

Montreal, October 28th 2020

Dear Editor,

Please find enclosed our manuscript entitled “**Prevalence and predictors of nonalcoholic fatty liver disease in South Asian women with polycystic ovary syndrome**”, that we here resubmit after revision according to the reviewers’ comments.

A point by point reply to the reviewers’ comments is attached to the submission. We are grateful to the editor and reviewers for the time and energy they dedicated to our work and we hope that the paper will now be suitable for publication in *World Journal of Gastroenterology*.

Kindest regards on behalf of all the co-authors and thank you for your consideration.

Dr Mohamed Shengir

Dr Giada Sebastiani

On behalf of all the coauthors

Response to Editor and Peer Reviewers

Comments	Author response	Revision to manuscript
Editor:		
We are pleased to inform you that, after preview by the Editorial Office and peer review, as well as CrossCheck and Google plagiarism detection, we believe that the academic quality, language quality, and ethics of your manuscript (Manuscript NO.: 59608, Observational Study) basically meet the publishing requirements of the World Journal of Gastroenterology. As such, we have made the preliminary decision that it is acceptable for publication after your appropriate revision. Upon our receipt of your revised manuscript, we will send it for re-review. We will then make a final decision on whether to accept the manuscript or not, based on the reviewers' comments, the quality of the revised manuscript, and the relevant documents. Please follow the steps outlined below to revise your manuscript to meet the requirements for final acceptance and publication.	We are very grateful for the careful review and positive and constructive comments of the editorial board and reviewers. We provide a point-by-point response to reviewer's comment below.	
Reviewer 1:		
GENERAL Scientific Quality: Grade C (Good) Language Quality: Grade B (Minor language polishing) Conclusion: Minor revision Specific Comments to Authors: no comments	We thank the reviewer for the careful review.	

Reviewer 2:		
<p>GENERAL</p> <p>Scientific Quality: Grade C (Good)</p> <p>Language Quality: Grade B (Minor language polishing)</p> <p>Conclusion: Major revision</p> <p>Specific comments to the Authors: This study was aimed to investigate the prevalence and predictors of NAFLD and liver fibrosis by transient elastography (TE) with associated controlled attenuation parameter (CAP) in PCOS patients from South Asia. It is an interesting study. However, several important issues should be noted and revised.</p>	<p>We thank the reviewer for the careful review.</p>	
<p>1. About study population: the subjects enrolled in this article were only “PCOS patients (mean age 36.3 years) with no significant alcohol intake or viral hepatitis”. The lack of control group made the CAP and liver stiffness mentioned in the result part inaccurate. An accurate value was very important to discover the exact association between PCOS and NAFLD. So, the control group need to supplement.</p>	<p>We appreciate this important comment. The purpose of the study was to determine the prevalence of NAFLD in an unselected and consecutive population of South Asian women with PCOS through a routine screening program. It would have been difficult to match a proper control group since this was a screening study. Previously, similar screening studies with transient elastography and CAP in at risk populations had the same design as our current one, without a control group. See, for example:</p> <ul style="list-style-type: none"> a) Kwok et al, “Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study”, <i>Gut</i> 2016; b) Benmassaoud et al, “Screening for nonalcoholic steatohepatitis by using cytokeratin 18 and transient elastography in HIV mono-infection”, <i>PLOS ONE</i> 2018; c) Saroli Palumbo et al, “ Screening for non-alcoholic fatty liver disease in inflammatory bowel diseases: a cohort study using transient elastography”, <i>Inflamm Bow Dis</i> 2019; d) Lai et al, “Screening for non-alcoholic fatty liver disease in 	<p>Text revised, page 7,11</p>

