Replacement of Transient Elastography (Fibro Scan) with Combination of Cheap and Readily Available Serum Indices and Development of Novel Fibrosis Index (NFI)

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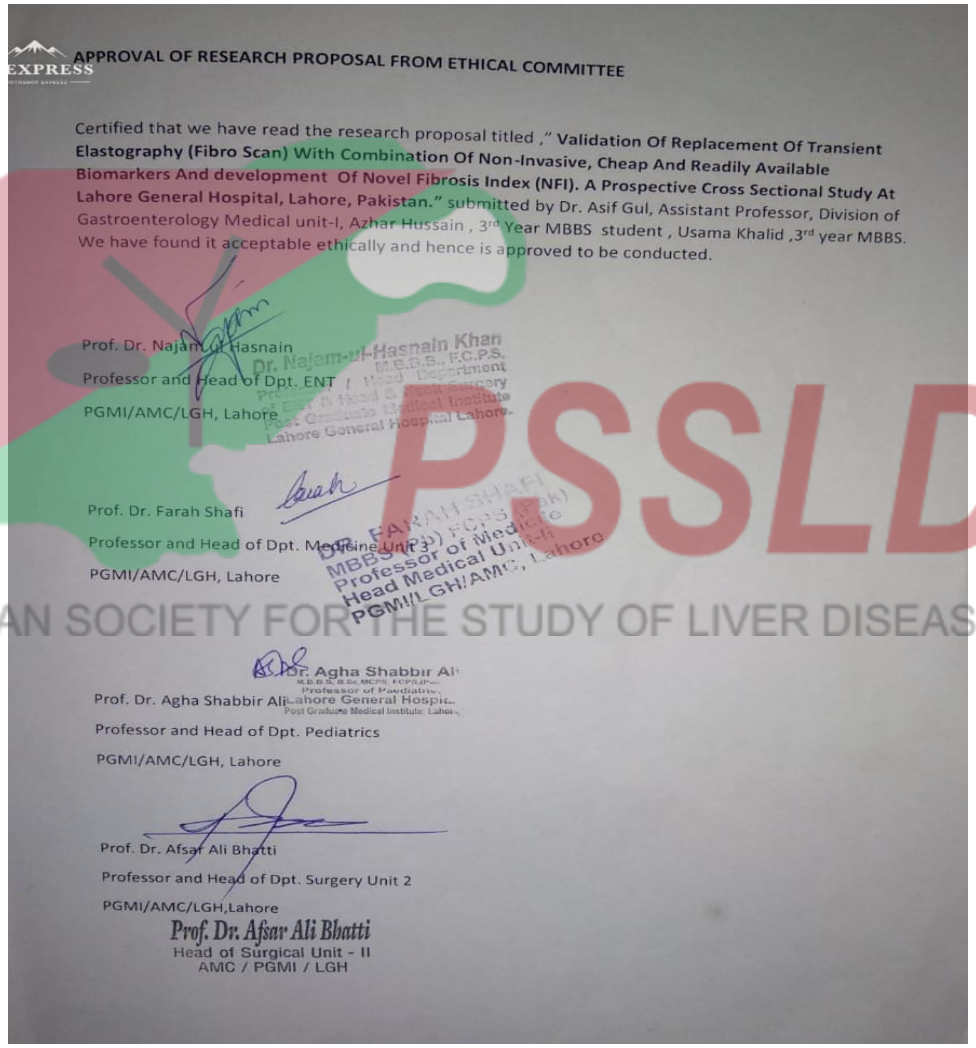
Ethical approval



EXPRESS

APPROVAL OF RESEARCH PROPOSAL FROM ETHICAL COMMITTEE

Certified that we have read the research proposal titled ," **Validation Of Replacement Of Transient Elastography (Fibro Scan) With Combination Of Non-Invasive, Cheap And Readily Available Biomarkers And development Of Novel Fibrosis Index (NFI). A Prospective Cross Sectional Study At Lahore General Hospital, Lahore, Pakistan.**" submitted by Dr. Asif Gul, Assistant Professor, Division of Gastroenterology Medical unit-I, Azhar Hussain , 3rd Year MBBS student , Usama Khalid ,3rd year MBBS. We have found it acceptable ethically and hence is approved to be conducted.

