Project Report Summary

QIBA 2014 Project Deliverables:

1. ***Literature review.*** Rank order list of potential confounders in order of perceived clinical importance.
2. ***Clinical study.*** Multivariate analysis of the effect of steatosis and inflammation on shear wave speed as determined by SWE.
    - Target recruitment 65-85.

QIBA 2014 Summary Report:

1. **Literature review:**
    - Comprehensive literature search comprising review of ~1,548 abstracts screened to identify all SWS papers and detailed review of ~ 102 SWS research papers completed.
    - Confounders identified (see detailed report below – pages 2-5).
    - Comprehensive report concerning confounders presented to QIBA US group and shared.
2. **Clinical study**
    - Target enrollment exceeded, with 242 subjects enrolled against a target of 85.
    - Single-reader pathology completed for all 242 subjects.
    - Statistical analysis including multivariate analysis completed (see detailed report attached – Pages 6-12).
3. **Work complete additional to listed deliverables:**
    - Completion of elastography eCRF, hosted at REDCap and publicly available.
    - Completion of pathology eCRF, hosted at REDCap and publicly available.
    - UPICT guidelines.
    - RSNA 2014 QIBA US poster: "RSNA/QIBA: Variability Sources and Potential Mitigation Strategies in Shear Wave Elastography for the Staging of Liver Fibrosis."

New Knowledge:

- Standard deviation within elastography values for each subject can be used as a quality factor.
- Standard deviation <20 appears to be the optimal quality factor in our dataset.
- Confirmation - Steatosis has no effect on SWS speed.
- Confirmation - Inflammation is an independent predictor of SWS.

Future Plans:

- **Manuscripts:**
    - Summary of Literature Review – "Technical and Clinical Confounders in Elastography".
    - Original research based on clinical study –
        1. Quality metrics for elastography.
        2. Establishing clinical confounders in elastography and correcting for their effects.

Note: Shear wave speeds have been documented as a measure of young's modulus of elasticity in kilopascals (kPa) throughout the report, and shear wave elastography (SWE) is the term used to represent the application of shear wave speeds to estimate liver fibrosis.

Detailed Report: Deliverable 1

Rank order list of potential confounders in order of perceived clinical importance:

- A literature review of 1,548 publications after a broad search was performed.
- 102 SWS and ARFI papers that studied confounders were identified.
- A Dropbox folder shared with the "QIBA SWS committee" contains a detailed Excel sheet reporting findings of these 102 papers.
- All potential confounders in the literature are:

Technical Factors	Imaging factors	Clinical Factors
1. Depth	1. Fasting/Meals	1. Steatosis
2. Probe	2. BMI	2. Inflammation
	3. Patient position	3. Right heart insufficiency
	4. Patient breathing	4. Cholestasis
	5. Lobe of liver	
	6. Reproducibility	

- Each parameter is described in detail in the shared Dropbox folder, with sub-folders containing research papers relevant to each parameter.
- Full-text of manuscripts that study these factors are available in these sub-folders.

Steatosis and inflammation are the most common pathological processes occurring in conjunction with fibrosis in chronic liver disease. A detailed literature review of these two factors found that:

- **Steatosis:** Extensive evidence shows that steatosis does not affect shear wave speed.
  - Relevant references are listed in **Annexure 1.**
- **Inflammation:** Extensive evidence inflammation increases shear wave speed, with some disagreement in the literature.
  - Inflammation influences SWS values **(References - Annexure 2)**
  - No correlation of SWS with inflammation **(References - Annexure 3)**

Annexure 1
(Steatosis has no effect on SWS)

References:

1. Yoneda M, Mawatari H, Fujita K, Endo H, Nozaki Y, Yonemitsu K, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). Dig Liver Dis [Internet]. 2008 May;40(5):371–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18083083&retmode=ref&cmd=prlinks

2. Friedrich-Rust M, Wunder K, Kriener S, Sotoudeh F, Richter S, Bojunga J, et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology. 2009 Aug;252(2):595–604.

3. Lupsor M, Badea R, Stefanescu H, Sparchez Z, Branda H, Serban A, et al. Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results. J Gastrointestin Liver Dis. 2009

Sep;18(3):303–10.

