MAYO CLINIC

Timucin Taner, MD, PhD
Mayo Clinic College of Medicine
200 First Street SW
Rochester, Minnesota 55905

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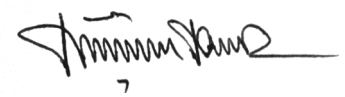
Jie Wang
Science Editor
World Journal of Gastroenterology

Dear Jie Wang,

Thank you for reviewing our opinion review titled **Significance of progressive liver fibrosis in Pediatric Liver transplants – A review of current evidence.** We appreciate the overall positive comments. We have edited the manuscript per the reviewer's comments. Please find below our point-by-point responses to the comments.

Please contact us if there are any questions or concerns regarding the manuscript.

Sincerely,



Timucin Taner, MD, PhD
Associate Professor of Surgery & Immunology
Surgical Director of Liver Transplantation
Mayo Clinic

Reviewer comments

1) *Page 3 – The sentence "Our own studies…" is not really clear to me.*

"Our own studies" implies the articles published by Taner et al from our center Mayo Clinic (references 12, 13). The wording has been modified to reflect this.

2) *Page 3 – It should be stated that liver biopsy is an imperfect gold standard (considerable sampling error).*

The sentence has been changed to: "liver biopsy remains the current gold standard for diagnosis of fibrosis though with some limitations which include sampling errors."

3) *Page 4 –Please specify that you are referring to Fibrotest in pediatric liver transplant patients.*

The sentence has been changed to: "Fibrotest in pediatric liver transplant patients is calculated from …"

4) *Page 4 - Why do the authors think that Fibrotest and ELF do not mirror liver fibrosis in pediatric liver transplant recipients?*

With the Fibrotest, the presence of rejection or cholestasis may cause non concordance with biopsy for fibrosis. Fibrosis can be present even with normal FT score. ELF was higher even in healthy transplant population suggesting that there is some altered extra cellular matrix turnover in pediatric liver allograft.

5) *Page 5 - Vibration-controlled transient elastography (and other non-invasive methods) have nearly replaced liver biopsy in adults (at least for staging liver fibrosis). Why is the situation in pediatric patients different? An advantage of transient elastography over liver biopsy is that it also provides information on portal hypertension.*

We thank the reviewer for highlighting this discrepancy in adult vs. pediatric liver transplant recipients. We agree that the elastography has become the primary method of fibrosis assessment in adults. The same cannot be said for pediatric transplant, due mainly to the limitations that include;

a. Requirement of pediatric probes
b. split grafts and midline position of allografts produce distorted signals
c. normal healthy transplant patients have higher score when compared to healthy non transplanted children

d. measuring spleen stiffness to diagnose portal hypertension in adults can be used in children however the published data in children is on biliary atresia and not on liver transplant recipients

The text has been edited to reflect these limitations in the revised manuscript.

6) *Page 5 - ARFI is not novel. There are many other US elastography methods - see Berzigotti et al. Dig Liver Dis 2018*

We agree that ARFI is not novel, thus the wording is now changed. All new elastography methods are still based on the ARFI technique. The differences in the techniques are due to software for pSWE (point shear wave elastography). These are used for characterizing other properties of liver tissue besides fibrosis like steatosis, focal liver lesions and portal hypertension. Our article pertains to progressive liver fibrosis and its quantification. Consequently, steatosis, portal hypertension and focal lesions are usually not encountered in the pediatric population.

7) *Page 5/6 - All of the mentioned studies on management approaches are non-randomized, and thus, of poor quality. Accordingly, the statement should be toned down. General comment: Fibrosis is not fibrosis. Always refer to the exact fibrosis stage when reporting clinical studies.*

We agree that the evidence is poor quality. We have now added this qualification to the text. Regarding the fibrosis scores, we avoided using fibrosis stage, as the studies cited reported two different score systems (METAVIR and LAFSc) to avoid confusion.

8) *Reference - Is "14" in table 2 a REF?*

This was an error, and the annotation has been deleted.