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# CONTRIBUTION OF SHEARWAVE ELASTOGRAPHY IN THE EVALUATION OF HEPATIC FIBROSIS: PERFORMANCES IN HEPATITIS B E ANTIGEN NEGATIVE CHRONIC INFECTION

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## ABSTRACT

**Background:** The assessment of liver fibrosis represents a crucial step in the diagnosis and monitoring of patients with hepatitis B e antigen (Hbe Ag) negative chronic infection. The accurate assessment of the stage of fibrosis has seen the development of new ultrasound elastography methods in recent years. Among these methods, 2D-Shear Wave Elastography (2D-SWE) represents a technological revolution in the field of elastography. **Aim:** The aim of this work was to evaluate the performance and diagnostic value of 2D-SWE, compared to transient elastography (FibroScan) and the Fibrosis-4 (Fib-4) index in the accurate assessment of liver fibrosis in Hbe Ag negative chronic infection. **Methods:** A prospective, analytic study was carried out at the gastroenterology department B of La Rabta hospital in Tunisia during the period between July 2019 and June 2020. In order to carry out this study, patients followed up for HBe Ag negative chronic infection during the study period had a blood test. Hepatic elasticity had been measured by Transient elastography (Fibroscan) and abdomino-pelvic ultrasound coupled with a two-dimensional Shear wave elastography in the radiology department of La Rabta hospital. The investigations were performed less than two weeks apart. The various data were recorded on pre-established individual data sheets. The data were entered on computer using IBM® SPSS Statistics® version 22 statistical analysis software. At the end of this work, descriptive and analytical statistics were generated from these data. A comparison between the results of SWE and those of Fibroscan was carried out. **Results:** Our population included 30 patients. The mean age of the patients was 45.47 years (31-70 years). The sex ratio (M/F) was 0.66. Clinical and biological examinations of all patients revealed no evidence of hepatocellular failure or portal hypertension. The upper endoscopy showed no signs of portal hypertension. A dysmorphic liver was found on abdominal ultrasound in a single patient whose origin was hepatic steatosis. The mean value of hepatic elasticity measured by Fibroscan was 5.4 Kpa with extremes ranging from 3.4 to 7.1 Kpa. No significant fibrosis was noted. The mean value of liver elasticity measured by Shearwave elastography was 6.3 Kpa with extremes ranging from 4.59 to 7.19 Kpa. We noted a statistically significant correlation between hepatic elasticity measured by Fibroscan and that measured by Shearwave elastography ($r = 0.428$, $p=0.018$) with an estimated concordance rate of 43.7%. **Conclusion:** 2D-SWE is a powerful, simple and accessible means of assessing liver elasticity in patients with Hbe Ag negative chronic infection. Its integration into our clinical practice could contribute to the diagnosis, management and follow-up of these patients.

**KEYWORDS:** Hepatitis B, Elastography, Fibrosis, Elasticity imaging techniques.

## INTRODUCTION

Despite scientific and therapeutic advances, hepatitis B virus (HBV) infection continues to spread throughout the world. It remains a major public health problem and still represents a considerable burden on a global and national scale. The World Health Organisation estimates that over two billion people worldwide are infected with the virus.[1] Mortality is mainly due to complications, in particular cirrhosis and hepatocellular carcinoma, with more than 686000 deaths in 2013.[2] In 2018, an estimated 240 million people are chronic carriers of HbsAg.[2] There are wide variations in prevalence, with a higher prevalence among young men from sub-Saharan Africa, the Middle East, South-East Asia and the Pacific.[3] A new terminology has recently been defined to differentiate the phases in the natural history of HBV. Inactive HBV carrier state becomes Hepatitis B e antigen (HBeAg) negative chronic infection (HBeAg-negative chronicinfection).[4] HBeAg-negative chronic infection is defined in HBeAg-positive patients by the presence of anti-Hbe antibodies, HBV DNA below 2000 IU/ml and normal transaminases.[2] Assessment of liver fibrosis is an essential step in diagnosing the absence or minimal fibrosis that characterises these patients.[2] Liver biopsy

is the gold standard.[5] However, the morbidity and mortality associated with this invasive procedure are not negligible.[5] In recent years, new non-invasive tests have been developed to accurately assess the stage of fibrosis. The new elastography techniques represent a non-invasive alternative to biopsy for assessing the stage of liver fibrosis. Among these techniques, Shear Wave elastography or Supersonic Shear Imaging represents a new technological development in the field of elastography. It was developed in 2004 by a French laboratory, the Ondes et Acoustiques de Paris VII laboratory, which had already developed the FibroScan® technique a few years earlier.[6] It was introduced into imaging in 2005 on a standard ultrasound scanner (AixPlorer, Supersonic Imagine, Aix-en-Provence).[6] Like FibroScan® and ARFI, it is based on the principles of impulse elastometry, measuring the speed of propagation of a shear wave in tissue.[6]

The main aim of our study was to evaluate the performance and diagnostic value of Shearwave ultrasound elastography, compared with impulse elastometry (Fibroscan) and the Fib4 score, in the accurate assessment of liver fibrosis in HBe Ag -negative chronic infection.

