Author's response to reviews

Title: Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis

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Author's response to reviews: see over
Dear Dr. Le Good,

Please find enclosed the revised version of our manuscript entitled "Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis" to be submitted for publication in *BMC Gastroenterology*.

Thank you very much for the detailed review of our manuscript and for giving us the opportunity for revision. We have specifically addressed all issues and concerns outlined by yourself and the reviewers in a detailed POINT-BY-POINT revision and made the appropriate changes and supplementations in the manuscript.

We would be grateful for consideration of the present manuscript to be published in *BMC Gastroenterology*.

Sincerely yours,

Prof. Dr. S. Zeuzem  Prof. Ch. Sarrazin  Dr. M. Friedrich-Rust
POINT-TO-POINT RESPONSE

REVIEWER #1:

Major comments
1. For clinical practice, it is favorable to have the diagnostic validity and yield for each test. These data are available for chronic hepatitis C and PBC in previous studies. The authors should give the information of cut-offs and their diagnostic validities and yields in patients as a whole, patients with chronic hepatitis C and PBC.

The diagnostic validity was calculated as requested using cut-offs validated in larger previous studies for the respective tests. The results are shown in Table 3 of the revised version of the manuscript and respective changes supplementations were made in the manuscript (s. Table 3 and page 7, para 2 and page 8, last para of the revised manuscript).

2. Combined use of various non-invasive tests might increase the diagnostic accuracy. The authors could try to combine direct serum marker with indirect serum marker or with FibroScan to increase the diagnosis of minor to moderate hepatic fibrosis.

The primary aim of the present study was to compare FibroTest, ELF, and transient elastography. The correlation of the different non-invasive methods was high and the study population was small, so no relevant improvement is expected from the combinations in the present study. We suggest to perform this in future large prospective studies. This suggestion was included in the discussion section of the revised manuscript (s. page 10, para 3 of the revised manuscript).

3. In the conclusion, the author stated that serum markers are informative in higher proportions of patients than FibroScan. The conclusion was made due to 8 patients in the study population had unreliable results of FibroScan. To make this conclusion, it should be cautious considering small study population without prospectively consecutive enrollment.

This statement was deleted from the revised manuscript (s. page 12, para 3 of the revised manuscript).

4. Minor comment
The references should be arranged in the same format.

All referenced were re-checked for correct format (s. Reference list of the revised manuscript).

REVIEWER #2

Major comments:
Abstract
1. In the Background: Alfa2 macroglobulin is a direct marker of fibrosis (more specific of liver than hyaluronic acid) and therefore the terminology direct and indirect markers is misleading and must be avoided, as well as the suggestion that only ELF reflects extracellular matrix metabolism. Both tests included components that reflect in the serum what’s happen in the liver. We suggest a descriptive sentence: "FibroTest (FT) is the most frequently used serum fibrosis marker and consists of an algorithm of five fibrosis markers (alfa2-macroglobulin, apolipoprotein A1, haptoglobin, GGT, bilirubin). The Enhanced Liver Fibrosis (ELF) test consists of an algorithm of three fibrosis markers (hyaluronic acid, amino-terminal propeptide-of-type-III-collagen, tissue-inhibitor of matrix-metaloproteinase-1)."

We corrected this accordingly in the revised version of the manuscript (s. page 2, para 1 of the revised manuscript).

Introduction
2. Delete as in the abstract the too commercial descriptions of the tests, one that would be direct and the other one indirect. Just describe: "FibroTest (FT) is the most frequently used serum fibrosis marker and consists of an algorithm of five fibrosis markers (alfa2-macroglobulin, apolipoprotein A1, haptoglobin, GGT, bilirubin). The Enhanced Liver Fibrosis (ELF) test consists of an algorithm of three fibrosis markers (hyaluronic acid, amino-terminal propeptide-of-type-III-collagen, tissue-inhibitor of matrix-metaloproteinase-1)."
We corrected this accordingly in the revised version of the manuscript (s. page 3, para 1 of the revised manuscript).

3. Delete "which reflect alteration in liver function" which is unfair. Rational exist for all the components of these two tests. The components of ELF are not organ-specific which is not mentioned.

