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RELATIONSHIP OF HYPERBILIRUBINEMIA AND HYPOALBUMINEMIA WITH FIBROSCANIN VARIOUS STAGES OF FIBROSISIN RNA POSITIVEHCVINFECTEDPATIENTS

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Abstract:

Background:*Hepatitis is a global problem affecting population of about 180 million worldwide with high prevalence rate in developing countries. In a report published by WHO in 2017,Hepatitis C is most prevalent in Egypt followed by Pakistan.*

Objectives :To determine the relationship between progressive stages of fibrosis and serum albumin & bilirubin level with fibroscan score and stages of fibrosis determined by fibrosacn score.

Material and Methods*: The retroprospective cross sectional study was conducted in medicine unit 1 and hepatitis clinic of Lahore General Hospital, Lahore starting from February 15, 2018 to January 11, 2019. We studied 1434HCV infected patients which were got CBC, LFTs, ELISA and fibro scan done to perfectly diagnose ongoing hepatitis C infection. In order to differentiate HCV fibrosis progression, we compared the relationship between progressive stages of fibrosis and serum albumin & bilirubin level.*

Results:A total of 1434 patients, comprising 552 men and 882 women, with mean
age of 42 ±12 years, were enrolled. Of these, 736 (51.3%) have fibrosis stage F0-F1, 100 (7%) have F2, 196 (13.7%) have F3, and 402 (28%) have stage F4.By applying Independent sample T test, the relationship between stage of fibrosis predicted by Fibro Scan and albumin level was found to be non-significant (p>0.05). By applying Independent T test, it was found that serum bilirubin rise was not significantly correlated with the Fibro Scan stage F1-F2 (P>0.05). But stage F3-F4 showed a significant proportional correlation with rise in serum bilirubin level (P<0.05).

Conclusion and Implications*: Independent T test results showed that serum bilirubin rise was not significantly correlated with the Fibro Scan stage F1-F2 (P>0.05). But stage F3-F4 showed a significant proportional correlation with rise in serum bilirubin level (P<0.05) and albumin level wasfound to be non-significant in various stages (p>0.05).*

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INTRODUCTION:

Hepatitis is a global problem affecting population of about 180 million worldwide with high prevalence rate in developing countries.[1]Of these about 71 million people are suffering from chronic hepatitis C infection.[2] In the report published by WHO in 2017, Hepatitis C is most prevalent in Egypt followed by Pakistan.[3] Chronic hepatitis C is the leading cause of liver fibrosis and end stage liver disease.[4]

Liver fibrosis is caused by excessive accumulation of extracellular matrix proteins which include collagen type 3. It is a healing response of liver towards the chronic injury.[5]

Liver biopsy is considered the Gold standard test for assessing liver fibrosis. Histologic examination of liver helps in finding the cause of injury and staging the fibrosis. To assess the stage of fibrosis various scales are used such as Metavir (I–IV) and Ishak score (stages I–V). Specific stains e.g. Sirius red, are used to quantify the degree of fibrosis using computer guided morphometric analysis. But due to its invasiveness, it caused patient discomfort and led to various complications. It has limited accuracy because of inter and intra observer variations and errors of sampling.[6]

Therefore, many studies have been done to evaluate usefulness of the non-invasive techniques for the assessment of liver fibrosis. The different modalities used include physical examination, biochemical (serum aminotransferases, serum albumen level, serum bilirubin level, collagen level) and hematologic tests (platelet count, RDW), serum surrogate fibrosis markers (AST to ALT ratio, Hyaluronic acid level, AST-Platelet ratio index), glycomics, radiologic imaging (CT, MRI, MRS, USG) and transient elastography (Fibroscan).[7,8]

Fibroscan is a novel non-invasive technique based on transient elastography for measurement of liver stiffness.[8] Transient elastography is based on the ability of elastic shear wave to propagate through the medium. The speed of propagation of the shear wave depends upon the stiffness of the medium i.e. the harder the medium, the higher the speed of propagation. Liver stiffness is measured by generating a shear wave within liver, then measuring its speed of propagation and calculating stiffness which is expressed in kilo pascals.[9] Advantages of fibroscan include rapidity, reproducibility, and less discomfort for the patient.[8]