4. Fierbinteanu-Braticevici C, Andronescu D, Usvat R, Cretoiu D, Baicus C, Marinoschi G. Acoustic radiation force imaging sonoelastography for noninvasive staging of liver fibrosis. World J Gastroenterol [Internet]. 2009 ed. 2009 Nov 28;15(44):5525–32. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19938190&retmode=ref&cmd=prlinks

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8. Motosugi U, Ichikawa T, Niitsuma Y, Araki T. Acoustic radiation force impulse elastography of the liver: can fat deposition in the liver affect the measurement of liver stiffness? Japanese journal of radiology. 2011 Sep 29;29(9):639–43.

9. Ebinuma H, Saito H, Komuta M, Ojiro K, Wakabayashi K, Usui S, et al. Evaluation of liver fibrosis by transient elastography using acoustic radiation force impulse: comparison with Fibroscan((R)). J Gastroenterol. 2011 Oct;46(10):1238–48.

10. Rizzo L, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S, et al. Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. Am J Gastroenterol. 2011 Dec;106(12):2112–20.

11. Chen S-H, Li Y-F, Lai H-C, Kao J-T, Peng C-Y, Chuang P-H, et al. Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C. BMC Gastroenterology [Internet]. 2012;12(105):105. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22877310&retmode=ref&cmd=prlinks

12. Guzmán-Aroca F, Frutos-Bernal MD, Bas A, Luján-Mompeán JA, Reus M, Berná-Serna J de D, et al. Detection of non-alcoholic steatohepatitis in patients with morbid obesity before bariatric surgery: preliminary evaluation with acoustic radiation force impulse imaging. Eur Radiol. 2012 Nov;22(11):2525–32.

13. Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology. 2012 Dec;56(6):2125–33.

14. Bota S, Sporea I, Sirli R, Popescu A, Jurchis A. Factors which influence the accuracy of acoustic radiation force impulse (ARFI) elastography for the diagnosis of liver fibrosis in patients with chronic hepatitis C. Ultrasound Med Biol. 2013 Mar;39(3):407–12.

15. Friedrich-Rust M, Buggisch P, de Knegt RJ, Dries V, Shi Y, Matschenz K, et al. Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B. J Viral Hepat. 2013 Apr;20(4):240–7.

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Annexure 2
(Inflammation affects SWS)

References:

1. Friedrich-Rust M, Wunder K, Kriener S, Sotoudeh F, Richter S, Bojunga J, et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology. 2009 Aug;252(2):595–604.

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5. Ebinuma H, Saito H, Komuta M, Ojiro K, Wakabayashi K, Usui S, et al. Evaluation of liver fibrosis by transient elastography using acoustic radiation force impulse: comparison with Fibroscan(®). J Gastroenterol. 2011 Oct;46(10):1238–48.

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7. Yoon KT, Lim SM, Park JY, Kim DY, Ahn SH, Han K-H, et al. Liver stiffness measurement using acoustic radiation force impulse (ARFI) elastography and effect of necroinflammation. Dig Dis Sci. Springer US; 2012 Jun;57(6):1682–91.

8. Guzmán-Aroca F, Frutos-Bernal MD, Bas A, Luján-Mompeán JA, Reus M, Berná-Serna J de D, et al. Detection of non-alcoholic steatohepatitis in patients with morbid obesity before bariatric surgery: preliminary evaluation with acoustic radiation force impulse imaging. Eur Radiol. Springer-Verlag; 2012 Nov;22(11):2525–32.

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Annexure 3
(Inflammation does not affect SWS)

1. Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology. Wiley Subscription Services, Inc., A Wiley Company; 2012 Dec;56(6):2125–33.

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Detailed Report: Deliverable 2

Multivariate analysis of the effect of steatosis and inflammation on shear wave speed.

Study Design:

- Consecutive patients scheduled for a liver biopsy in our hospital underwent elastography prior to the liver biopsy.
- 10 elastography values were obtained from the tight upper lobe via an intercostal approach.
- Liver biopsies were read by a single sub-specialist pathologist (as per the detailed Pathology case report form).

Study Results:

Recruitment: 242

Pathology Review: Completed for 242 cases

Results:

1. Summary and evaluation of best statistical method to calculate representative value of liver stiffness. **(Annexure 1)**
2. Fibrosis **(Annexure 2)**
    - Shear wave speed (SWS) represented by a young's modulus of elasticity in kPa correlate with fibrosis stage ($p<0.001$, $r=0.498$)
    - Receiver-operating characteristic (ROC) curves showed an area under the curve (AUROC) of **0.84 (0.78-0.91).**
3. Steatosis **(Annexure 3)**
    - Steatosis does not correlate with SWS ($p = 0.229$, $r = -0.086$)
4. Inflammation **(Annexure 4)**
    - SWS correlates with the total activity score as assessed by the METAVIR scoring system ($p <0.001$, $r = 0.398$).
5. Multivariate analysis **(Annexure 5)**
    - Inflammation and fibrosis are independent predictors of SWS ($p<0.001$) while steatosis is not a significant predictor.
    - The effect of inflammation on fibrosis differs in each stage of fibrosis. Subgroup analysis to follow.