This was deleted as requested (s. page 3, para 1 of the revised manuscript).

Results

4. In the Table 1 (The patients characteristics), it is more suitable to give the means and the medians for biochemical parameters (AST, ALT and GGT) in the absolute value (units: IU/L) and not in number of the upper limit of normal (ULN), as the ULN for each parameter is dependent on the laboratory. (Ferard et al Clin Chem Lab Med 2005;43:549–553. and Ferard et al. Clin Chem Lab Med 2006;44:400–406)

This was changed accordingly in the revised manuscript (s. Table 1 of the revised manuscript).

Discussion

5. Delete in the 1st paragraph: "which demonstrated excellent diagnostic accuracies for the diagnosis and exclusion of liver cirrhosis, but only moderate diagnostic accuracies for discriminating mild (F0-1) from significant fibrosis (F2-4)." This sentence is a methodological error repeated for years when the spectrum effect and the absence of true gold standard are not taken into account. The differences in unadjusted AUROCs are a mathematical consequence of the spectrum effect (Poynard et al Clin Chem 2008). Furthermore biopsy even of 25 mm has the same spectrum effect versus the true gold standard the large surgical biopsy (Bedossa et al Hepatology 2003). Therefore, relatively to biopsy the performance between adjacent stages are equivalent than between extreme stages.

This was deleted as requested (s. page 9, para 1 of the revised manuscript).

6. In the 4th paragraph: the same remark as above the sentence "One study (23) has compared the FibroTest as an algorithm of indirect fibrosis markers with ELF as an algorithm of extracellular matrix metabolism..." is too commercial. The words indirect and extracellular matrix metabolism must be deleted.

This was deleted as requested (s. page 10, para 1 of the revised manuscript).

7. In the 8th paragraph: Authors cited the studies conducted with biomarkers in order to prove their prognostic value in terms of mortality and morbidity. The authors cited for the ELF score, the 6-years prognostic value evaluated in PBC patients and in a mixed etiology cohort and for FT, the 5-years prognostic value in HCV patients. It is fair to cite also the evaluations of the 4-years prognostic value of FT in HBV patients (Ngo et al. PLoS One. 2008; 3:e2573) and of the 10-years prognostic value of FT in patients with alcoholic liver disease (Naveau et al. Hepatology. 2009;49:97-105).

These additional studies were cited in the revised version of the manuscript (s. page 11, para 2 of the revised manuscript).

Minor comments:

Introduction

1. Delete "e" at the end of macroglobuline and bilirubine.

This was corrected accordingly (s. page 3, para 1 of the revised manuscript).

Materials and Methods

2. In the chapter on Blood Markers, the 2nd paragraph the reference 15 for the high risk of false positive/negative results is wrong (I advice replacement with the reference 29).

This was corrected accordingly (s. page 5, para 3 of the revised manuscript).

Results

3. In the 2nd paragraph, there is some confusion in the attribution of significance (p value) quoted between brackets as p<0.0001; it is not clear if the p value is related to the comparison of correlations of ELF and FT with
histology or the p value is related to the significance of correlation with histology of both ELF and FT (all $p<0.0001$).

The p value is related to the significance of correlation with histology of both ELF and FT (all $p<0.0001$). This was corrected accordingly (s. page 8, para 1 of the revised manuscript).

Discretionary Revisions
1. In the Table 2 (Results chapter), the adjusted AUROC is computed using an algorithm combining the observed DANA of the study with the observed AUROC for advanced fibrosis. The algorithm of calculation of adjusted AUROCs in order to avoid spectrum bias was done for FT in HCV patients and published by Poynard et al (reference 17). It is to be highlighted that the algorithm of Poynard et al (reference 17) is applicable only in HCV patients and only for FT. Assuming artificially that, using other methods (TE and ELF) and in other pathologies, the spectrum bias have the same profile as for FT in HCV, authors extrapolated the FT-specific algorithm to adjust all the AUROCs.

This was further clarified in the materials and methods-statistical analysis section where the calculation of DANA is described (s. page 7, para 1 of the revised manuscript).