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The Role of Spleen Stiffness Measurement to Assess Liver Fibrosis in Chronic Hepatitis B: A Review of Current Literature

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ABSTRACT

Chronic Hepatitis B (CHB) is a significant health concern, especially in Indonesia, which increases liver-related morbidity and mortality. As liver fibrosis is often assessed with liver biopsy, an invasive procedure with several limitations, noninvasive alternatives such as transient elastography (TE) to measure liver stiffness measurement (LSM) have gained popularity. Furthermore, a new promising tool for evaluating liver fibrosis, spleen stiffness measurement (SSM), has emerged as another noninvasive alternative. This literature review examines SSM's role in assessing liver fibrosis and its relationship with LSM. The review synthesized findings on the correlation between spleen stiffness measurement (SSM) and liver fibrosis. CHB-induced liver fibrosis involves a complex pathophysiology ranging from immune-mediated hepatocyte injury to extracellular matrix deposition, and portal hypertension. All the changes mentioned affect liver and spleen stiffness, supported by research that demonstrated a positive correlation between the two. Moreover, SSM may have more diagnostic value in some instances, where LSM are deemed unreliable, such as ascites or obesity. Although SSM shows promise as a noninvasive marker for liver fibrosis, further studies are essential to enlighten the correlation between LSM and SSM and validate its diagnostic accuracy in clinical practice.

Keywords: Chronic hepatitis B; liver fibrosis; liver stiffness; spleen stiffness.

INTRODUCTION

Chronic hepatitis B (CHB) is a significant health issue with high morbidity and mortality. According to the World Health Organization (WHO), in 2019, nearly 296 million individuals were affected worldwide, causing an estimated 820,000 deaths, mainly due to cirrhosis and hepatocellular carcinoma (HCC) [1]. The average prevalence of CHB in Indonesia is approximately 2.1%, classified as a region of intermediate prevalence [2]. Its prevalence has driven the Indonesian Minister of Health to prevent further transmission [3].

The hallmark complication of CHB, liver fibrosis, is caused by the chronic inflammatory response and hepatocyte injury. Liver fibrosis is characterized by excessive extracellular matrix deposition in the liver and can lead to complications such as portal hypertension, advanced liver fibrosis, and cirrhosis [4]. The assessment of liver fibrosis is essential for determining the severity of the disease and following management.

The gold standard of liver fibrosis assessment is liver biopsy. However, as it is an invasive procedure with several risks, developing noninvasive alternatives is essential. One such alternative is transient elastography (TE), which can measure liver stiffness [5]. TE has been proven effective in liver fibrosis staging, but in certain conditions, such as obesity or ascites, the TE result may be unreliable [6].

Emerging evidence suggests that spleen stiffness measurement (SSM) can be an alternative noninvasive diagnostic tool to assess liver fibrosis. Moreover, studies have demonstrated a correlation between SSM and liver fibrosis severity [7]. Anatomically and functionally, the spleen is connected to the liver through the portal venous system, which undergoes changes in stiffness due to portal hypertension and fibrosis. An increase in portal tension can damage the spleen, causing spleen stiffness and inducing TGF- β1 production, which can lead to exacerbating liver fibrosis as a result. In other words, spleen fibrosis has a role in increasing liver fibrosis [8, 9]. Unlike LSM, SSM may be less affected by inflammation. Thus, SSM can be a promising candidate for fibrosis assessment. However, the data on its diagnostic accuracy needs to be improved, and further research is needed to validate its use.

This literature review aims to understand the role of SSM in predicting liver fibrosis and its capability to augment or replace invasive methods by synthesizing recent study findings. It will explore the pathophysiological link of spleen stiffness to liver fibrosis and the correlation between LSM and SSM. By synthesizing recent study findings, this review clarifies the potential role of SSM in enhancing the noninvasive liver fibrosis assessment.