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BACKGROUND

03:47

Every 03:47 minutes someone dies from hepatitis C in Pakistan

(World Health Organization. Pakistan tackles high rates of hepatitis from many angles. 11 July 2017)

- According to WHO report 2018, Pakistan has the second highest prevalence of hepatitis C, affecting about 9% of country's population (1,2).
- Chronic viral infection cause multiple waves of inflammation which involves deposition of extracellular matrix resulting in scarring and progressive fibrosis over time ultimately leading to liver cirrhosis (3) .

- Identification of infected individuals early in the disease process is the crucial point of management and follow-up. It is the assessment of progression to cirrhosis that is high priority in devising treatment plan of each patient (4).

- There had been an era of liver biopsy but it is obsolete nowadays because its has many shortcomings like bile leakage, hemorrhages, infection, severe right hypochondriac pain, lacerations and other severe complications(5).

- EASL recommend the use of NITs (MRI and transient elastography i.e. Fibro Scan) which are precise and specific but are not cost- effective and patient's pocket friendly.

- So, various non-invasive biomarkers and indices of fibrosis have been developed by many scientists for reliable assessment of progression of fibrosis in hepatitis C (6).

Objective

Validation of pre-existing indices and our newly developed index, Novel Fibrosis Index(NFI) and its correlation to transient elastography (Fibro scan)

Materials and Methodology

Study

Cross sectional comparative study

Setting

Hepatitis Clinic and Gastroenterology Unit; Lahore General Hospital, Lahore

Period

Started in 11 Feb 2017 to 29 July 2019.

Inclusion Criteria

- Hepatitis C infected patients confirmed by presence of HCV RNA in their serum by PCR.

Exclusion Criteria

- The patients having hepatocellular carcinoma and co-infection of hepatitis B and C were excluded.

Calculation and Development of Novel Fibrosis Index (NFI)

- Novel Fibrosis Index (NFI) was developed by observing the various relationships and variations of **serum bilirubin, alkaline phosphatase, platelet count and serum albumin** in various liver fibrosis stages from liver functions test (LFTs) and complete blood count (CBC) :

- $$NFI = \left[\frac{Bilirubin \times (ALP)\text{^}2}{Platelet\ Count\ (Albumin)\text{^}2}\right] - n$$

Where n= 2000 and “n” is constant that is introduced to accommodate measurement in small values that is more convenient to use.

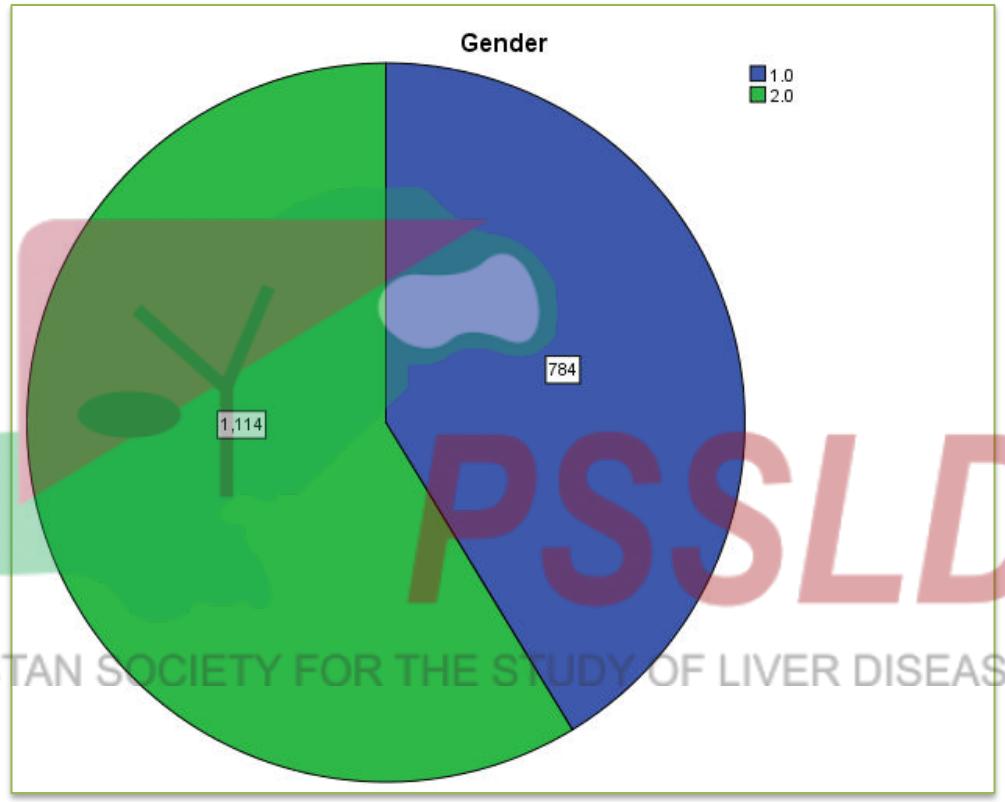
- We compared the fibro scan score determined fibrosis stages and fibrosis indices;