Fibrosis is divided into five degrees depending upon the fibroscan score: as F0-F1 (no or mild fibrosis, with fibroscan score 2.5-7 kPa), F2 (moderate fibrosis with few septa, fibroscan score of 7-9.5 kPa), F3 (severe fibrosis with numerous septa, fibroscan score 9.5-12.5 kPa), F4 (cirrhosis, fibroscan score >12.5 kPa).[8,10]

Another useful non-invasive method to assess degree of fibrosis and cirrhosis is serum albumin level. Serum albumin level is decreased in severe liver fibrosis and cirrhosis due to decreased hepatocyte synthesis, sodium and water retention that further dilutes the serum albumin.[11]

Correlation has also been found between serum bilirubin level and liver cirrhosis. In liver cirrhosis bilirubin clearance is decreased due to distortion in portal blood flow. Also, portosystemic shunting and splenomegaly occurs that leads to increased hemolysis causing increase in bilirubin production. As a result, there is a rise in unconjugated serum bilirubin which can be used as a specific marker of liver disease.[12]

Aim of this study is to establish correlation of serum albumin and bilirubin level with the degree of liver fibrosis and cirrhosis and make a comparison of its accuracy and effectiveness with that of Fibroscan in predicting the extent of liver damage and the clinical outcome.

METHOD:

1. This study was held at Lahore General Hospital, Lahore. HCV positive patients were identified. Later, we threw light on our study plan for clarification of patient's concepts about the whole process and informed consent from patients who were willing to involve in procedure. This was a retroprospective cross- sectional study. This study took place from February15, 2018-January11,2019.
2. Fibrosis staging were performed on the basis of fibroscan score using Ziol transient elastography break points which was carried out at medicine department, Ameer-ud-din medical college, Lahore in accordance with METAVIR assessment criterion[19]. Fibrosis have five degrees of fibrosis starting from **F0**= no fibrosis, **F1**=mild fibrosis having no septa, **F2**=moderate fibrosis with a few septa, **F3**=intense fibrosis with numerous septa and no cirrhosis and **F4**=cirrhosis.
3. Using Third Wave Technology of USA, HCV geno typing was done for12different genotypes of Hepatitis C virus.
4. For further bio chemical evaluation, samples of

serum collected from different subjects which were kept at- 70°C.Different assessment tools like liver function tests (LFTs), bilirubin levels ,hemoglobin value and albumin levels were calculated for every subject.

Statistical analysis

SPSS version 22 was used to analyze the data. p value of less than 0.05 was considered statically significant. To signify the marked association between stages of liver fibrosis and continuous variables, Spearman's rank correlation was used. We used student t-test to relate arithmetic means and parameters while to relate categorical data we used chi square(X2). Various univariate and multivariate regression analysis was performed for various variables.

RESULTS:

Patients

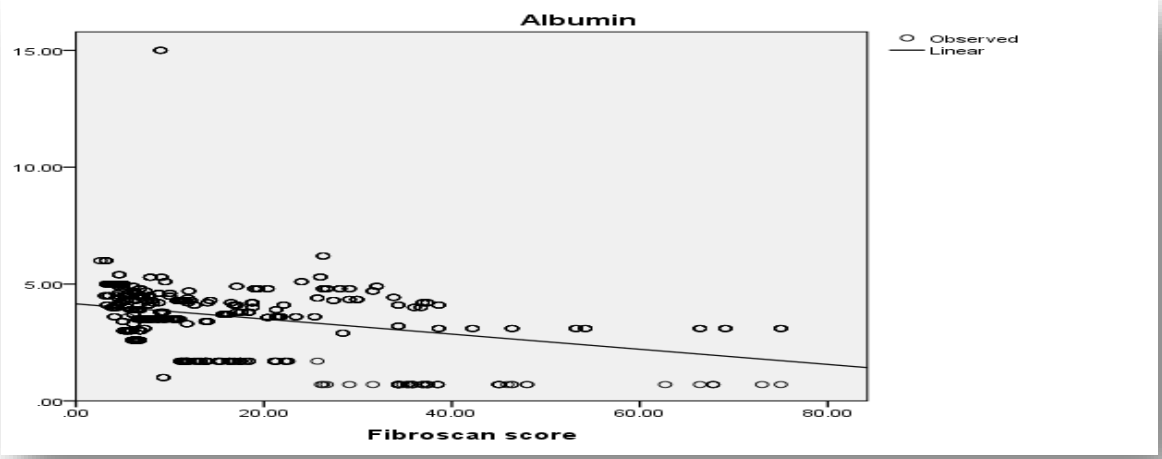
A total of 1434 patients, comprising 552 men and 882 women, with mean age of 42 ±12 years, were enrolled. Of these, 736 (51.3%) have fibrosis stage F0-F1, 100 (7%) have F2, 196 (13.7%) have F3, and 402 (28%) have stage F4. Other characteristics of the patients are given in Table 1.