REVIEW CONTENT

1. Chronic Hepatitis B

- ***Definition of Hepatitis B Infection***

Hepatitis B infection is an infection of the liver caused by the hepatitis B virus (HBV) and can cause acute and chronic infections [10]. Chronic hepatitis B infection can lead to complications, such as cirrhosis and liver cancer, both of which can cause death. The difference between acute and chronic hepatitis B is that patients diagnosed with hepatitis B are those who have been HbsAg seropositive for more than 6 months.

- ***Epidemiology of Chronic Hepatitis B***

In 2019, the prevalence of chronic hepatitis B infection was estimated to reach 296 million people, with 1.5 million new cases per year. In the same year, the mortality rate caused by hepatitis B infection reached 820,000 deaths, primarily due to complications of cirrhosis and hepatocellular carcinoma [10]. According to Indonesian Basic Health Research 2013, the prevalence of hepatitis in Indonesia was 1.2%, with 21.8% of all hepatitis cases being hepatitis B infection cases. For data from Indonesian Basic Health Research 2018, there is no mention of the number of hepatitis B infection cases. The average prevalence of hepatitis B in Indonesia is 2.1% [11].

- ***Natural History of Chronic Hepatitis B***

The natural progression of hepatitis B infection is strongly influenced by the host's immune response at the time of infection. Infection during infancy generally causes no symptoms, but there is more than a 90% chance that it will develop into a chronic infection. Children up to the age of five have a 20% chance of becoming a chronic infection. After five years of age, more precisely in adulthood, there is a 90% chance of developing an acute infection [12].

The natural course of chronic hepatitis B infection is divided into four phases: immunotolerant, inflammatory, inactive, and immune escape. The immunotolerant phase is characterized by normal ALT levels, high HBV DNA, and positive HBeAg. The inflammatory phase, especially in adolescent or adult patients, is characterized by ALT flares, negative HBeAb, and positive HBeAg. The inactive phase generally occurs in patients with chronic infection and is characterized by a decrease in HBV DNA, positive HBeAb, and normalization of liver function. The last phase, the immune escape phase, has an increase in ALT and an increase in HBV DNA accompanied by positive HBeAb [12, 13].

2. Liver Fibrosis

- ***Definition of Liver Fibrosis***

Liver fibrosis is a condition where there is an accumulation of extracellular matrix in response to an injury that can be caused by viral infection, drug use, autoimmunity, alcohol abuse, and others. Liver fibrosis commonly occurs in chronic liver disease. Advanced liver fibrosis can lead to cirrhosis, portal hypertension, or liver failure [14]. Regardless of its aetiology, liver fibrosis is described by molecular mechanisms, such as hepatocyte cell death, chronic inflammation accompanied by cytokine release, activation of liver stellate cells, and damage to the endothelial or epithelial layers [15].

- ***Pathogenesis of Liver Fibrosis***

The liver parenchyma consists of epithelial or hepatocytes, endothelial cells, and resident non-parenchymal cells (stellate liver cells and Kupffer cells) [16]. Stellate liver cells (HSCs) are mesenchymal cells that are dormant in the subendothelial space of Disse located between the sinusoid endothelium and hepatocytes. These cells store vitamin A in the form of lipid droplets. Due to the presence of injury, liver stellate cells will be activated and decrease the expression of genes, such as glial fibrillary acidic protein (GFAP) and peroxisome proliferator-activated receptor gamma (PPARγ), thereby turning vitamin A-rich cells into vitamin A-poor and myofibroblasts [17].

Stellate liver cells are the primary source involved in liver fibrosis, but the process of liver fibrosis is also influenced by several other cells;

(1) Portal fibroblasts: These cells are located in the connective tissue of the portal area, so the recruitment and activation of fibroblasts into myofibroblasts in ischemia- and cholestasis-related diseases is significant. The contribution of these cells is significant in biliary diseases [18].

(2) Bone marrow-derived cells and circulating fibrocytes: After liver injury, the bone marrow supplies myofibroblast-like cells that may participate in the development of liver fibrosis [19]. However, the contribution of such cells to collagen formation in liver injury is quite limited.

