

Anita Kiani, M.D.

Department of Abdominal Imaging,
Rennes University Hospital Rennes 35033, FRANCE

a.kiani@hotmail.fr

+33 (0) 2.99.28.43.09

Response letter

Dear Editor,

Thank you very much for your time reviewing our article.

We carefully considered the reviewers' comments and adapted our article accordingly. We hope that you will be satisfied. Please let me know if you need anything else or if anything is wrong. We would be happy to answer any question you may have.

Sincerely,

Anita KIANI.

Reviewer 1: *In this study authors have aimed to evaluate the performance of elastography by ultrasound with ARFI in determining fibrosis stages in patients with ALD undergoing alcoholic detoxification in relation to biopsy. There are some issues that should be taken care. For example;*

1. Authors had used Wilcoxon's test for non-normally distributed variables. Can they explain why they had not perform the Mann Whitney U test?
 - **We agree. It was a Mann Whitney U test that was performed in our study. In French, we call it Wilcoxon test or Wilcoxon-Mann-Whitney test instead of Mann Whitney U test. Of course, it isn't the Wilcoxon signed-rank test. We changed in "statistical analysis": Comparisons between groups were made using t-tests for normally distributed variables, Mann Whitney U test for non-normally distributed variables.**
2. Results for γ -glutamyl transpeptidase, alkaline phosphatase, AST, ALT, ferritin and mean alcohol consumption do not seem as the parametric distribution due to the high level of standard deviations. Therefore, authors should firstly perform the Kolmogorow Smirnow analysis and then use parametric or non-parametric tests as appropriate. They should use mean \pm SD or median (25th-75th inter quartile ranges) respectively.
 - **Kolmogorow Smirnow analysis was performed to differentiate parametric and non-parametric parameters. Table 1 was changed and mean \pm SD or median (25th-75th inter quartile ranges) was used respectively.**

Table 1 Clinical and biochemical characteristics of patients with alcoholic liver disease.

Kolmogorow Smirnow analysis was performed, followed by parametric or non-parametric tests.

Mean±SD or median [25th-75th interquartile ranges] was used respectively.

Characteristic	Normal values	Patients included (n=82)
Sex (male/female)	NA	69/13
Age (y)	NA	43.8±10
Body mass index (kg/m ²)	NA	22.9±4.3
AST (IU/L)	0-35	62.0 [44 - 98]
ALT (IU/L)	0-35	67.0 [40 - 105]
γ-glutamyl transpeptidase (IU/L)	5-36	316.0 [141 - 654]
γ-globulin (g/L)	7-15	8.7 [7.4 - 10.4]
Alkaline phosphatase (IU/L)	30-120	90.5 [66 - 121]
Prothrombin (%)	70-130	101.2±12.4
Platelets (x10 ⁹ /L)	180-390	191.5±71.7
Iron (μmol/L)	18-22	16.2±8.1
Ferritin (μg/L)	male: 30-300 female: 20-150	478.0 [310.5 - 787.5] 404.0 [216.0 - 783.0]
Albumin (g/L)	40-60	39.0±4.9

3. Authors should present the results for univariate and multivariate ordinal regression analyses in separate table. I especially wonder the effect of gender since 84% of the patients is male. This may result with the gender bias in analysis.

- **Results for univariate and multivariate ordinal regression analyses were presented in separate table. We also present you here following a column with a multivariate analysis forced with gender as the reviewer wondered the effect.**

Characteristic	Univariate analysis OR (95%) <i>p-value</i>	Multivariate Analysis OR (95%) R ² =0.61; STPOA*: 0.76
ARFI	29.06 [8.59-98.33] <i>p</i> <0.0001	40.71 [9.94 - 166.7] <i>p</i> <0.0001
Sex Female Male	1 2.43 [0.79-7.42] <i>p</i> =0.12	
Age <50 y.o. ≥50 y.o.	1 4.01 [1.55 -10.39] <i>p</i> =0.004	1 4.73 [1.43 - 15.66] <i>p</i> =0.01
Body mass index	1.07 [0.97-1.18] <i>p</i> =0.19	

AST	1.00 [0.992 - 1.01] <i>p</i> =0.98	
ALT	0.99 [0.98 - 0.999] <i>p</i> =0.04	
γ -glutamyl transpeptidase	1.00 [1.000 - 1.002] <i>p</i> =0.05	
γ -globulin <10 \geq 10	1 7.42 [2.34 - 23.56] <i>p</i> =0.003	1 9.67 [2.19 - 42.63] <i>p</i> =0.004
Alkaline phosphatase	1.01 [1.001 - 1.012] <i>p</i> =0.02	
Prothrombin	0.002 [0.001-0.06] <i>p</i> =0.001	
Platelets	1.00 [0.99 - 1.01] <i>p</i> =0.93	
Iron	1.03 [0.97 - 1.08] <i>p</i> =0.33	
Ferritin	1.001 [1.000 - 1.002] <i>p</i> =0.06	
Albumin	0.90 [0.82 - 1.00] <i>p</i> =0.05	

