Behind the Decrease of Liver Stiffness After Successful Hepatitis C Virus Eradication with Direct-Acting Antiviral Agents

Mauro Giuffrè[1,2], *Flora Masutti*[3], *Ivo Maria Crosato*[4], *Roberto Luzzati*[1,4], *Lory Saveria Crocè*[1,2,3]

[1]*Department of Medical Surgical and Health Sciences, University of Trieste, Trieste, Italy*
[2]*Fondazione Italiana Fegato, Trieste, Italy*
[3]*Liver Clinic, Trieste University Hospital, Trieste, Italy*
[4]*Infectious Disease Department, Trieste University Hospital, Trieste, Italy*

Cite this article as: Giuffrè M, Masutti F, Maria Crosato I, Luzzati R, Saveria Crocè L. Behind the decrease of liver stiffness after successful hepatitis c virus eradication with direct-acting antiviral agents. *Turk J Gastroenterol.* 2022;33(2):169-170.

Dear Editor,

We have read with great interest the article entitled "Significant Decrease in Liver Stiffness Detected by Two-Dimensional Shear-Wave Elastography After Treatment with Direct-Acting Antiviral Agents in Patients with Chronic Hepatitis C,"[1] which was recently published in *Turkish Journal of Gastroenterology*. The authors concluded that successful hepatitis C virus eradication considerably decreased liver stiffness measurement (LSM) in a relatively short period (12 weeks after treatment).

However, we would like to highlight some concerning issues raised from a critical reading of the article. In particular, our concerns regard patient stratification and how it may affect the actual results of the study.

First of all, what are the criteria that the authors applied to diagnose liver cirrhosis? The authors have stratified the patients into 2 subgroups: cirrhotic versus non-cirrhotic. However, from a graphical analysis of the box-plots in Figure 5, it appears that >50% of patients in the non-cirrhotic groups showed LSM compatible with liver cirrhosis[2,3] before treatment and <25% showed 12 weeks after the end of the treatment. The pre-treatment diagnosis of cirrhosis should not rely only on LSM. As shown in a recent study, patients may show LSM compatible with liver cirrhosis before treatment, without being cirrhotic at all.[4,5] Indeed, cirrhotic patients showed a median LSM reduction of 14%, whereas those who were improperly diagnosed as such showed a median LSM reduction that ranged from 37 to 57.5%.[4] According to a recent meta-analysis, around 50% of patients with baseline LSM compatible with advanced liver fibrosis (F3 or F4 stages), 6-12 months after achieving SVR12, showed post-treatment LSM consistent with lower degrees of fibrosis.[6]

Our second concern regards the absence of patients' stratification according to serum transaminases and how they may have impacted LSM decrease. Besides, the authors reported only the mean without standard deviation; therefore, the reader cannot understand the actual distribution of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) among the patients. Once more, a correct stratification is of uttermost importance given that the decrease of LSM is higher in patients with baseline ALT $\geq$ 2 times the upper limit of normality (ULN).[7] In particular, the probability of overestimation of 2 or more fibrosis grades is equal to 50% for AST and ALT values in the range of 2 ULN.[4] Serum transaminases have been linked to the degree of necro-inflammatory activity of the liver parenchyma. This concept should be taken into consideration for a critical evaluation of LSM results because it has been proven that before viral eradication LSM is mostly influenced by tissue congestion and inflammation due to viral activity, rather than actual fibrosis.[8,9] Therefore, it is safe to assume that it is markedly affected by hepatic congestion and inflammation, and that serum transaminase levels can be used to estimate the amount of ongoing damage indirectly. Besides,

Corresponding author: ***Mauro Giuffrè****, e-mail:* ***gff.mauro@gmail.com***
Received: ***August 18, 2020*** *Accepted:* ***November 26, 2020*** *Available Online Date:* ***December 24, 2021***

DOI: ***10.5152/tjg.2021.20736***

to address this issue, inflammation-adjusted cut-offs have been proposed, despite their employment in the clinical practice is still in debate.[10]

We believe that if the authors address these issues, the overall quality of their research will improve, by discussing an ongoing debate on fibrosis stratification in patients with ongoing liver injury.