1. AST to ALT Ratio (AAR)
2. AST to Platelet index (APRI)
3. Fibrosis Index (FI)
4. Fibrosis-4 (Fib-4)
5. Age to Platelet index (API)
6. Pohl score
7. Fibrosis Cirrhosis Index (FCI)
8. Novel Fibrosis Index (NFI)

Statistical Analysis

- SPSS version **22**
- A p value **< 0.05** = statistically significant.
- **The student t-test**
- **The univariate regression analysis**
- **Receiver Operating Curves (ROC)=** Area Under ROC curves (AUROC) , cutoff points, sensitivities and specificities

Results



Distribution of patients according to gender (n=1898)

Descriptive statistics of study population (n=1898)

Variable	Mean ± S.D
Age of Patient	41.55 ±12.89
Albumin	3.64 ±1.36
ALT	78.19 ±171.66
AST	74.19 ±64.91
Bilirubin	1.19 ±1.22
Platelet count	302.31 ±229.09
Alkaline Phosphatase	301.94 ±137.80
Fibro scan score	13.35 ±13.00
Baseline Viral Load	1101257.9±6075925.9

Descriptive statistics of different fibrosis indices (n=1898)

Variable	Mean ± S.D
AAR	1.06 ±0.54
APRI	0.87 ±1.03
FI	0.38±2.9
Fib-4	1.71 ±1.88
FCI	0.78±1.98
API	2.89±2.86
Pohl Score	0.66±0.47
NFI	23.11±23.21

Comparison of different fibrosis indices in stages F0-F1 & F2 by independent sample t test (n=1898)

Variable	Fibrosis Stage	Mean ± S.D	p value
AAR	F0-F1(1034)	1.11±0.69	0.01
	F2(112)	1.00±0.14	
APRI	F0-F1(1034)	0.53±0.65	0.001
	F2 (112)	0.75±0.61	
FI	F0-F1(1034)	-2.97±30.81	0.001
	F2 (112)	1.44±2.52	
Fib-4	F0-F1(1034)	1.18±1.36	0.003
	F2 (112)	1.43±0.75	
FCI	F0-F1(1034)	0.27±0.40	0.001
	F2 (112)	0.40±0.22	
API	F0-F1(1034)	2.35±2.64	0.001
	F2 (112)	3.75±2.70	
Pohl Score	F0-F1(1034)	0.64±0.48	0.001
	F2(112)	0.82±0.38	
NFI	F0-F1(1034)	7.35±6.34	0.001
	F2 (112)	8.75±8.	