Table.1	Frequency	Percent	Valid Percent	Cumulative Percent
Gender				
Female	882	61.5	61.5	61.5
Male	552	38.5	38.5	100.0
Total	1434	100.0	100.0	
Occupation				
Housewife	519	36.2	36.2	36.2
Laborer	854	59.6	59.6	95.7
Working Lady	61	4.3	4.3	100.0
Total	1434	100.0	100.0	
Marital Status				
Married	1332	92.9	92.9	92.9
Unmarried	94	6.6	6.6	99.4
3.0	8	.6	.6	100.0
Total	1434	100.0	100.0	
Fibrosis stage				
F0-F1	736	51.3	51.3	51.3
F2	100	7.0	7.0	58.3
F3	196	13.7	13.7	72.0
F4	402	28.0	28.0	100.0
Total	1434	100.0	100.0	

Correlation of fibrosis stage with serum albumin level

The Linear Curve Estimation Analysis and Pearson Correlation coefficient showed a linear relationship between Stage of fibrosis by FibroScan and reduction in serum albumin level (R value is 0.306), given in Table 2.

By applying Independent sample T test, the relationship between stage of fibrosis predicted by FibroScan and reduction in albumin level was found to be non-significant (p>0.05).



Correlation of stage of fibrosis and serum bilirubin level

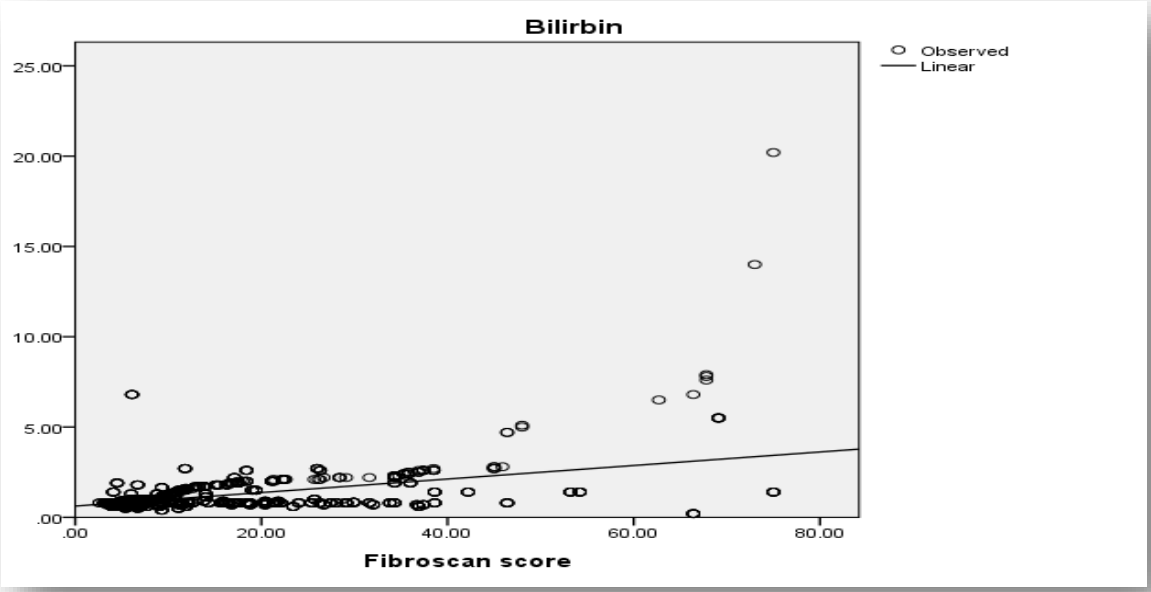
The Linear Curve Estimation Analysis and Pearson Correlation coefficient showed a linear relationship between stage of fibrosis and increase in serum bilirubin level (R value is 0.471). given in Table 4.