## METHODS

It was a prospective, analytical study carried out in the gastroenterology department B of the Rabta Hospital in Tunisia. During the 1-year period between July 2019 and June 2020, the records of 30 patients treated for HBe Ag -negative chronic infection were collected.

We have included all patients aged 18 or over, with a positive HBsAg and anti-Hbe antibodies, HBV DNA less than 2000 IU/ml and normal transaminases.

We have exluded patients with associated chronic liver diseases, cardiac hepatopathy, neoplasia with hepatic metastases, hepatocellular carcinoma, HBV-HDV co-infection and patients in whom Shearwave elastography or Transient elastography was not possible.

In order to carry out this study, patients followed up for HBe Ag negative chronic infection during the study period had a blood test. Hepatic elasticity had been measured by Transient elastography (Fibroscan) and abdomino-pelvic ultrasound coupled with a two-dimensional Shear wave elastography in the radiology department of La Rabta hospital. We used a Resona 7 ultrasound scanner from the Chinese manufacturer Mindray. This device uses the 2D shearwave technique with the « Sound Touch Elastography » module, which is a module integrated into the ultrasound scanner with an exclusive « Ultrasound Wide Beam Tracking Technology » that enables 2D two-dimensional analysis and measurement of the degree of hepatic elasticity in real time. Liver elasticity measurements are obtained from the median of 10 measurements.

The investigations were performed less than two weeks apart. The various data were recorded on pre-established individual data sheets. The data were entered on computer using IBM® SPSS Statistics® version 22 statistical analysis software. At the end of this work, descriptive and analytical statistics were generated from these data. A comparison between the results of SWE and those of Fibroscan and Fib 4 SCORE was carried out. Statistical analysis was performed using Chi square test and student t test. In all statistical tests, p-value $<0.05$ was considered statistically significant.

## RESULTS

Our population included 30 cases.

The mean age was 45.47 ± 9.76 years and ranged from 31 to 70 years.The sex ratio was 0.66. There was a predominance of women: 18 women (60%) and 12 men (40%).

Ten patients were active smokers.Chronic alcoholism was noted in two patients.Scarification was noted in two patients.Unprotected sexual activity was noted in two patients.No patients were drug addicts.

Three patients were diabetic and two were hypertensive. All patients were diagnosed incidentally following a laboratory check-up.All patients were asymptomatic. No clinical signs of hepatocellular insufficiency or portal hypertension were found on examination.The mean duration of patient follow-up was 30.40 months (4-120 months).

The mean ASAT level was around 18.18 and the mean ALAT level was 17.12. The mean GGT level was 20.53. No cases of cytolysis or cholestasis were noted. The mean viral load was 614.63, with extremes ranging from 31 to 999. The results of the biological check-up are detailed in **Table I.**

**Table I: The results of the biological check-up.**

| | Average | Median | Standard deviation | Minimum value | Maximum value |
|---|---|---|---|---|---|
| **Viral load** | 614 | 632 | 379 | 31 | 999 |
| **Albumin** | 42 | 42 | 3 | 36 | 47 |
| **Alkaline phosphatase** | 106 | 82 | 58 | 45 | 272 |
| **Alanine transaminase** | 18 | 19 | 4 | 10 | 27 |
| **Aspartate transaminase** | 17 | 17 | 3 | 7 | 23 |
| **Gamma-glutamyl** | 20 | 20 | 7 | 9 | 39 |

| | | | | | |
|---|---|---|---|---|---|
| **transferase** | | | | | |
| **Total Bilirubin** | 6 | 6 | 2 | 3 | 13 |
| **Indirect Bilirubin** | 0.6 | 1 | 0.6 | 0 | 2 |
| **Direct Bilirubin** | 6. 2 | 5 | 2 | 3 | 11 |
| **Platelets** | 209647 | 199000 | 65572 | 58000 | 352000 |
| **Prothrombin Time** | 97 | 100 | 4 | 83 | 100 |
| **International normalized ratio** | 0.9 | 1 | 0.01 | 0.9 | 1 |
| **Alpha-2-Globulin** | 7 | 7 | 1.1 | 5 | 10 |
| **Gammaglobulin** | 12 | 13 | 3.9 | 7 | 18 |

No endoscopic signs of portal hypertension were noted.The echo-structure of the liver on abdominal ultrasound was homogeneous in 29 patients. A dysmorphic liver was found in only one patient, wich the origin was hepatic steatosis.
No cases of splenomegaly were noted.