Comparison of different fibrosis indices in stages F3 & F4 by independent t test (n=1898)

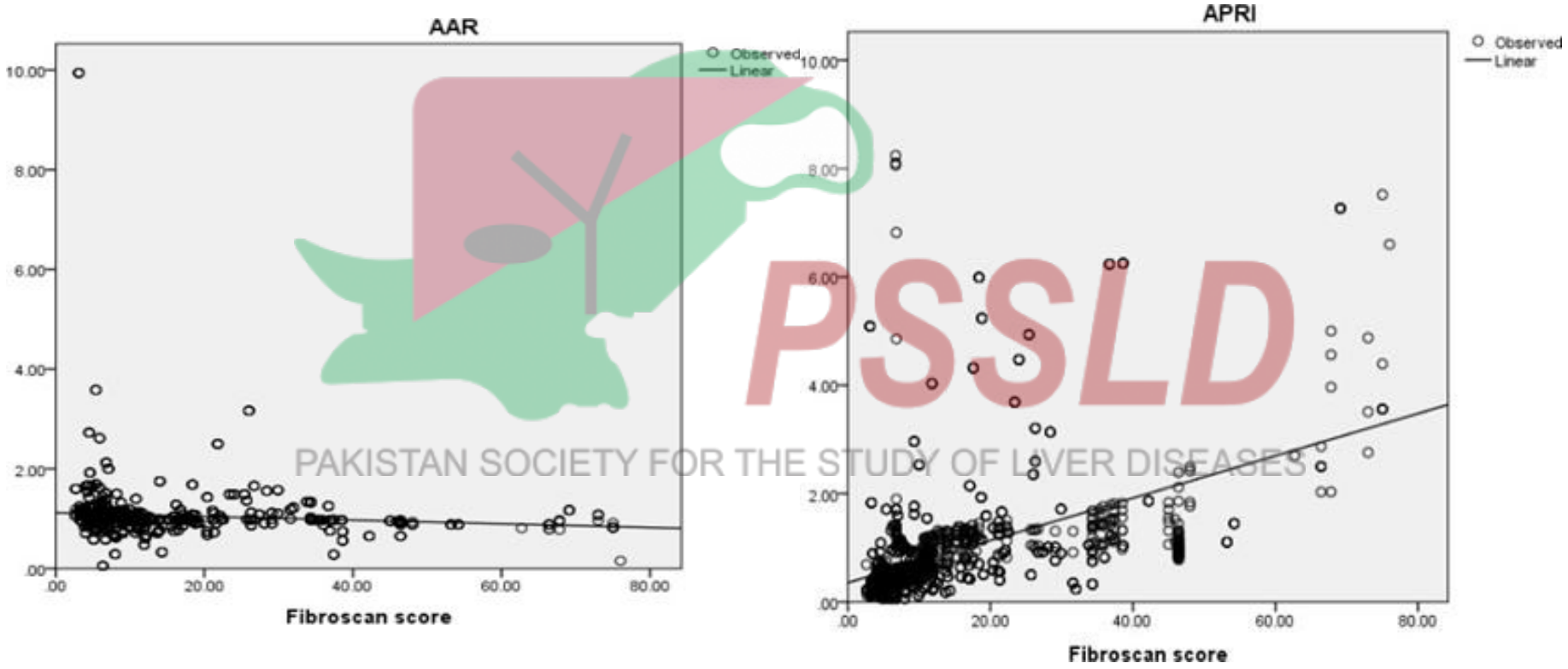
	Fibrosis Stage	Mean± S.D	p value
AAR	F3 (253)	0.95±0.20	0.04
	F4 (499)	1.04±0.34	
APRI	F3 (253)	0.80±0.62	0.001
	F4 (499)	1.64±1.42	
FI	F3 (253)	2.31±1.27	0.02
	F4 (499)	3.18±1.16	
Fib-4	F3 (253)	1.56±1.11	0.001
	F4 (499)	2.95±2.61	
FCI	F3 (253)	0.66±0.95	0.002
	F4 (499)	2.00±3.48	
API	F3 (253)	4.00±3.11	0.020
	F4 (499)	3.46±2.93	
Pohl Score	F3 (253)	0.83±0.37	0.03
	F4(499)	0.58±0.49	
NFI	F3(253)	11.35±11.34	0.001
	F4(499)	30.74±30.78	

