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RELATIONSHIP OF DERANGEMENTS IN VARIOUS BLOOD INDICES AND COAGULOPATHY WITH LIVER STIFFNESS INDEX (LSI) IN VARIOUS STAGES OF FIBROSIS IN HEPATITIS C

[1]Azhar Hussain, [2]Ijaz Khalid, [3]Rameen Fatima and, [4]Dr. Muhammad Asif Gull

[1]3rd year MBBS, Ameer Ud Din Medical College, Lahore, [2]Final year MBBS, Ameer Ud Din Medical College, Lahore, [3]Final year MBBS, Ameer Ud Din Medical College, Lahore, [4]MBBS, FCPS Gastroenterology, Associate Professor of gastroenterology, Lahore General Hospital/ Ameer Ud din Medical College, Lahore, Pakistan.

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Abstract:

Background: *Liver performs a lot of functions of liver and damage to hepatocytes leads to dysfunction; multiple chemicals are released from it due to structural cell damage like ALT, AST and many others and cause functional loss leading to changes in albumin, bilirubin and clotting factors.*

Methods: *The prospective cross sectional study was conducted in medicine wards and hepatitis clinic of LGH/AMC, Lahore from February 22, 2018 to January 21, 2019. We studied 251 HCV infected patients which were got CBC, LFTs, ELISA and PCR done to perfectly diagnose ongoing hepatitis C infection and then, fibro scan were performed for staging of fibrosis. In order to differentiate HCV fibrosis progression, we compared the relationship of derangements in various blood indices and coagulopathy with liver stiffness index (LSI) in various stages of fibrosis in hepatitis C.*

Results: *The independent t test result of variables like Patient Age, Baseline Viral Load, TLC, Neutrophil Count, Platelet Count, MCV, MCH, MCHC, Hb, Hct, ALT, AST, ALP, Albumin, PT, APTT for fibrosis stages F0 –F1 and F2 have statistically significant result with fibro scan score or liver stiffness index with p values < 0.05 except TLC, Neutrophil Count, Platelet Count, MCV, MCH, MCHC, Hct, ALT, AST, ALP, Albumin, PT, APTT while for F3 and F4, all of these variables found to be significant except TLC, MCV, MCH, MCHC and Hct.*

They were able correlate to stage of liver fibrosis with correlation coefficient indexes or R squared values of 0.827,0.822, 0.798, 0.902, 0.878, 0.735, 0.981, 0.952, 0.86 and 0.846 respectively.

Conclusions: *Various blood indices (TLC, Neutrophil Count, Platelet Count, MCV, MCH, MCHC, Hband Hct) and coagulopathy (prolonged PT and aPTT) showed a positive association with liver stiffness index (LSI) in various stages of fibrosis in hepatitis C.*

Corresponding author:

AzharHussain,

3rd year MBBS, Ameer Ud Din Medical College,
Lahore Pakistan, Email address: azharnewton0786@gmail.com

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INTRODUCTION:

Hepatitis has more prevalence in developing countries with low to limited national per capita income (1). According to WHO report 2017, Egypt has highest prevalence and Pakistan has the second highest Prevalence (2). According to 2018's survey, 18 million Pakistanis are infected with hepatitis B or C which are about 9% of country's population and the number of people loosing life to hepatitis every-day in Pakistan is 400.

Liver contains different types of tissues in it like hepatic cells, hepatic stellate cells, sinusoids, intrahepatic lymphocytes. These cells form specific structure of portal triad (1).

Liver get Injured by certain type of insults and get repaired by healthy tissue, but this occur only in conditions that are not of longer periods. When the insult is continuous and happen to occur for an extensive period of time, healing process of liver changed, and instead or healthy tissue scarring occur which contain connective tissue like collagen. But this connective tissue is only replacing liver in structural form and does not perform any function which were previously done by healthy hepatic cells. This effects the overall functionality and performance of liver. And if it is not properly diagnosed and insult is continuing to effect hepatic tissue, the fibrosis keeps on increasing in size and if become large enough can lead to liver cirrhosis. Liver cirrhosis is the last stage of liver fibrosis and from there hepatic dysfunctional symptoms start (2).

So, it will be very wise to detect the injury causing phenomenon and carefully controlling it to prevent progression of fibrosis in early and damage of liver to become permanent.