The mean value of hepatic elasticity measured by Fibroscan was 5.4 Kpa with extremes ranging from 3.4 to 7.1 Kpa. No significant fibrosis was noted. The mean value of liver elasticity measured by Shearwave elastography was 6.3 Kpa with extremes ranging from 4.59 to 7.19 Kpa. The mean value of the Fib 4 score was 1.04 with extremes ranging from 0.3 to 3.95.

We noted a statistically significant correlation between hepatic elasticity measured by Fibroscan and that measured by Shearwave elastography (r = 0.428, p=0.018) with an estimated concordance rate of 43.7%.

Our study showed no significant correlation between Fib4 score and Fibroscan liver elasticity measurement (r=0.284; p= 0.269) with an area under the ROC curve (AUROC) of 0.4.

**Table II: Correlation between hepatic elasticity measured by Fibroscan, Shear wave elastography and FIB 4 SCORE.**

| | r | p |
|---|---|---|
| **SWE and Fibroscan** | 0,428 | 0,018 |
| **SWE and FIB4 SCORE** | 0,284 | 0,269 |

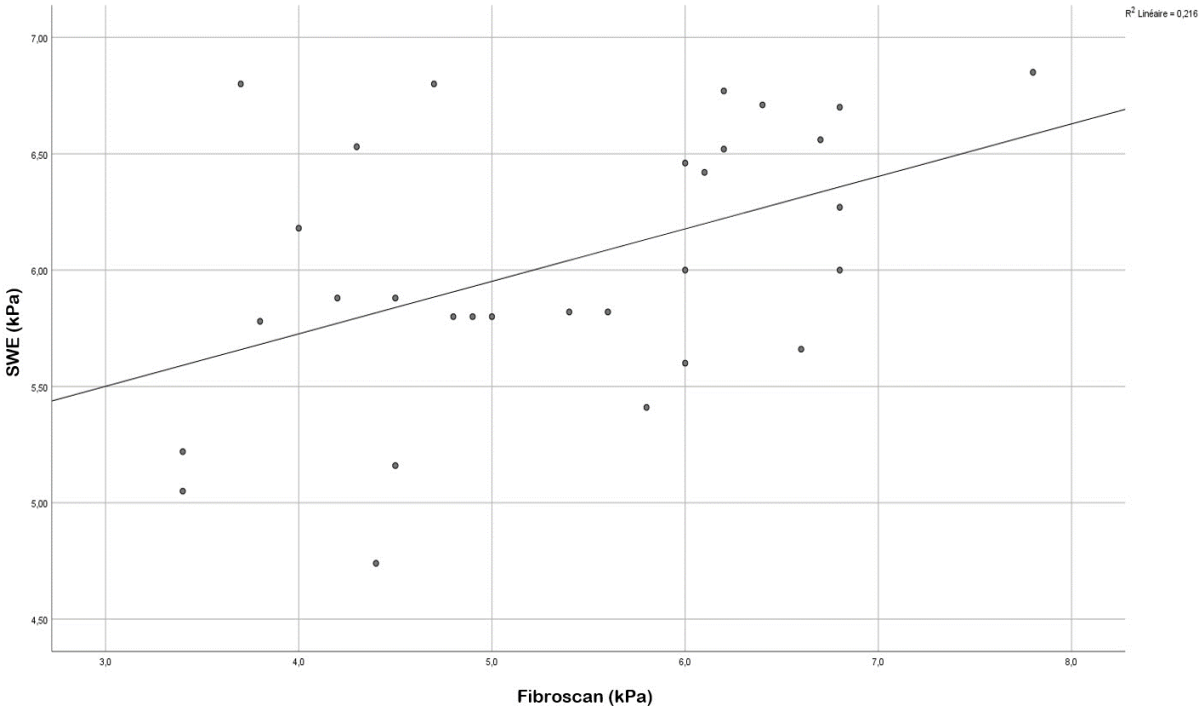


**Fig. 1: Correlation between Shear wave elastography and Fibroscan liver elasticity measurement.**

## DISCUSSION

Based on literature data, 2D-Shear Wave Elastography (2D-SWE) represents a technological revolution in the field of elastography.The aim of this work is to evaluate the performance and diagnostic value of 2D-SWE, compared to transient elastography (FibroScan) in the accurate assessment of liver fibrosis in Hbe Ag negative chronic infection.