Annexure 1 – Statistical Analysis

Total number of patients recruited = 242
Pathology available = 242

Excluded = 28
Allografts = 24
Granulomatous = 1
Not enough images/very poor images = 3

Total number of cases included in analysis = 214

Statistical method used to calculate Median SWE value as an estimate of Young's modulus in kPa.
Different statistical methods of calculating the SWE value or selecting patients based on the obtained SWE values were tested and are listed below:

	Abbreviation	Explanation
1.	All	All cases without exclusion of any SWE values
		Excluding certain SWE values for each subject
2.	IQR	Median SWE value is calculated after dropping off values below the 25th percentile and above the 25th percentile.
3.	TM5	Mean SWE value is calculated after dropping off the lower 5% and highest 5% values.
4.	TM10	Mean SWE value is calculated after dropping off the lower 5% and highest 10% values.
5.	TM25	Mean SWE value is calculated after dropping off the lower 5% and highest 25% values.
		Selecting subjects
6.	SD<20	Excluding cases that have a standard deviation of ≥20 in the obtained SWE values.
7.	SD<10	Excluding cases that have a standard deviation of ≥10 in the obtained elastography values.
8.	SD<5	Excluding cases that have a standard deviation of ≥5 in the obtained elastography values.

	All	IQR	TM5	TM10	TM25	SD<20	SD<10	SD<5
Total	**214**	**214**	**214**	**214**	**214**	**195**	**179**	**160**
F0	73	73	73	73	73	63	61	58
F1	88	88	88	88	88	81	75	67
F2	26	26	26	26	26	26	23	20
F3	21	21	21	21	21	20	17	14
F4	6	6	6	6	6	5	3	1
SC	0.41	0.41	0.368	0.368	0.397	**0.498**	**0.456**	0.431
AUROC	0.79	0.79	0.77	0.77	0.78	**0.84**	**0.855**	0.86

- Statistical methods used to obtain the representative SWE value without excluding any cases did not show better results.
- However, selecting cases that have a relatively uniform SWE value i.e. standard deviation less than 20 and standard deviation less than 10 did show a significant improvement in accuracy. Hence cases that had a standard deviation <20 amongst all obtained SWE values, were selected for analysis. Median SWE values were used.

Annexure 2 - Fibrosis

All Measurements:

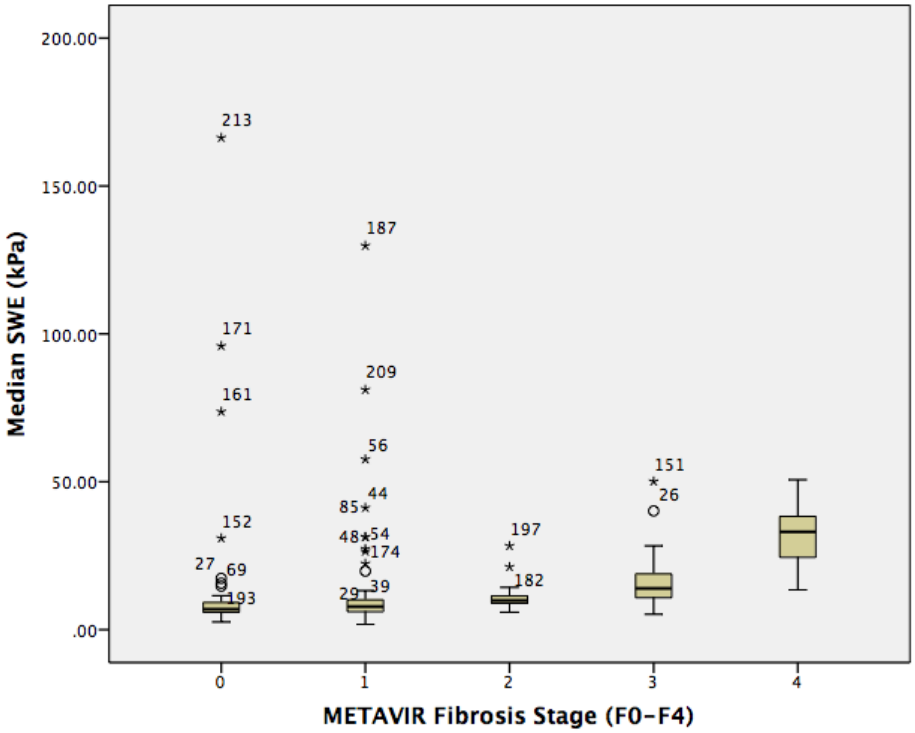


Figure 1: SWE values as plotted against Fibrosis stages (F0-F4) for all enrolled cases (n=214)

Selecting cases with standard deviation less than 20.

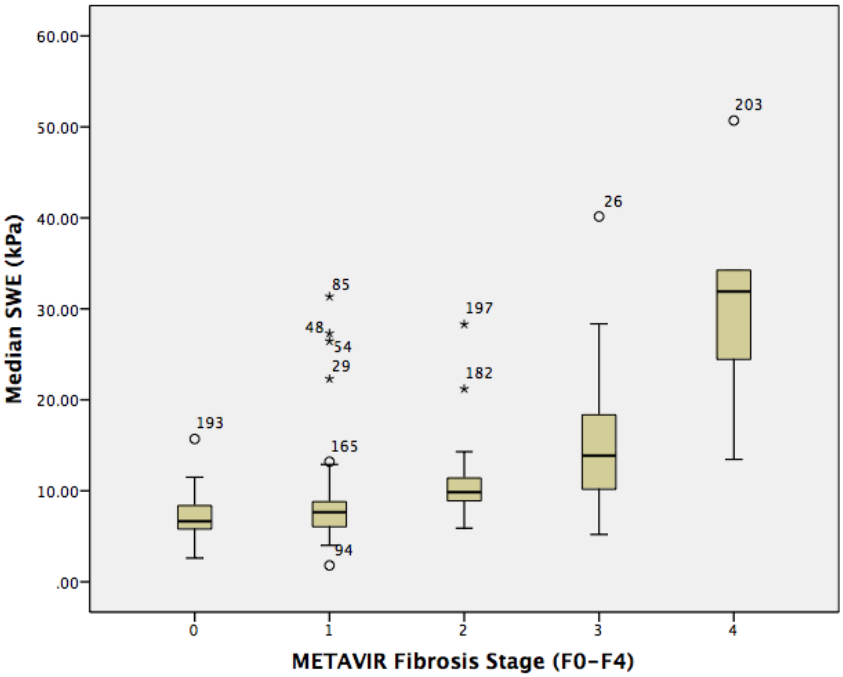


Figure 2: SWE values as plotted against Fibrosis stages (F0-F4) for selective cases when standard deviation in obtained SWE values less than 20 (n=195)

Values for each fibrosis grade for selective patients (n=195)

Fibrosis	F0	F1	F2	F3	F4
Median	6.65	7.65	9.85	13.88	31.9
Mean	7.18	8.49	10.83	15.86	30.95
95%CI	6.61-7.75	7.44-9.55	8.96-12.71	12.02-19.69	13.94-47.96
Std.Dev	2.26	4.78	4.65	8.20	13.70
Min.	2.6	1.80	5.90	5.20	13.45
Max.	15.70	31.35	28.30	40.15	50.70

Area under the ROC curve

- **Area under the ROC curve to differentiate significant fibrosis (F2-F4) from lesser degrees of fibrosis (F0-F1) is 0.84 (0.78-0.91)**