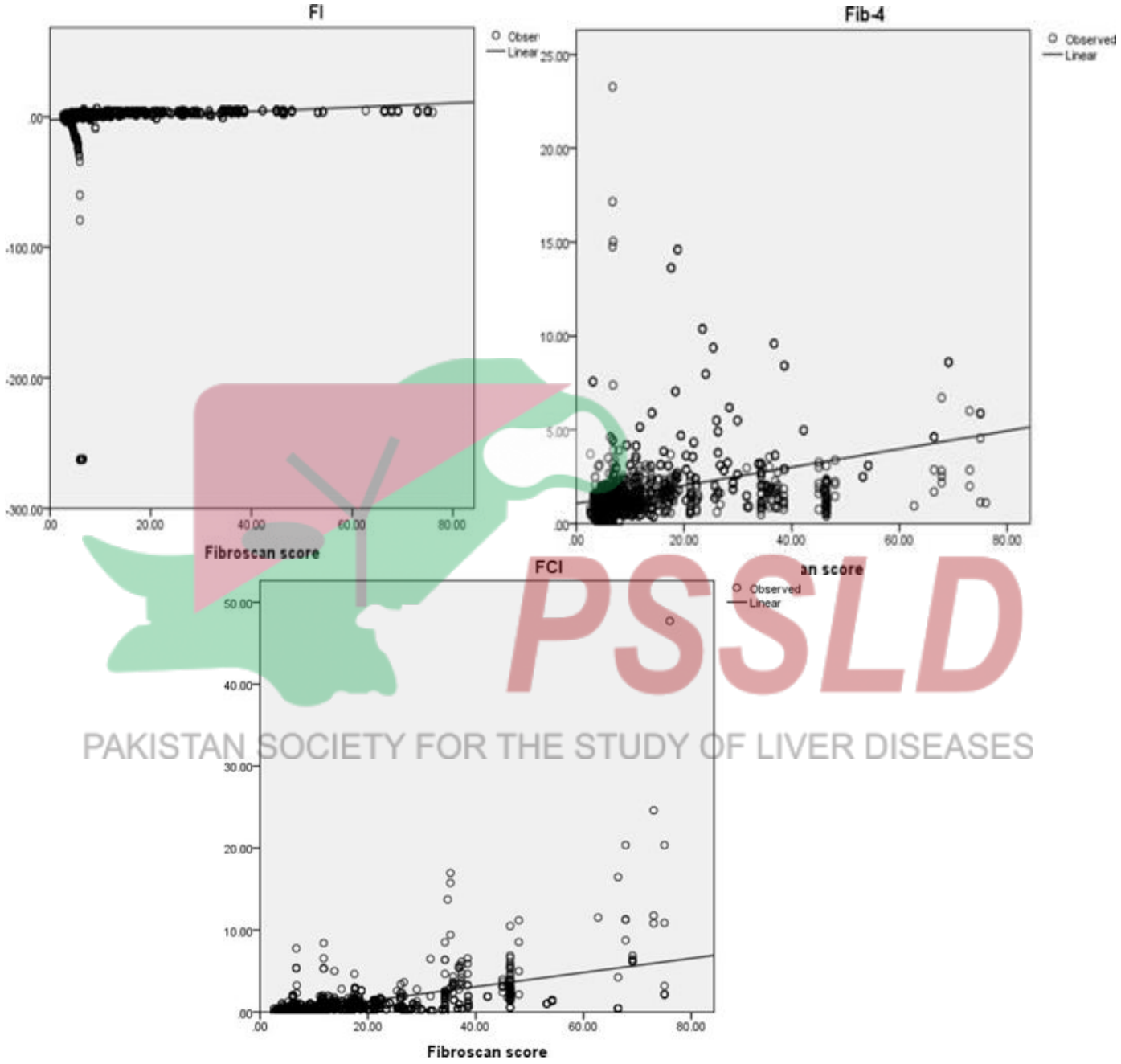
Correlation of different fibrosis indices with fibro scan score by univariate analysis (n=1898)