	<p>patients with type 2 diabetes mellitus using transient elastography”, <i>J Gastroenterol Hepatol</i> 2019;</p> <p>e) Mikolasevic et al, “Screening for nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus using transient elastography - a prospective, cross sectional study”, Mikolasevic et al, <i>Eur J Intern Med</i> 2020.</p> <p>However, we fully agree with the reviewer comment on the need to prove the accuracy of transient elastography and CAP measurements. As such, we validated our TE measurements by reporting also the mean (standard deviation) liver stiffness and CAP measurements from another routine screening program for liver fibrosis that is running at our centre: patients with chronic hepatitis B. We included only female patients aged <50 years old, for an appropriate comparator with our PCOS population. Young patients with HBV are known to have low prevalence of NAFLD (Joo EJ et al, <i>Hepatology</i> 2016; Wang B et al, <i>Mol Med Rep</i> 2019;). As part of routine assessment at our centre, HBV also undergo CAP quantification during Fibroscan examination. In 125 female patients with HBV aged <50 years old, we found an mean CAP measurement of 214 dB/m (SD 55.5). NAFLD prevalence as per CAP criteria (>288 dB/m) was only in 8% in these young female patients with chronic HBV, which is much lower than patients with PCOS in our current study. We have added this information in the methods and results sections.</p> <p>See below the table of the first 25 HBV patients. We can provide the whole database of 125 patients upon request.</p>	
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	<table><tr><th>Gender</th><th>Age</th><th>probe type</th><th>Valid measures</th><th>E_med (kPa)</th><th>E_IQR / E_med (%)</th><th>CAP_med. (dB/m)</th></tr><tr><td>F</td><td>30</td><td>XL</td><td>10</td><td>4.8</td><td>29%</td><td>240</td></tr><tr><td>F</td><td>44</td><td>XL</td><td>10</td><td>8.6</td><td>14%</td><td>214</td></tr><tr><td>F</td><td>40</td><td>XL</td><td>10</td><td>9.0</td><td>18%</td><td>250</td></tr><tr><td>F</td><td>40</td><td>XL</td><td>10</td><td>4.8</td><td>29%</td><td>240</td></tr><tr><td>F</td><td>25</td><td>M</td><td>10</td><td>5.3</td><td>13%</td><td>246</td></tr><tr><td>F</td><td>36</td><td>M</td><td>10</td><td>4.4</td><td>14%</td><td>222</td></tr><tr><td>F</td><td>43</td><td>M</td><td>10</td><td>7.6</td><td>28%</td><td>259</td></tr><tr><td>F</td><td>38</td><td>M</td><td>10</td><td>5.8</td><td>29%</td><td>227</td></tr><tr><td>F</td><td>39</td><td>M</td><td>10</td><td>6.9</td><td>19%</td><td>170</td></tr><tr><td>F</td><td>38</td><td>M</td><td>10</td><td>6.9</td><td>29%</td><td>224</td></tr><tr><td>F</td><td>43</td><td>M</td><td>10</td><td>7.1</td><td>24%</td><td>261</td></tr><tr><td>F</td><td>19</td><td>M</td><td>10</td><td>4.6</td><td>17%</td><td>158</td></tr><tr><td>F</td><td>41</td><td>M</td><td>11</td><td>3.6</td><td>28%</td><td>229</td></tr><tr><td>F</td><td>37</td><td>M</td><td>10</td><td>2.8</td><td>7%</td><td>182</td></tr><tr><td>F</td><td>40</td><td>M</td><td>9</td><td>4.8</td><td>8%</td><td>233</td></tr><tr><td>F</td><td>41</td><td>M</td><td>10</td><td>4.0</td><td>20%</td><td>232</td></tr><tr><td>F</td><td>42</td><td>M</td><td>12</td><td>4.6</td><td>17%</td><td>194</td></tr><tr><td>F</td><td>43</td><td>M</td><td>10</td><td>2.5</td><td>8%</td><td>279</td></tr><tr><td>F</td><td>45</td><td>M</td><td>10</td><td>4.0</td><td>20%</td><td>295</td></tr><tr><td>F</td><td>36</td><td>M</td><td>10</td><td>3.7</td><td>24%</td><td>100</td></tr><tr><td>F</td><td>42</td><td>M</td><td>10</td><td>4.1</td><td>5%</td><td>174</td></tr><tr><td>F</td><td>37</td><td>M</td><td>10</td><td>2.9</td><td>7%</td><td>255</td></tr><tr><td>F</td><td>36</td><td>M</td><td>11</td><td>4.5</td><td>7%</td><td>170</td></tr><tr><td>F</td><td>45</td><td>M</td><td>10</td><td>3.5</td><td>14%</td><td>191</td></tr><tr><td>F</td><td>43</td><td>XL</td><td>12</td><td>4.7</td><td>11%</td><td>219</td></tr></table>	Gender	Age	probe type	Valid measures	E_med (kPa)	E_IQR / E_med (%)	CAP_med. (dB/m)	F	30	XL	10	4.8	29%	240	F	44	XL	10	8.6	14%	214	F	40	XL	10	9.0	18%	250	F	40	XL	10	4.8	29%	240	F	25	M	10	5.3	13%	246	F	36	M	10	4.4	14%	222	F	43	M	10	7.6	28%	259	F	38	M	10	5.8	29%	227	F	39	M	10	6.9	19%	170	F	38	M	10	6.9	29%	224	F	43	M	10	7.1	24%	261	F	19	M	10	4.6	17%	158	F	41	M	11	3.6	28%	229	F	37	M	10	2.8	7%	182	F	40	M	9	4.8	8%	233	F	41	M	10	4.0	20%	232	F	42	M	12	4.6	17%	194	F	43	M	10	2.5	8%	279	F	45	M	10	4.0	20%	295	F	36	M	10	3.7	24%	100	F	42	M	10	4.1	5%	174	F	37	M	10	2.9	7%	255	F	36	M	11	4.5	7%	170	F	45	M	10	3.5	14%	191	F	43	XL	12	4.7	11%	219	
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2. In the study design part, it was mentioned that NAFLD was defined as CAP >288 dB/m. Significant liver fibrosis (stage 2 and higher out of 4) was defined as TE measurement >8.0 kPa. But As we all know, the values of liver fibrosis measured by transient elastography would be influenced by many factors, including liver enzyme levels and cholestasis. In this article, how to differentiate real fibrosis from elevated	<p>We fully understand the reviewer’s comment.</p> <p>Regarding bilirubin, we added mean and standard deviation values to Table 1; no patient in our cohort had high bilirubin, as such no patient was at risk for false positive result of TE measurement due to elevated bilirubin/cholestasis.</p> <p>As for ALT, significant elevated ALT (>10 times upper limit of normal) is indeed associated with significant risk of false positivity of</p>	Text revised, Table 1, page 12																																																																																																																																																																																						