Many different types of insults cause liver fibrosis which include a number of metabolic abnormalities and viral infection and certain others. Metabolic abnormalities include Wilson disease, hemochromatosis and alpha 1 antitrypsin deficiency. Hepatitis B and C in chronic form are the major contributors of liver fibrosis. In previous few years the prevalence hepatitis C to cause lover cirrhosis has substantially increased. So, in this research we will be focusing on patients of fibrosis in which like cause is hepatitis c (3).

There has been a lot of functions of liver which and damage to it leads to dyafunction, multiple chemicals are released from it due to structural cell damage like ALT, AST and many others. And functional loss result in changes of albumin, bilirubin, clotting factors etc. (3)

With fibrosis there is release of ALT and AST from damaging cells and there level get increase in body. Albumin synthesis disrupts which cause a low level of albumin in body. Liver have effects clotting profile and make bleeding easier. Haemoglobin also get decreased causing anemia.(3)

Liver fibrosis not only damages liver itsellf but also have worse effects on ither organs especially heatt and kidneys. Due to dyslipidimea there are mire chances of ischemis heart disease and decline in renal functions as well. (3)

So we can have different levels of such markers to have a clue of fibrosis, its stage and prognosis.

MATERIALS AND METHOLOGY:

1. Thisstudywasheld at Lahore General Hospital, Lahore.HCVpositivepatientswereidentified.Later ,we threwlight onourstudy planforclarificationofpatient'sconcepts about thewhole processandinformed consentfrompatientswhowerewillingtoinvolveinprocedure.Thiswasaprospective cross-sectionalstudy.This study took place fromMarch,2018-January17,2019.Subjects who were on immunosuppressivetherapyorhadclinicallydiagnosedHepatitisor AIDS or anytypeofhepatocellular carcinoma cancer were not includedSubjects which were non-compliantaboutundertakingthe biopsyorpatients in whom itwascontraindicatedwerealsoeliminatedfromthestudy. Everypossiblesideeffectandadvantageof liverbiopsywasexplained tothe patients andafterearning theconsent wegathered information aboutdemographicdetails,biochemicalandvirologicaldata.
2. Fibrosis staging were performed on the basis of fibroscan score which wascarriedoutatmedicine department,Ameer-ud-dinmedical college,lahorein accordance withMETAVIRassessment criterion[19]. Fibrosishavefivedegreesoffibrosis starting from F0= nofibrosis,F1=mildfibrosishavingnosepta,F2=moderatefibrosiswith afewsepta,F3=intensefibrosiswith numerousseptaandnocirrhosis and F4=cirrhosis.
3. Forfurtherbiochemicalevaluation, samples of serumcollectedfromdifferent subjects which werekept at- 70°C.Different assessment tools like liver function tests (LFTs), bilirubin levels

,heamoglobin value ,albumin levels and PLTwerecalculatedforeverysubject.

4. Using ThirdWaveTechnology of USA,HCVgenotypingwasdone for12different genotypes of Hepatitis C virus.

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 data 251 patients of fibrosis were included in the study, of which 103(41%) were males and 148(59%) were females as Shown in table below.

Frequency Table showing gender distribution

Gender

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	103	41.0	41.0	41.0
	Female	148	59.0	59.0	100.0
	Total	251	100.0	100.0	

Total 251 patients had different stages of fibrosis. Patients of F1 stage were 22(8.8%), F2 were 134(53.4%), F3 staged patients are 31(12.4%), F4 64(25.5%) as shown in below table.

Fibrosis Stage

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	F0-F1	22	8.8	8.8	8.8
	F2	134	53.4	53.4	62.2
	F3	31	12.4	12.4	74.5
	F4	64	25.5	25.5	100.0
	Total	251	100.0	100.0	

Determination of fibrosis stage using different variables of blood indices. The means and standard deviation of

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Patient Age	248	14.0	71.0	42.028	12.8562
Baseline Viral Load	251	221.00	13129102.00	985484.2072	2411168.11411
FibroScan Score	251	3.3	46.4	11.589	9.7672
TLC	243	3.30	12370.00	3298.4271	3741.22145
Neutrophil Count	179	50.0	79.0	62.106	8.2900
Platelet Count	251	77000.0	607000.0	240673.434	93202.1644
MCV	251	60.8	102.0	83.330	8.0775
MCH	251	15.2	35.6	26.834	3.9369
MCHC	243	23.6	38.9	31.719	2.5227
Hb	131	7.0	30.3	12.915	3.6719
Hct	238	21.60	54.00	38.5188	5.91852
ALT	237	14.0	200.0	60.405	40.8495
AST	233	17.0	212.0	58.343	40.7430
ALP	222	102.0	898.0	315.261	132.2610
Albumin	251	.49	5.50	2.5743	1.82915
PT	251	13.7	17.5	15.019	1.0299
APTT	251	26.0	46.2	35.264	2.5203
Valid N (listwise)	88				