Fibro scan score vs

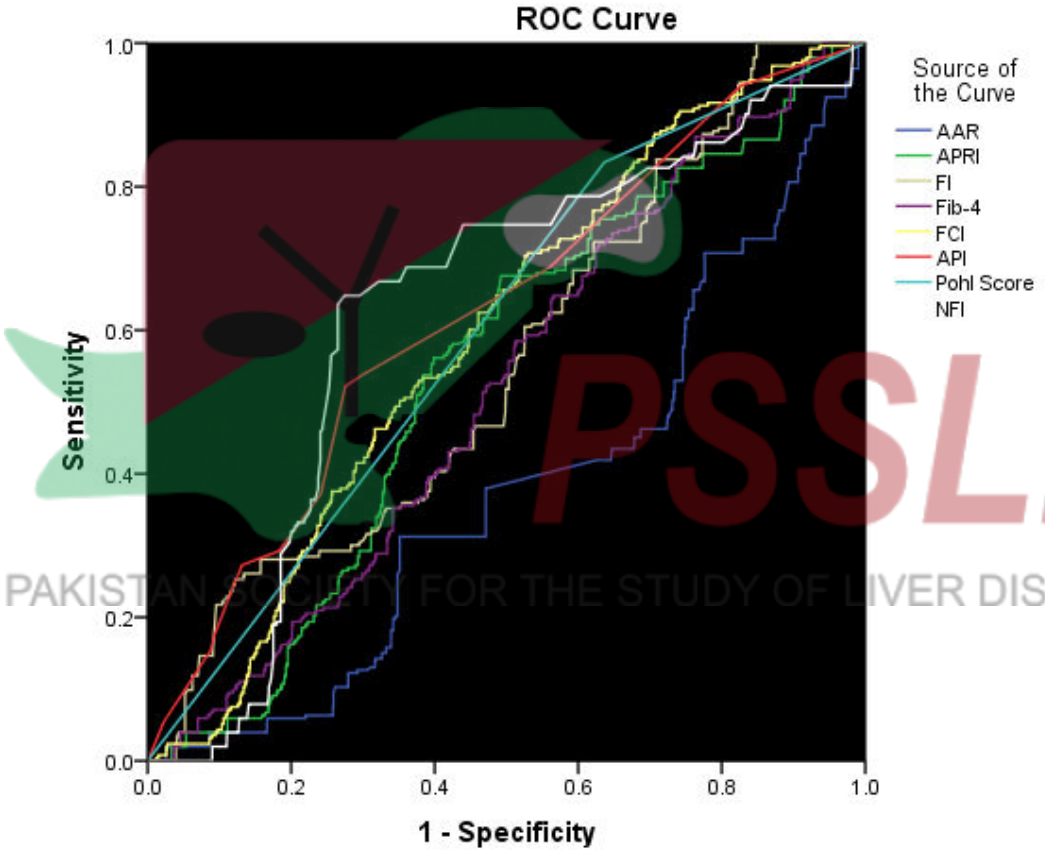
Variable	AAR	APRI	FI	FIB-4	FCI	API	Pohl Score	NFI
p value	0.02	0.001	0.384	0.02	0.04	0.023	0.01	**0.001**
R squared value	**0.848**	**0.711**	**0.003**	**0.61**	**0.74**	**0.529**	**0.360**	**0.776**

Scatter plots for different fibrosis indices with fibro scan score (n=1898)