measured values influenced by liver enzyme and other factors?	<p>the Fibroscan examination, with increased liver stiffness due mostly to necroinflammation rather than liver fibrosis. Even milder elevations of ALT (>2 times upper limit of normal) could increase the risk of false positivity (Perazzo et al, International J Hepatol 2015). We thus conducted a sensitivity analysis, as per reviewer recommendation. Despite elevated ALT were observed in 23 patients (22.8%) in our study, none had ALT > 10 times upper limit of normal. Only 9 (8.9%) had ALT > 2 times upper limit of normal, of whom 3 had significant liver fibrosis (see Table below). If we would exclude these patients from the analysis, the prevalence of significant liver fibrosis would be: 6.9% in the whole cohort study, 4.3% if the 9 patients with ALT >2 times upper limit of normal were excluded. These data have now been added in the manuscript.</p> <table><tr><th>Patient #</th><th>PCOS duration (yrs)</th><th>HOMA-IR</th><th>BMI (kg/m²)</th><th>ALT (IU/l)</th><th>Triglycerides (mmol/l)</th><th>Liver stiffness (kPa)</th><th>CAP (dB/m)</th></tr><tr><td>2</td><td>5</td><td>1.3</td><td>31.8</td><td>53</td><td>0.87</td><td>6.1</td><td>302</td></tr><tr><td>3</td><td>9</td><td>10.8</td><td>34.1</td><td>102</td><td>2.42</td><td>9.9</td><td>375</td></tr><tr><td>4</td><td>11</td><td>3.2</td><td>31.8</td><td>62</td><td>0.93</td><td>10</td><td>317</td></tr><tr><td>11</td><td>7</td><td>10.9</td><td>30.1</td><td>88</td><td>1.36</td><td>9.3</td><td>373</td></tr><tr><td>13</td><td>6</td><td>5.4</td><td>28.3</td><td>53</td><td>1.12</td><td>3.1</td><td>270</td></tr><tr><td>15</td><td>7</td><td>5.9</td><td>31.2</td><td>78</td><td>1.66</td><td>6.1</td><td>346</td></tr><tr><td>16</td><td>9</td><td>7.9</td><td>36.4</td><td>101</td><td>1.37</td><td>6.1</td><td>386</td></tr><tr><td>17</td><td>3</td><td>3.8</td><td>27.9</td><td>66</td><td>2.91</td><td>6</td><td>324</td></tr><tr><td>23</td><td>9</td><td>2.1</td><td>30.2</td><td>58</td><td>2.38</td><td>7.4</td><td>315</td></tr></table>	Patient #	PCOS duration (yrs)	HOMA-IR	BMI (kg/m ²)	ALT (IU/l)	Triglycerides (mmol/l)	Liver stiffness (kPa)	CAP (dB/m)	2	5	1.3	31.8	53	0.87	6.1	302	3	9	10.8	34.1	102	2.42	9.9	375	4	11	3.2	31.8	62	0.93	10	317	11	7	10.9	30.1	88	1.36	9.3	373	13	6	5.4	28.3	53	1.12	3.1	270	15	7	5.9	31.2	78	1.66	6.1	346	16	9	7.9	36.4	101	1.37	6.1	386	17	3	3.8	27.9	66	2.91	6	324	23	9	2.1	30.2	58	2.38	7.4	315	
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3. There isn't any information about some important clinical characteristics such as bilirubin levels which could also affected the CAP.	Thank you for this comment. As stated above, no patient in our cohort had elevated bilirubin. Bilirubin values have now been added to Table 1.	Text revised, Table 1.																																																																																
4. The references between 2019~2020 should be added.	Recent references were added, currently 11 references are between 2019-2020. Thanks for this comment.	Text revised, page 19-26																																																																																
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Scientific quality: The manuscript describes a clinical and translational research of the prevalence and predictors of nonalcoholic fatty liver disease in South	We thank the science editor for the careful review and positive feedback.																																																																																	