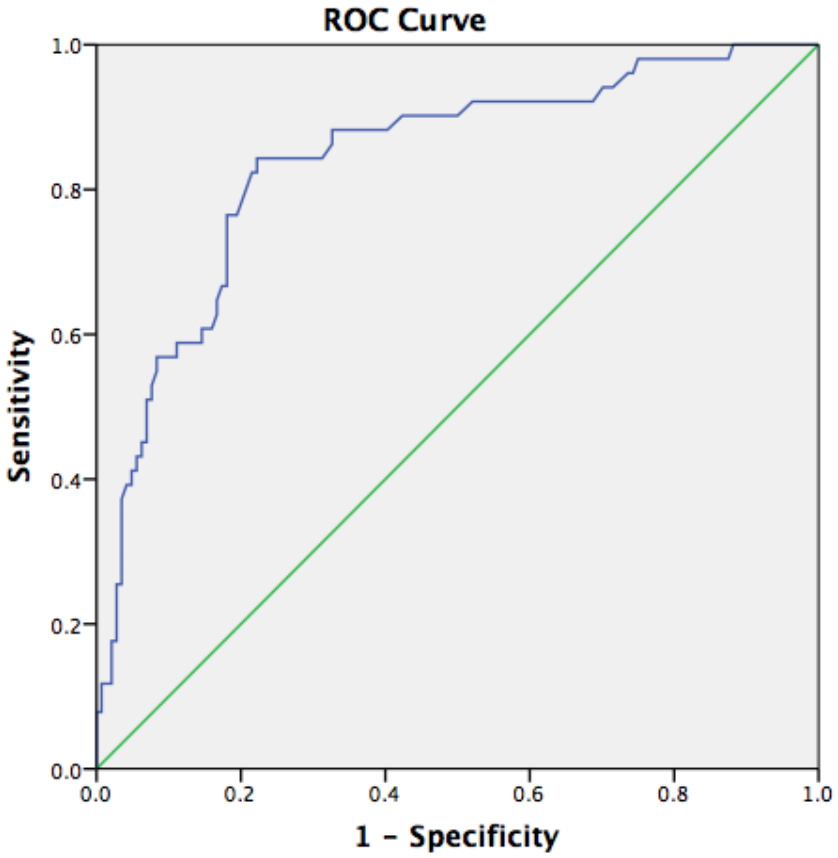
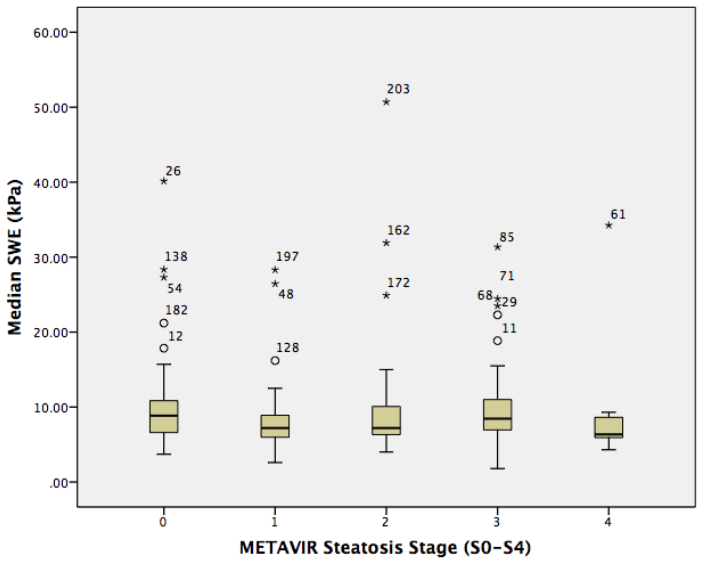


Figure 3: Receiver operating characteristic curve that differentiates higher degrees of fibrosis (F2-F4) from lesser degrees of fibrosis (F0-F1).