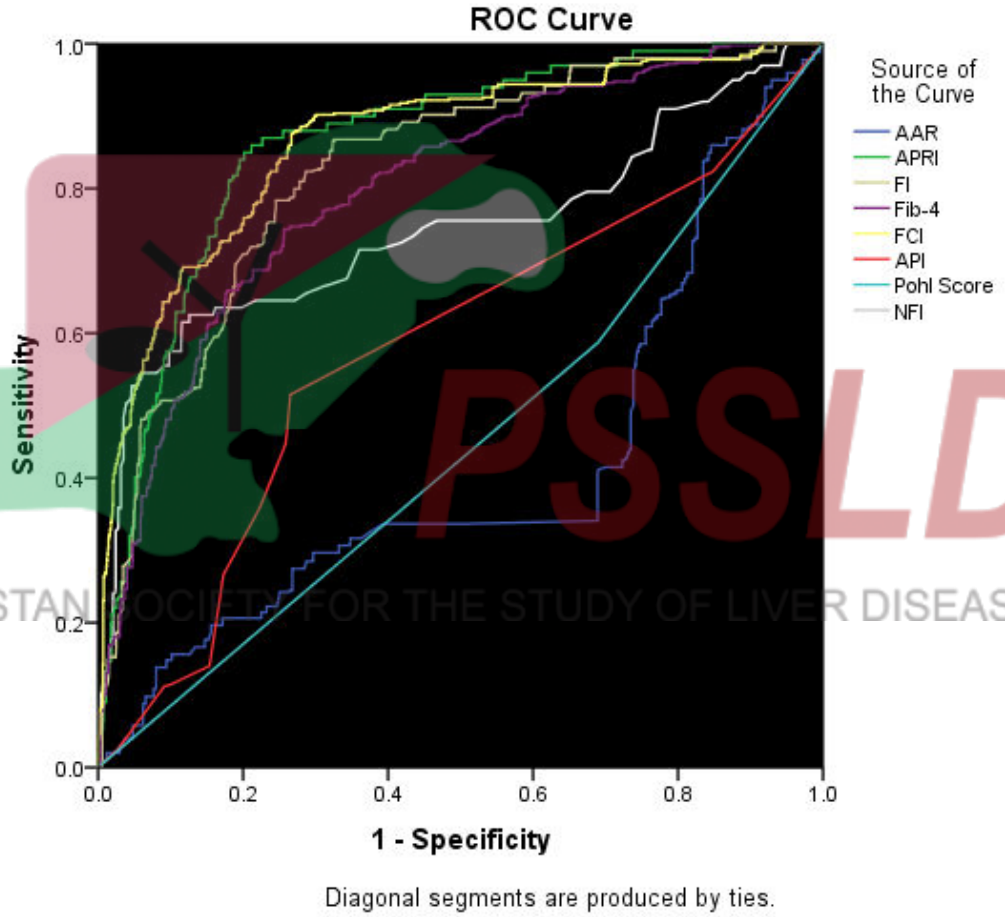




ROC curves for different fibrosis indices in fibrosis stage 3 (n=1898)



ROC curves for different fibrosis indices in fibrosis stage 4 (n=1898)



ROC Curve Analysis

AAR				
stage	Cutoff value	Spec%	Sens%	AUC
F0-F3	< 1	41.9	62.5	0.377
F	> 1	37.6	62.8	0.412

APRI				
stage	Cutoff value	Spe%	Sen%	AUC
F0-F3	< 0.5	68.0	56.2	0.54
F4	> 1.5	87.6	74.8	0.864

FIB-4				
stage	Cutoff value	Spe%	Sen%	AUC
F0-F3	< 1.45	65.4	51	0.521
F4	> 3.25	72.3	53.2	0.801

FI				
stage	Cutoff value	Spe%	Sen%	AUC
F0-F3	< 2.1	34.4	82.2	0.556
F4	> 3.3	92.3	78.1	0.826

API				
stage	Cutoff value	Spe%	Sen%	AUC
F0-F3	<2.5	58.4	70	0.624
F4	>2.5	60	78.1	0.578

Pohl Score				
stage	Cutoff value	Spe%	Sen%	AUC
F0-F3	0	58.4	30	0.499
F4	1	78.1	38.1	0.599

FCI				
stage	Cutoff value	Spe%	Sen%	AUC
F0-F3	< 0.131	57.4	37	0.499
F4	> 1.25	88.1	78.1	0.867

Table 3. ROC Curve analysis for validation of NFI for F3 and F4 in 1898 HCV infected patients.

	NFI			
stage	Cut off value	Spe%	Sen%	AUC
F3	> 11.64	75.1	61.1	0.609
F4	> 30.94	72.1	81.1	0.831

(NFI= Novel Fibrosis Index)

Conclusions and Implications of study

- Our NFI was not only able to predict Cirrhosis (F4) but also predicted F3 with considerable sensitivity and specificity that is why better index than previously developed indices.
- Easy to follow-up the progression of fibrosis with no repercussions and affordable to patients as compared to Fibro scan.