Footnotes:
(TLC=Total Leukocyte Count, MCV= Mean Corpuscular Volume, MCH= Mean Corpuscular Hemoglobin, MCHC=Mean Corpuscular Hemoglobin Concentration, Hb= Hemoglobin, ALT= Alanine Aminotransferase, AST= Aspartate Aminotransferase, PT= Prothrombin Time, APTT= Activated Partial Prothrombin Time)
Patient Age, Baseline Viral Load, FibroScan Score, TLC, Neutrophil Count, Platelet Count, MCV, MCH, MCHC, Hb, Hct, ALT, AST, ALP, Albumin, PT, APTT were 42.028±12.8562, 985484.2072±2411168.11411, 11.589±9.7672, 3298.4271±3741.22145, 62.106±8.2900, 240673.434±93202.1644, 83.330±8.0775, 26.834±3.9369, 31.719±2.5227, 12.915±3.6719, 38.5188±5.91852, 60.405±40.8495, 58.343±40.7430, 315.261±132.2610, 2.5743±1.82915, 15.019±1.0299, 35.264±2.5203 respectively.

The independent t test result of variables like Patient Neutrophil Count, Platelet Count, MCV, MCH,

The independent T-test results of different variables like Patient Age, Baseline Viral Load, FibroScan Score, TLC, Neutrophil Count, Platelet Count, MCV, MCH, MCHC, Hb, Hct, ALT, AST, ALP, Albumin, PT, APTT show statistically significant relation with fibrosis stage F0-F1 and F2 with fibroscan score of p values given below in table.

Group Statistics

	Fibrosis Stage	N	Mean	Std. Deviation	Std. Error Mean	P value
Patient Age	F0-F1	21	31.714	5.9257	1.2931	0.000
	F2	132	40.939	13.1525	1.1448	
Baseline Viral Load	F0-F1	22	231466.5000	449607.82993	95856.71142	0.028
	F2	134	490064.2239	704096.94535	60824.71196	
TLC	F0-F1	22	3045.5327	3342.96911	712.72341	0.928
	F2	130	3124.0734	3823.57764	335.34994	
Neutrophil Count	F0-F1	15	58.600	6.3449	1.6382	0.57
	F2	96	62.521	7.4805	.7635	
Platelet Count	F0-F1	22	265590.909	40699.4315	8677.1479	0.517
	F2	134	273343.522	94163.7420	8134.5084	
MCV	F0-F1	22	82.791	7.4357	1.5853	0.914
	F2	134	82.601	7.6181	.6581	
MCH	F0-F1	22	26.268	3.2609	.6952	0.797
	F2	134	26.487	3.7450	.3235	
MCHC	F0-F1	22	31.750	.9937	.2119	0.922
	F2	130	31.782	2.7340	.2398	
Hb	F0-F1	11	13.773	1.1542	.3480	0.019
	F2	72	12.717	1.9082	.2249	
Hct	F0-F1	22	39.3668	4.22459	.90069	0.674
	F2	125	38.8310	5.69504	.50938	
PT	F0-F1	22	14.755	.8868	.1891	
	F2	134	14.885	.9719	.0840	0.556
APTT	F0-F1	22	34.773	.8691	.1853	0.168
	F2	134	35.241	3.2695	.2824	

Age, Baseline Viral Load, FibroScan Score, TLC, MCHC, Hb, Hct, ALT, AST, ALP, Albumin, PT,

APTT for fibrosis stages F3 and F4 have statistically significant result with fibro scan score of p values given below in table.