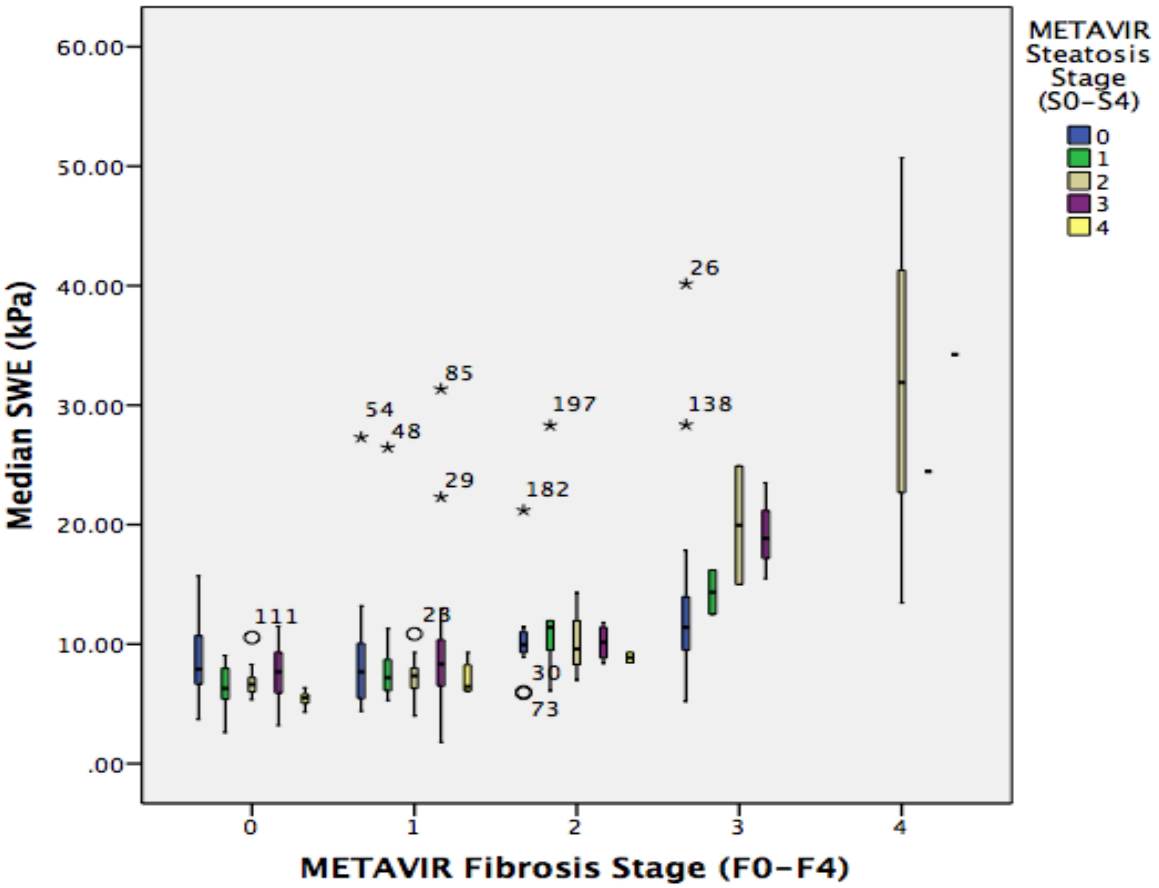
Annexure 3 - Steatosis

Steatosis Stage	Number
0	70
1	39
2	31
3	40
4	15
Total	195

Table: Number of subjects in each stage of steatosis



Box and whisker plot that charts median SWE values for each steatosis stage



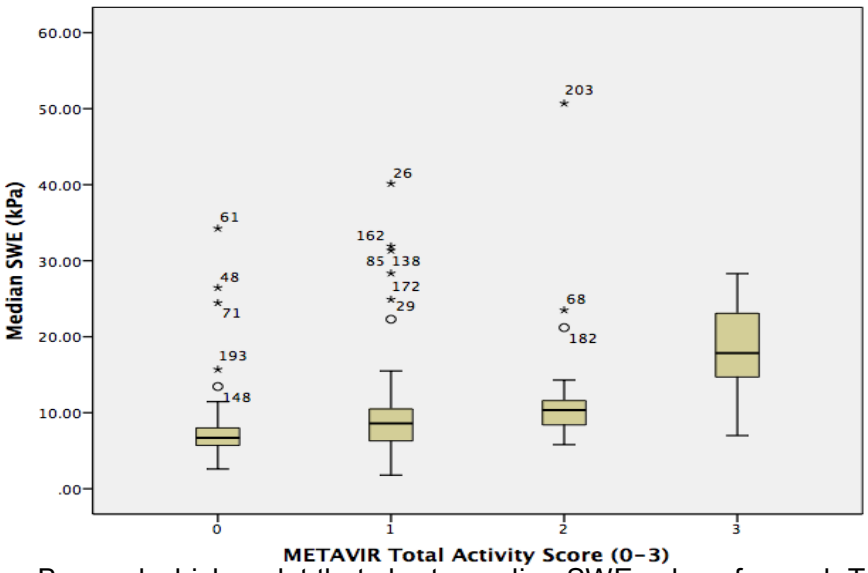
Box and whisker plot that charts median SWE values for each steatosis stage within each fibrosis stage. Steatosis stages are color coded as per the index on the top-right.