By applying Independent T test, it was found that serum bilirubin rise was not significantly correlated with the FibroScan stage F1-F2 (P>0.05). But stage

Independent Samples Test

F3-F4 showed a significant proportional correlation with rise in serum bilirubin level (P<0.05). Given in the table 5.

	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	Sig.	T	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
F0-F2 Equal variance assumed	41.795	.060	-2.579	834	.0670	-.32457	.12584	-.57157	-.07757
F3-F4 Equal variances not assumed	41.795	.000	-1.240	101.683	.018	-.32457	.26183	-.84393	.19480



Independent Samples Test

Bilirubin		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
F0-F2	Equal variances assumed	1.463	.227	-.542	834	.588	-.02876	.05307	-.13293	.07541
	Equal variances not assumed			-.842	205.199	.401	-.02876	.03416	-.09611	.03858
F3-F4	Equal variances assumed	30.432	.000	-3.292	596	.001	-.37778	.11476	-.60316	-.15240
	Equal variances not assumed			-4.459	513.570	.000	-.37778	.08472	-.54422	-.21134

DISCUSSION:

Pakistan has one of the highest HCV infection ratesWorldwide.[13,14,15]HCV prevalence in general population of Pakistan is about 5%. One out of 20 Pakistanis has already been subjected to HCV infection at some stage of their life.[16]

Chronic hepatitis C is the leading cause of liver fibrosis and end stage liver disease.[4]Our study was aimed at finding the changes in serum albumin and bilirubin level with progressing liver fibrosis, to find if it could be used as an effective serum marker in the early diagnosis, management and prognosis of the chronic liver disease.

According to Imbert-Bismut, bilirubin maybe used as a marker of liver injury and can assess the disease progression and fibrosis stages in chronic HCV patients.[17] Previous researches on serum markers for chronic liver injury indicated that changes in four serum markers ALP, bilirubin, albumin and platelet count have a high potential to differentiate different fibrosis stages and cirrhosis at given cutoff values.[8] Our research was focused on two of these 4 serum markers i.e. albumin and bilirubin by comparing their levels in each stage of fibrosis determined by FibroScan. In accordance with previous researches our research showed linear relation between progressive

stages of fibrosis and reduction in serum albumin level. Also, the relationship was linear between progressive stages of fibrosis and increasing bilirubin levels of serum. On applying Independent T test, it was found that the correlation between individual stages of fibrosis and decreasing levels of albumin was erroneous to specify any cutoff values. While correlation between rising level of serum bilirubin and early stages of fibrosis F1-F2 was not significant. But in later stages of fibrosis F3-F4 a significant relationship was found. This shows that only albumin and bilirubin levels alone cannot be used as effective indicators for fibrosis and chronic liver injury.They must be used in combination with other serum markers like AST to ALT ratio, Hyaluronic acid level, AST-Platelet ratio index and novel noninvasive techniques like FibroScan,CT, MRI, MRS, USGto better predict the level of chronic liver injury and fibrosis.

CONCLUSION AND IMPLICATIONS:

Independent T test results showed that serum bilirubin rise was not significantly correlated
with the FibroScan stage F1-F2 (P>0.05). But stage F3-F4 showed proportional
correlation with rise in serum bilirubin level (P<0.05) and albumin found to be non-significant in various stages (p>0.05).

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