Peer Review: Externally peer-reviewed.

Author Contributions: Consept – M.G., F.M., I.M.C., R.L., L.S.C.; Design - M.G.; Supervision - R.L., L.S.C.; Materials M.G., F.M., I.M.C., R.L., L.S.C.; Data Collection and/or Processing –M.G.; Analysis and/or Interpretation –M.G., F.M., I.M.C., R.L., L.S.C.; Literature Search – M.G., F.M., I.M.C., R.L., L.S.C.; Writing Manuscript – M.G., F.M., I.M.C., R.L., L.S.C.; Critical Review – M.G., F.M., I.M.C., R.L., L.S.C.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Main Points

- *Serum transaminases represent a confounding factor for liver elastography.*
- *Serum transaminases lead to fibrosis overestimation.*
- *Correct patients' stratification by serum transaminases is crucial when interpreting elastography measurements.*

REFERENCES

1. Yaraş S, Sezgin O, Üçbilek E, Özdoğan O, Altıntaş E. Significant decrease in liver stiffness detected by two dimensional shear-wave elastography after treatment with direct-acting antiviral agents in patients with chronic hepatitis C. Turk J Gastroenterol. 2020;31(2):142-147. [CrossRef]

2. Sporea I, Bota S, Gradinaru-Taşcău O, Sirli R, Popescu A, Jurchiş A. Which are the cut-off values of 2D-shear wave elastography (2D-SWE) liver stiffness measurements predicting different stages of liver fibrosis, considering transient elastography (TE) as the reference method? Eur J Rad. 2014;83(3):e118-e122. [CrossRef]

3. Giuffrè M, Macor D, Masutti F, et al. Spleen Stiffness Probability Index (SSPI): a simple and accurate method to detect esophageal varices in patients with compensated liver cirrhosis. Ann Hepatol. 2020;19(1):53-61. [CrossRef]

4. Giuffrè M, Fouraki S, Comar M, Masutti F, Crocè LS. The importance of transaminases flare in liver elastography: characterization of the probability of liver fibrosis overestimation by hepatitis C virus-induced cytolysis. Microorganisms. 2020;8(3). [CrossRef]

5. Giuffrè M, Fouraki S, Campigotto M, et al. Alanine aminotransferase and splenoportal dynamics affect spleen stiffness measured by point shearwave elastography in patients with chronic hepatitis C in the absence of significant liver fibrosis. J Ultrasound. 2021;24(1):67-73. [CrossRef]

6. Singh S, Facciorusso A, Loomba R, Falck-Ytter YT. Magnitude and kinetics of decrease in liver stiffness after antiviral therapy in patients with chronic hepatitis C: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018;16(1):27-38.e4. [CrossRef]

7. Pons M, Santos B, Simón-Talero M, et al. Rapid liver and spleen stiffness improvement in compensated advanced chronic liver disease patients treated with oral antivirals. Therap Adv Gastroenterol. 2017;10(8):619-629. [CrossRef]

8. Xie LT, Xu DX, Tian G, et al. Value of two-dimensional shear wave elastography for assessing acute liver congestion in a Bama minipig model. Dig Dis Sci. 2018;63(7):1851-1859. [CrossRef]

9. Piecha F, Paech D, Sollors J, et al. Rapid change of liver stiffness after variceal ligation and TIPS implantation. Am J Physiol Gastrointest Liver Physiol. 2018;314(2):G179-G187. [CrossRef]

10. Mueller S, Englert S, Seitz HK, et al. Inflammation-adapted liver stiffness values for improved fibrosis staging in patients with hepatitis C virus and alcoholic liver disease. Liver Int. 2015;35(12):2514-2521. [CrossRef]