Response to reviewer's comments

1. The word version document of the article has been provided.
2. Double spacing undertaken.
3. Comments section has been added.
4. Institutional review board statement has been signed and provided.
5. Conflict of Interest statement has been signed and provided.
6. Data sharing statement has been signed and provided.
7. Institutional animal care and use committee statement plus animal care and use statement. We have added in the cover letter that animals were not used.
8. Biostatistics statement has been signed and provided.
9. PubMed citation numbers and DOI citation have been added to the reference list and all authors have been listed. This has been revised throughout. I have provided the first page of the papers without PMID and or DOI. For those references that have not been indexed by PubMed, I have provided a copy of the first page with the full reference
10. Legends have been added to the figures describes in the discussion.
11. Second figure has been made more legible.
12. We have specified the units for Shear Wave Elastography (SWE) readouts in the methodology section of the manuscript.
13. All words abbreviated have been written in full initially including in the manuscript.
14. Age and gender has been added to the demographics text.
15. The information displayed in Table 1.1 to 1.5 has been modified as follows: - Table 1.1 now displays a demographic summary of age, gender and institution from which patients were recruited; Table 1.2 displays a demographic summary of the viral infections encountered; Table 1.3 displays a correlation between fibrosis staging by SWE and biopsy as well a correlation between fibrosis staging by APRI and biopsy. Tables 1.4 and 1.5 remain.
16. Elastography average and standard deviation as categorized in Table 1.3 and 1.4 have been removed because these did not add value.
17. Yes, it would be interesting to compare the accuracy of SWE across the three centers however in this study all SWE was performed in one center (Aga Khan University Hospital) to reduce SWE operator variability. In addition SWE equipment was not available in the other two centers. The authors agree that it would be interesting to compare SWE across centers in a follow-up study.
18. The results have been described in the order suggested.
19. The "Figure 1.7.3.1", "Figure 1.10.3.1" and "Table 1.10.3.1" that were mentioned in "Discussion" have been listed as Figure 4 and 5 and Table 3 respectively.
20. In "Introduction", the descriptions about characteristics and pathogenesis of liver fibrosis have been added. We have refered to and cited papers in Food Chem Toxicol. 2013;62:120 and Chem. Commun., 2015,51, 11064. All references have subsequently been arranged and numbered correctly.
21. **Statistical issues**

- The logistic regression methods need to be better explained

- The models used in this publication are all linear logistic models. The models were used to predict the histology groupings (for example F0-1 vs F2-4) using the predictor variables elastography median and APRI scores, age, gender and steatosis. The two histology groups to be compared were classified as 0 or 1. The histology grouping is essentially a variable with binary outcomes. The predictor variables were then used to assess their significance and importance in accurately predicting the histology based groupings

- Have authors tested nonlinear relationship between SWE readout and fibrosis stages?
  - No we have not. There was one key consideration that led to this decision. It was felt that since the linear model analysis using only SWE and steatosis shows an AUROC of 0.944 for the primary F0-1 vs F2-4 comparison, that a non-linear model (and there would be many to choose from) would not add much value. In addition to budgetary and time restrictions which would have substantially delayed the publication, ad-hoc unspecified analyses could lead to spurious findings.

- In addition, for Table 2, it will be helpful to provide the odds ratio and 95% CI for steatosis
  - Table 2 presents the results of the logistic regression analysis with all of the variables in the model. The only variables that were significant were SWE median and steatosis. The other variables were not significant at the 0.1 level except for APRI score which was significant only for the F0-1 vs F2-4 grouping. Table 3 presents the reduced model which includes only SWE median and steatosis. The AUROC of 0.944 for both models is identical implying a minimal or no influence from the variables excluded from the model. In fact, the confidence limits presented in Table 3 are extremely close to the ones we observed for the analysis presented in Table 2 but are not presented in the manuscript.

- The discussion on combining SWE and APRI or steatosis is a stretch in clinical use, as these values are not addable. The current study does not provide validation cohort to validate the regression algorithm
  - Our goal was to evaluate SWE and APRI in concert with other variables to see if a model that would be less expensive and easier to implement in practice could be used to minimize or reduce the number of liver biopsies. Given that the study included patients with one or more several viral diseases, it would have been very difficult to validate the results via another small study. We believe that this study – following some additional analysis – could establish the ground work for additional larger studies that could validate and perhaps refine these results.
- It is however valuable to provide some quantitative measure of how steatosis or BMI may be a limitation when using SWE and decrease its accuracy, a situation that may be very similar to Transient elastography

    - We agree. Unfortunately, when this study was initiated, the patients' height was not always recorded. As a result, BMI was not always available. A subgroup analysis could be performed using all of the variables considered in the study in addition to BMI. However, such a study would be smaller and potentially could introduce biases and/or spurious findings, as is true of any subgroup analysis.

- The elastography results seen in various viral entities are of limited value as this is not a prospective cohort study that specifically aim to recruit such patients in equal proportion (Table 1.3, first paragraph of discussion). The limited sample size does not allow meaningful conclusion. Such results can be considered as supplement
    - The goal of the study was not to restrict attention to the various viral entities but to see if an overall picture would emerge. Given the high degree of accuracy obtained (AUROC of 0.944 for the primary endpoint), the implication is that the model developed her may have broad usage. However, this needs to confirmed in a larger study with larger cohort sizes representing each of the viral entities encountered in this study.

- Further, the recommended use of APRI & elastography is not supported by the current study. It appears that the article argued quite convincingly that when SWE and APRI are in disagreement, SWE is much more likely to be accurate.
    - The results of this study indicate that APRI, in the presence of SWE and steatosis, is not a useful predictor of the histology results. However, the joint usage of SWE and steatosis is supported by the findings of this study. We agree that SWE is a much more accurate predictor than APRI (Table 1).

- On a statistical note, AUROC is not the percentage "chance of correctly identifying a patient's Fibrosis grouping" (pg 12). The latter is dependent on the cutoffs, when done correctly, will approximate AUROC. For example, in this study, F0 vs F1-4, only 82% of the time the SWE assignment was correct, whereas AUROC was 0.88
    - We stand corrected. The AUROC is a weighted average of the probabilities obtained from different cutoffs. So a high AUROC value is representative of high predictive probabilities across a broad range of cutoff values. The statement has been reworded.

- There appears to be a good correlation between the Elastography median scores and the Histology Fibrosis scores (Table 1.4)" The correlation can be expressed in a graph, that would be more clear
    - A box-plot has been provided.