Thank You

PSSLD

PAKISTAN SOCIETY FOR THE STUDY OF LIVER DISEASES

References

1. Liaw and YF (2009) Antiviral therapy of chronic hepatitis B: opportunities and challenges in Asia. J Hepatol 51(2): 403-410.

2. World Health Organization. Pakistan tackles high rates of hepatitis from many angles. 11 July 2017. Available from: http://www.who.int/news- room/featurestories/detail Pakisan-tackles-high-rates-of-hepatitis-from- many-angles .Accessed at 29 November, 2018.

3. Vegnente A, Larcher VF, Mowat AP .Duration of chronic active hepatitis and the development of cirrhosis.*Arch Dis Child*. 1984;59(4):34.

4. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383:1749-61

5. Iredale JP. Models of liver fibrosis: exploring the dynamic nature of inflammation and repair in a solid organ. J Clin Invest. 2007;117(3):539.

6. Keltch B, Lin Y, Bayrak C. Comparison of AI techniques for prediction of liver fibrosis in hepatitis patients. J Med Syst. 2014;38(8):60.

7. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovirdisoproxilfumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468-75.

8. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.

9. Husain A Saleh, Ahmad H Abu-Rashed.Liver biopsy remains the gold standard for evaluation of chronic hepatitis and fibrosis. *Journal of gastrointestinal and liver diseases 16 (4), 425, 2007* .

10.Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group.Hepatology 1994;20:15-20.

11. Sanai, F. M., &Keeffe, E. B. (2010). Liver biopsy for histological assessment: The case against. *Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association*, *16*(2), 124-32.

12. CsochatzisEA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review andeconomic evaluation. Health Technol Assess 2015;19:1-409. v-vi.

13.AVEGAIL FLORES, SUMEET K. ASRANI. Elastography in Overweight and Obese Patients With Chronic Liver Disease. Clinical Gastroenterology and Hepatology 2015;13:1510–1512

14.Sobia Attaullah, Sanaullah Khan and Ijaz Ali, (2011) Hepatitis C virus genotypes in Pakistan: a systemic review ; virol J ©2011 Attaullah et al; licensee BioMedCentral Ltd.

15.Pornpen Thampanitchawong and Teerha Piratvisuth , (1999) World Journal of Gastroenterology ; Liver biopsy: complications and risk factors.

16. Waqar Ahmad†, Bushra Ijaz+ ,et al.(2011) A comparison of four fibrosis indexes in chronic HCV: Development of new fibrosis-cirrhosis index (FCI) BMC Gastroenterology 2011 © Ahmad et al; licensee BioMed Central Ltd. 2011

17.Schmid P, Bregenzer A, Huber M, et al. (2015) Progression of Liver Fibrosis in HIV/HCV Co-Infection: A Comparison between Non-Invasive Assessment Methods and Liver Biopsy. PLoS ONE 10(9): e0138838

18.Crossan C, Tsochatzis EA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assess 2015;19:1-409.

19. EASL Clinical Practice Guidelines: management of hepatitis C virus infection.
J Hepatol. 2014 Feb;60(2):392-420. doi: 10.1016/j.jhep.2013.11.003. Epub 2013 Dec 9.

20.EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis . J Hepatol 2015 vol. 63 j 237–264

21. Leon A. Adams1, Richard K. Sterling2. (2017) Journal of Hepatology; Developing a new algorithm to diagnose advanced liver fibrosis: A lift or a nudge in the right direction?

22. Fallatah HI. Noninvasive biomarkers of liver fibrosis: an overview. *AdvHepatol.* 2014; 2014.

23. Ahmed, Zohair & Ren, (2018). Universal Index for Cirrhosis (UIC index): The development and validation of a novel index to predict advanced liver disease. Hepatic Medicine: Evidence and Research. Volume 10. 133-138. 10.2147/HMER.S160616.

24. Boursier J, de Ledinghen V, Zarski JP, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. Hepatology. 2012;55(1):58-67.2

25. Zarski JP, Sturm N, Guechot J, et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. J He-patol. 2012;56(1):55-62.