<p>Asian women with polycystic ovary syndrome. The topic is within the scope of the WJG.</p> <p>Classification: Grade C and Grade C.</p> <p>Summary of the Peer-Review Report: This study was aimed to investigate the prevalence and predictors of NAFLD and liver fibrosis by transient elastography (TE) with associated controlled attenuation parameter (CAP) in PCOS patients from South Asia. It is an interesting study.</p> <p>Format: There are 3 tables and 5 figures. A total of 55 references are cited, including 9 references published in the last 3 years. There are no self-citations.</p> <p>Language evaluation: Classification: Grade B and Grade B.</p>		
1. Please provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and Written informed consent.	These documents have been provided, as requested.	Documents attached to the submission
2. The authors need to fill out the STROBE checklist with page numbers.	The STROBE checklist has been attached to the submission.	Document attached to the submission
3. I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)	The study was not funded. This has now been added in the manuscript. The investigators received only personal salary/research awards but no operating grant supported this study. We have attached the copy of the salary award.	Text revised, page 2
4. I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.	A PowerPoint file containing Figures 1, 2 and 3 has been provided. Please note, however, that the figures generated with STATA software (Figures 4 and 5) cannot be modified.	Document attached to the submission

5. I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.	The PMID and DOI have been added to the reference list.	Text revised, page 17-25
6. I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.	The “article highlight” section has been added at the end of the main text.	Text revised 16-17
7. The author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.	References have been formatted as requested.	Text revised, page 19-26
8. Please don’t include any *, #, †, §, ‡, ¥, @...in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as ^a P < 0.05, ^b P < 0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, ^c P < 0.05 and ^d P < 0.01 are used, and a third series of P values is expressed as ^e P < 0.05 and ^f P < 0.01.	Symbols have been removed from the manuscript. Superscript letters have been used for statistical significance, as requested.	Text revised, page 2, Table 1, Table 3
Editorial office director:		
1. I have checked the comments written by the science editor. I have changed the manuscript type “clinical and translational research” to “observational study”. The author should fill out each item of the STROBE checklist with page numbers.	The STROBE checklist has been attached to the submission.	Document attached to the submission

Company editor-in-chief:		
1. I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.	Thank you for the positive feedback.	