastography results is also a limitation, since in schistosomal patients it is an unusual technique and there are still no well-established protocols (BOURSIER et al., 2008; DIETRICH et al., 2017; TARU et al., 2023). The need for an experienced physician/professional to obtain measurements of liver and splenic stiffness is also highlighted, since this method is integrated into a standard ultrasound system.

5 CONCLUSIONS

Based on what was evaluated in the present chapter, it is highlighted that US and hepatic and splenic elastography are important methods for the evaluation of PPF, tissue stiffness and portal hypertension in schistosomiasis mansoni. In addition, these techniques have been highlighted, mainly because they are non-invasive, when compared to the gold standard, and have a medium cost. The objectivity of the results of elastography in relation to ultrasonography is also highlighted, because although the latter is widely used, it still has the limitations of being operator-dependent and the difficulties of operators in adhering to the Niamey protocol.

When comparing the performance of ET and pSWE in patients with schistosomiasis mansoni, it is noteworthy that ET has been more used and with better results when compared to pSWE in the differentiation of clinical forms and stage of fibrosis, besides being promising in the prediction of esophageal varices. The pSWE, however, has shown better results in the analysis of splenic stiffness when compared to the hepatic one. There are still few studies applying 2D-SWE elastography in the evaluation of patients with schistosomiasis mansoni. In general, we highlight the need for further studies using elastography in the evaluation of portal hypertension and, consequently, the prediction of the presence of esophageal varices and risk of digestive hemorrhage in these patients.

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