Our study showed a good correlation between 2DSWE measurements and Fibroscan® (r= 0.428) with an estimated concordance rate of 43.7%.

Our study is unique, it was the first prospective Tunisian study to investigate the diagnostic performance of Shearwave ultrasound elastography in the accurate assessment of liver fibrosis in patients with HbeAg-negative chronic infection. The multidisciplinary nature of our work, involving gastroenterologists and radiologists, is also a strong point.

In our study, the mean age was 45.47 years. Our results were consistent with the literature. In most cohorts of patients with Hbe- Ag negative chronic infection, the population was young.[1-3] Indeed, advanced age is one of the main factors in the progression of liver disease. This could be explained by the greater number of co-morbidities in elderly patients, which may increase the risk of hepatic fibrosis.[1]

With regard to gender, a predominance of females has been reported in the majority of series in the literature, suggesting that the risk of progression to liver disease is low.[1-3] An Italian meta-analysis and several other studies have shown that the higher frequency of alcohol consumption and viral co-infections in males are factors in the progression of liver fibrosis.[1,4-6] This was the case in our study, where we found a predominance of women with little chronic alcoholism and few viral co-infections.

In our series, only two patients had a history of scarification, unprotected sexual intercourse was noted in two patients and none of the patients were drug addicts. These results could be explained by the predominance of women among the patients included in our study. These hepatitis risk factors have been shown to be more common in males.[7,8] However, the prevalence of these factors in our study may be underestimated due to under-reporting.

In our series, two patients were hypertensive and three patients were diabetic. There were no cases of obesity. In accordance with the literature, the prevalence of comorbidities, and essentially of metabolic syndrome, in patients followed for HBe Ag -negative chronic infection was low. In fact, the population included was young, as in most cohorts, which could explain the low incidence of comorbidities.[2,3] Also, in accordance with the literature, our series did not include patients being followed for another chronic liver disease, including NASH, which is strongly associated with obesity, dyslipidaemia, type 2 diabetes and metabolic syndrome.[3,9-11]

The mean value of hepatic elasticity measured by Fibroscan was 5.4 Kpa, with extremes ranging from 3.4 to 7.1 Kpa. No significant fibrosis was noted. Data from the literature corroborate the results of our study and confirm that the mean hepatic elasticity of patients with HBeAg-negative chronic infection is significantly lower than that observed in patients with HBeAg-negative chronic hepatitis.[3,12,13] Liver elasticity < 7.2 kPA corresponds to no or minimal fibrosis, which is part of the definition of HBeAg-negative chronic infection.[14]

The mean value of hepatic elasticity measured with 2D-SWE was 6.3 Kpa, with extremes ranging from 4.59 to 7.19 Kpa. These results are consistent with the literature. Indeed, Sporea et al showed in their study that the best threshold value assessed by 2D-SWE to predict a stage of F≥1 liver fibrosis was more than 7.1 kPa (AUROC=0.825).[15] Also, several studies have proven that 2D-SWE has excellent performance for non-invasive staging of liver fibrosis in hepatitis B patients.[16,17]

In accordance with the literature, we noted a statistically significant correlation between liver elasticity measured with Fibroscan and that measured with Shearwave elastography ($r = 0.428$, $p=0.018$) with an estimated concordance rate of 43.7%. Indeed, Foncea et al and several other studies have found a good correlation between the measurements of the two techniques, with statistical significance.[15,18,19]

## LIMITATION AND OUTLOOK

The major limitation of the study was the small number of included patients and the monocentric nature of the study. Our study was also restrictive, focusing only on patients with HBe-Ag negative chronic infection who did not have significant fibrosis. This restrictive nature of the study did not allow us to determine statistically significant threshold values for predicting significant fibrosis based on the results of the 2DSWE, which could be the subject of other comparative studies on a larger scale in order to confirm the results of our work.

## CONCLUSION

In conclusion, our study showed that 2D-SWE is a high-performance, simple and accessible method for assessing liver elasticity in patients with Hbe- Ag negative chronic infection. Its integration into our clinical practice could represent an alternative that couldcontribute to the diagnosis, management and follow-up of these patients.

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