(3) Epithelial-to-mesenchymal transition (EMT) cells: Epithelial cells can contribute to the replacement of damaged or dead hepatocytes through a biological process known as epithelial-to-mesenchymal transition (EMT) (Cannito et al., 2017). This process promotes the migration of epithelial cells and their accumulation in the interstitium space of the tissue so that they can transform into mesenchymal cells. However, the role of EMT in liver fibrogenesis is still controversial and, therefore, considered of little relevance [20].

In addition to the three cells above, endothelial cells are also found to transform mesenchymal cells in renal and cardiac fibrosis. However, the role of endothelial cells in liver fibrosis is still unknown.

Myofibroblast cells will proliferate and migrate to areas where hepatocyte cells are damaged, where they will secrete extracellular matrix. In addition, myofibroblast cells secrete vascular endothelial growth factor (VEGF), which induces the proliferation of stellate liver cells [21]. Some myofibroblasts can undergo apoptosis or inactivation when the etiology has been eradicated, causing recovery from fibrosis [22]. In addition, Natural Killer (NK) cells activated by interferon-γ (IFN-γ) also play a role in the resolution of liver fibrosis by eliminating stellate liver cells [23].

In chronic liver injury, extracellular matrix production and deposition exceeds the extracellular matrix's degradation, resulting in fibrosis due to fibrosis septa and collagen. In addition, these changes in extracellular matrix composition directly promote fibrogenesis. The deposition of extracellular matrix in the Disse space will cause fenestration damage to the endothelial layer, which will cause damage to the bidirectional plasma flow in the sinusoid lumen and hepatocyte cells, which normally function for metabolic exchange. Therefore, changes in liver function occur [17]. The remodeling and accumulation of the extracellular matrix can also change the consistency of the liver organ to become more complex so that there is an increase in liver stiffness [24].

In chronic hepatitis B infection, liver fibrosis, known as post-necrotic or bridging fibrosis, is characterized by extracellular matrix deposition in the form of portal-central fibrotic septa due to portal-central bridging necrosis [18]. Therefore, vascular damage (formation of new blood vessels and Porto-central shunting) in the portal system may occur earlier and faster, so portal hypertension will also develop earlier [25]. In addition, hepatitis B virus is a non-cytopathic virus in hepatocyte cells where it can evade the innate immune system so that the response of CD4+ and CD8+ T lymphocytes is ineffective and activates an adaptive immune response that can cause liver parenchyma injury, hepatocyte cell death, and contribute to the fibrogenic development of chronic liver disease [26].

3. Liver Stiffness Measurement

- ***Definition of Liver Stiffness Measurement***

Liver stiffness Measurement is a parameter used to assess the condition of the liver. Factors including fibrosis, congestion, and inflammation influence increased liver stiffness. Determining the degree of liver fibrosis with liver stiffness is done as a noninvasive alternative to biopsy. Liver stiffness can also be used in all chronic liver diseases, such as hepatitis B, hepatitis C, NAFLD, and others [27].

- ***The Use of Transient Elastography in LSM***

Two-dimensional Transient Elastography (TE) and low-frequency ultrasound (50 Hz) liver stiffness examination with Fibroscan is one of the noninvasive ways to measure the degree of liver fibrosis in patients with chronic liver disease [28]. This method is painless, fast, and has fewer complications [29]. In addition, Fibroscan can detect earlier degrees of fibrosis [30]. Therefore, Fibroscan can be considered an alternative to liver biopsy as one of the enforcers of diagnosing the degree of liver fibrosis [31]. The results of the liver stiffness examination are expressed in kilopascals (kPa) with a range of 2.5 - 75 kPa.

Measurements will be taken at the seventh to ninth intercostal space on the patient's right side from the anterior axillary line to the midaxillary line. The patient is directed to be in the dorsal decubitus position with the right hand in the maximal abduction position. The probe will be placed vertically on the skin surface. The liver area to be measured is unobstructed by large vascular structures and is at least six centimeters thick. The measurement depth is about 25 - 26 mm below the skin surface. Then, at least ten measurements will be taken [32].