Group Statistics

	Fibrosis Stage	N	Mean	Std. Deviation	Std. Error Mean	P value
Patient Age	F3	31	49.065	12.2527	2.2007	0.068
	F4	64	44.250	11.7622	1.4703	
Baseline Viral Load	F3	31	505418.0323	758271.52269	136189.58585	0.001
	F4	64	2514495.4375	4298094.91431	537261.86429	
TLC	F3	31	4404.7742	3972.18477	713.42544	0.144
	F4	60	3197.3087	3563.74153	460.07705	
Neutrophil Count	F3	20	55.000	3.8389	.8584	0.000
	F4	48	65.333	9.6345	1.3906	
Platelet Count	F3	31	254774.194	78597.1627	14116.4671	0.000
	F4	64	156875.000	50395.1056	6299.3882	
MCV	F3	31	85.181	5.1067	.9172	0.508
	F4	64	84.144	10.0975	1.2622	
MCH	F3	31	27.339	2.7606	.4958	0.825
	F4	64	27.513	4.8744	.6093	
MCHC	F3	31	31.965	2.0029	.3597	
	F4	60	31.447	2.6931	.3477	0.348
Hb	F3	12	12.567	1.5023	.4337	0.751
	F4	36	13.167	6.4175	1.0696	
Hct	F3	31	41.0606	3.38306	.60761	0.000
	F4	60	36.2440	7.15823	.92412	
PT	F3	31	14.884	.9385	.1686	0.016
	F4	64	15.456	1.1257	.1407	
APTT	F3	31	34.710	.8244	.1481	0.000
	F4	64	35.750	1.2599	.1575	

variables	TLC	Neutrophil count	Platelet count		MCV	MCH	MCHC	Hb	Hct	PT	APTT
P value	.000	.000	.000		.000	.000	.000	.000	.000	.000	.000
R square value	.827	.822	.798		.902	.878	.735	.981	.952	.867	.846

The univariate analysis:
Univariate analysis of TLC, Neutrophil Count, Platelet count, MCV, MCH, MCHC, Hb, Hct, PT, APTT showed significant relationship with pearson's correlation co-officient (R) values given below in table.

DISCUSSION:

Hepatic cirrhosis caused by chronic hepatitis C infection and NAFLD are leading contributors in deaths caused by chronic diseases. Cirrhosis doesn't develop simultaneously but it takes a mean infection time of approximately 30 years and it may occur in different ages with different age ranges i-e 10-50 years [3,4]. Fibrosis in connective tissue followed by its extension in hepatic tissue in hepatitis C infection is an evidence of cirrhosis.[5]

In Pakistan, 3a was the most prevalent genotype [14] and our study also depicted same results. There were large number of patients with F0-F1 i-e none or initial fibrosis stage while F2 and F3 stages of fibrosis, and cirrhosis (F4) were a remarkably associated with older ones. Mean age greater than 40 years were found to be significantly related to marked fibrosis and cirrhosis and our study augmented the results of other studies as well [12]. The stage of fibrosis was not found to be statistically significant relationship with gender or occupation but laborers were found to be more affected by hepatitis C infection and advanced stages of fibrosis i-e F2 and F3 and cirrhosis and this finding can be attributed to poor hygiene, sanitation, lack of awareness and low socioeconomic status [1,2].

Liver fibrosis is more prevalent in older patients and its incidence is more common in females than in males. Platelet count is statistically significant in fibrosis stages. Platelet count decreases as fibrosis stage increase. Mechanism for thrombocytopenia is found to be due to antibody formation in one of the studies specifically platelet glycoprotein specific antibodies. (4)

Some studies also conclude that platelet count become lower in cirrhosis due to decrease in thrombopoietin production (5)

There is a statistically significant relationship between neutrophil count and stages of liver fibrosis. Neutropenia can occur due to side-effect of antiviral therapy (6), or this may be due to hypersplenism, autoimmune neutropenia (7) or direct bone marrow involvement (8). One study also show that number of neutrophils are far less in hepatitis c patients than in normal patients. Patients have as low as 1000 count but none has less than 500 (9).

We also found statistically significant relationship of hb, MCV and MCH fibrosis stages. Mechanism of these changes is most commonly due to autoimmune hemolytic anemia. the incidence become more increased with treatment with ribavirin (10).

There is also statistically significant relationship of PT and APTT with fibrosis stage. Due to liver damage there is reduced production of clotting factors II, V, VII, IX, X, XI and XIII and increased production of Von Willebrand factor and VIII due to endothelial damage. Most of these are found in advanced liver disease (11).

CONCLUSION:

Various blood indices (TLC, Neutrophil Count, Platelet Count, MCV, MCH, MCHC, Hband Hct) and coagulopathy (prolonged PT and aPTT) showed a positive association with liver stiffness index (LSI) in various stages of fibrosis in hepatitis C.

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