Spearman's Correlation with steatosis (r=-0.086 p = 0.229)

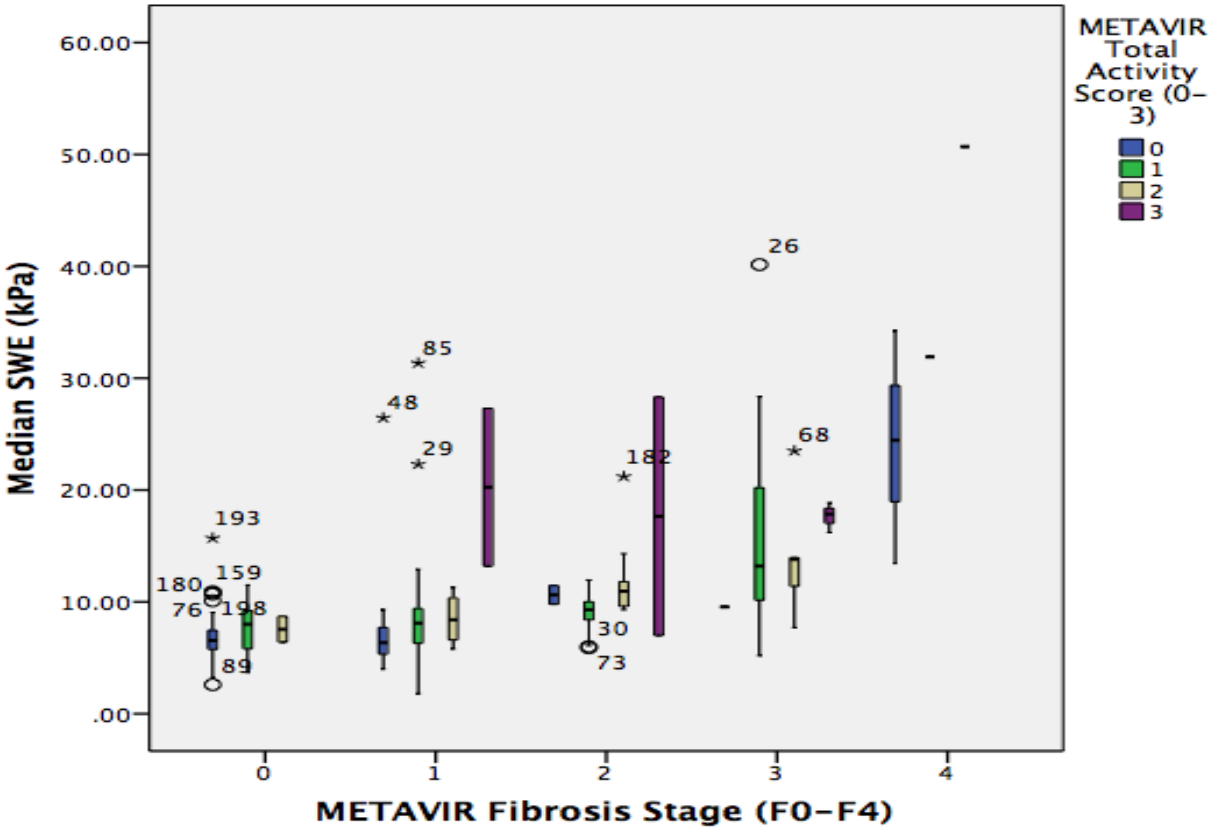
Annexure 4 - Inflammation

TAS Score	Number
0	70
1	91
2	27
3	7
Total	195

Table: Total activity score (TAS) On METAVIR staging system



Box and whisker plot that charts median SWE values for each Total activity score that represents inflammation on the METAVIR system.



Box and whisker plot that charts median SWE values for each inflammation stage within each fibrosis stage. Total activity scores are color coded as per the index on the top-right.

Spearman's correlation with the total activity score p<0.001, r= 0.398

Annexure 5
Multivariate regression analysis to study the effect of steatosis and inflammation on SWE in the presence of fibrosis

Tests of Model Effects

Source	Type III		
	Wald Chi-Square	df	Sig.
(Intercept)	591.943	1	.000
MET_TAS	32.659	3	.000
MET_Fibrosis	144.164	4	.000
MET_Steatosis	4.344	4	.361
MET_Fibrosis * MET_TAS	39.081	10	.000

Dependent Variable: Median SWE (kPa)
Model: (Intercept), MET_TAS, MET_Fibrosis, MET_Steatosis, MET_Fibrosis * MET_TAS

1. Inflammation and fibrosis are independent predictors of SWE ($p<0.001$) while steatosis is not a significant factor.
2. The effect of inflammation on fibrosis differs in each stage of fibrosis.