The cut-off value of liver stiffness in chronic hepatitis B patients with Fibroscan for significant fibrosis (METAVIR F2/F3/F4) is ≥ 7.2 kPa, advanced fibrosis (METAVIR F3/F4) is ≥ 8.1 kPa, cirrhosis (METAVIR F4) is ≥ 11 kPa [33]. According to a study in 2014, the cut-off values for each degree of fibrosis are F0-F1 (≤ 6 kPa), ≥F2 (7.2 kPa), ≥F3 (8.1 kPa), and F4 (11 kPa) [34]. According to another study in 2014, the cut-off values of fibrosis F0, F1, F2, F3, and F4 are 4.64 ± 0.70, 6.06 ± 1.29, 6.34 ± 1.10, 12.89 ± 3.49, and 17.28 ± 4.27, respectively [35]. Liver stiffness is divided into three categories, namely, nonsignificant (<7.5 kPa), significant (7.5 - 10.1 kPa), and advanced (>10.1 kPa) [36].

- ***Factors Affecting LSM in Transient Elastography***

Fibroscan examination of liver stiffness cannot be performed in all patients. There are several limitations where the patient's condition may interfere with the measurement of liver parenchyma depth from Fibroscan, namely obesity (BMI above 25 kg/m2), narrowing of the intercostal gap, ascites, and pregnancy [6, 30]. In addition, the results of Fibroscan can also be affected by elevated ALT levels (ALT 2 times above the upper limit of normal), the position of the probe, and the operator's experience [28].

4. Spleen Stiffness Measurement

- ***Definition of Spleen Stiffness Measurement***

Spleen stiffness measurement is a benchmark used for spleen organ examination. An increase in splenic rigidity is not only due to static liver resistance caused by liver fibrosis. However, it can also express sinusoidal vasoconstriction, portal blood flow congestion, and portal hypertension caused by splenic fibrosis. Spleen stiffness is also affected by increased pressure in the portal vein, causing congestion and architectural changes in the splenic vasculature and fibrosis in the splenic organs [37].

- ***The Use of Transient Elastography in SSM***

Transient Elastography (TE) with Fibroscan can measure spleen stiffness and liver stiffness and is a noninvasive, quick, painless, and easy way to determine the degree of liver and spleen fibrosis. The device has a probe that can produce vibrations with low frequency (100 Hz for spleen stiffness) and moderate amplitude. Thus, it will produce elastic shear waves spreading throughout the tissue. The speed of the wave is influenced by the stiffness of a tissue, where the more complicated the tissue is, the faster the wave will spread. There are several criteria in determining whether a measurement is successful or not: (1) at least ten valid measurements, (2) a success rate of at least 60%, and (3) an interquartile range of at least 30% of the median measurement [38].

For the spleen stiffness examination, the patient is directed to be in the dorsal decubitus position, and the probe is placed at the ninth to eleventh intercostal space on the posterior sinistra axillary line. The probe is positioned perpendicular to the skin [32]. The patient is measured at least ten times, and the median of the measurements is taken as the final result. The Fibroscan result will be expressed in kilopascals (kPa). The cut-off value of spleen stiffness in chronic hepatitis B patients in determining the degree of liver fibrosis is F2-F3 (36 kPa) and cirrhosis/F4 (46 kPa) [7]. According to another study, the cut-off values of spleen stiffness F0, F1, F2, F3, F4 are e 13.83 ± 2.60, 17.96 ± 3.85, 22.93 ± 5.97, 33.64 ± 12.38, and 57.53 ± 16.40, respectively [35].