STPOA*: Score test for the proportional Odds Assumption

Characteristic	Multivariate Analysis OR (95%) With gender forced in the model <i>R</i> ² =0.62; STPOA : 0.63
ARFI	57.97 [12.33 - 272.52] <i>p</i> <0.0001
Sex Female Male	1 0.39 [0.08-1.78] <i>p</i> =0.22
Age <50 y.o. \geq 50 y.o.	1 5.86 [1.66 - 20.71] <i>p</i> =0.006
Body mass index	
AST	
ALT	
γ -glutamyl transpeptidase	
γ -globulin <10	1

≥10	9.19 [2.01 - 42.09] <i>p</i> =0.01
Alkaline phosphatase	
Prothrombin	
Platelets	
Iron	
Ferritin	
Albumin	

4. In the abstract section authors should delete the following sentence "All patients gave written informed consent and the study was ethically approved"
 - **The sentence "All patients gave written informed consent and the study was ethically approved" was deleted.**

Reviewer 2: Dear Authors, I have read with great interest Your manuscript entitled "Acoustic radiation force impulse imaging for assessing liver fibrosis in alcoholic liver disease: a prospective study among patients undergoing alcoholic detoxification". The study showed the interesting algorithm between ARFI and biochemical parameters for the prediction of presence of cirrhosis. The results of this study were similar to previous literatures regarding the ARFI usefulness in the diagnosis of liver fibrosis, but, interestingly, the investigation was carried out within European population of patients with ALD undergoing alcoholic detoxification. Although it is a study with relatively small amount of cases to final conclusions, it will be helpful for further research in this field among specific subpopulation. The paper makes original contribution and it is clinically exhaustive. The manuscript is well written, seems accurate and well organized. The authors clearly presented any doubts concerning the investigation conducted by them. I only make minor corrections for the presentation of graphs and bibliography:

1. Figure 1- to unify subsections A and B should be capitalized in Figure 1;
 - **A and B were capitalized in Figure 1**
2. Figure 3- Y-axis should be described;
 - **Description was added for Y-axis "ARFI (m/s)" and for X-axis "Fibrosis"**
3. Figure 4- enter the alphabetic indication (A, B, C) for each chart.
 - **A, B and C were entered for each chart**

4. Perform correction for the appropriate bibliography style according to requirements for WJG, eg.: the name of the first author should be typed in bold-faced letters; page numbers should be complete
 - **The corrections were made for an appropriate bibliography style according to requirements for WJG.**

Editor's suggestions:

1. **The title was changed to be shorter (13 words): "Acoustic radiation force impulse imaging for assessing liver fibrosis in alcoholic liver disease"**
2. **Authors' departments were adapted to example.**
3. **Institutional review board statement was provided in a PDF format and signed by the corresponding author. Statement was mentioned as a footnote in the manuscript text.**
 - **The local ethics committee approved this study.**
4. **Clinical trial registration statement was provided in a PDF format and signed by the corresponding author. The registered URL and registration identification number were mentioned as a footnote in the manuscript text.**
 - **"This study is registred at <https://clinicaltrials.gov/ct2/show/NCT01789008?term=NCT01789008&rank=1>**
 - **The registration identification number is NCT01789008."**
5. **Informed consent statement was provided in a PDF format and signed by the corresponding author. Statement was mentioned as a footnote in the manuscript text.**
 - **"All study participants, or their legal guardian, provided informed written consent prior to study enrollment."**
6. **Conflict of interest statement was provided in a PDF format and signed by the corresponding author. Statement was mentioned as a footnote in the manuscript text.**
 - **"No conflict of interest."**
7. **Data sharing statement:**
 - **"No additional data are available."**
8. **Biostatistics statetement was mentioned in the text, and a certificate of statistical review signed by a biostatistician was provided in PDF format.**
 - **"The statistical methods of this study were reviewed by Jeff Morcet from**

Decomposable figure of Figures, whose parts were movable and could be edited, were provided. If you need anything else, please let me know, I can provide you original images by email.

The manuscript was updated according to the Guidelines and Requirements for Manuscript Revision-Prospective Study.

Please let me know if you need anything else or if you want me change something.