5. Correlation Between Spleen Stiffness and Advanced Liver Fibrosis

In chronic hepatitis B infection, liver fibrosis is a pathological process caused by viral liver damage [39]. This liver damage leads to liver stellate cells (HSCs) activation. This cell activation will promote fibroblast proliferation and accumulation of extracellular matrix, resulting in fibrosis [40]. The presence of fibrosis will increase liver stiffness, which will cause dysregulation of liver sinusoid endothelial cells and increase intrahepatic vascular resistance [41]. This microvascular dysfunction will cause increased pressure in the portal vein, which can lead to portal hypertension [42]. This increase in portal pressure may predispose liver fibrosis to progress to an advanced stage and worsen the portal hypertension itself [43]. This increase in portal pressure leads to congestion, spleen swelling, lymphoid tissue hyperactivation, angiogenesis, and fibrogenesis [46]. Fibrosis in the spleen will increase spleen stiffness. Furthermore, it will also induce splenic red pulp macrophages to produce TGF-β1, which is fibrogenetic. This TGF-β1 can enter the portal bloodstream so that it enters the liver, aggravating fibrosis in the liver. [8].

In addition, increased pressure in the sinusoids can also induce a stretching force on the perisinusoid cells (liver stellate cells, endothelial cells, hepatocyte cells, and macrophages). Liver stellate cells themselves are known to contract and respond to mechanical forces. Thus, the deposition of collagen is a result of increased stress [44]. In addition, spleen stiffness is also gaining attention as a noninvasive indicator of portal hypertension [45].

On the other hand, the stiffer the liver, the greater the pressure required to maintain adequate blood flow. Increased portal pressure can only maintain a portion of the portal flow. Therefore, the hepatic artery becomes the only blood vessel with high enough pressure to maintain hepatic blood flow. The increased pressure in the hepatic artery is triggered by the hepatic arterial buffer response (HABR) and hypoxic signaling. This leads to the development of prolonged fibrosis that is uniform and independent of etiology [44].

6. Recent Advances

In recent years, research has significantly advanced in assessing liver fibrosis in noninvasive diagnostic methods. Although liver biopsy is still considered the gold standard for liver fibrosis assessment, it is undeniable that innovative approaches increasingly replace it with minimal procedural risks and patient discomfort. One of the approaches, transient elastography (TE), has gained popularity as a noninvasive method for liver stiffness evaluation and liver fibrosis diagnosis. As transient elastography can provide a noninvasive, simple, and cost-effective method for liver stiffness evaluation and liver fibrosis diagnosis, it is a potential alternative method [47]. Another study reported a correlation between spleen stiffness and the degree of liver fibrosis [48]. The higher the spleen stiffness value, the higher the degree of liver fibrosis. In addition, several studies concluded that spleen stiffness can be one way to assess liver fibrosis, especially in conditions where LSM can be challenging [49, 50]. A study also states that combining LSM and SSM can efficiently improve the diagnosis of liver fibrosis [51].

Another area of interest is noninvasive liver fibrosis assessment using clinical parameters and biochemical tests, such as the APRI, KING scores, FIB-4 index, AST/ALT ratio, Zeugma scores, etc. These models were found to be reliable and simple methods for noninvasive liver fibrosis assessment. Moreover, they can improve diagnostic accuracy by ruling out advanced liver fibrosis in patients [52, 53].

CONCLUSION

Among the noninvasive diagnostic tools that have gained popularity, spleen stiffness measurement (SSM) is one of the leading markers in evaluating liver fibrosis. Studies have highlighted the correlation between SSM and liver fibrosis stages. Studies have also demonstrated the anatomical connection between the two organs, spleen and liver, which provides an advanced understanding of the pathophysiology of the liver and spleen stiffness. Furthermore, SSM can distinguish advanced liver fibrosis as well as diagnose portal hypertension. Unlike LSM, SSM shows more potential in conditions where LSM may be less reliable. The recent advances in understanding the pathophysiological mechanism

that influences liver and spleen stiffness, along with other clinical and biochemical parameters, have the potential to improve the patient's outcomes. Further research is required to validate SSM utility in a clinical setting and its threshold.

COMPLIANCE WITH ETHICAL STANDARDS

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No conflict of interest is to be disclosed.

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