ORIGINAL ARTICLE

Stratification of variation of Prothrombin Time (PT) and Activated Partial Prothrombin Time (APTT) with Fibro Scan measured Liver Stiffness Index (LSI) in different stages of fibrosis

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ABSTRACT

Background: In most cases, hepatitis C progresses gradually to chronic disease.Clotting profile has been integral part of comprehensive assessment of patients presenting with liver impairment. We studied variation of PT, APTT with Fibroscan score in determining stages of fibrosis.

Methods: The retro-prospective cross sectional study was carried out at LGH, Lahore from February 14, 2018 to January 14, 2019. We studoed on 260HCV infected patients, patients having coagulationpathologies other than liver impairment were excluded.Patients were assessed for PT, APTTand fibrosisstage was determined by Fibroscan score. To determine the significant association between continuous variables and liver fibrosis stages, Spearman's rank correlation was used.

Results: For stage F0-F1 and F2, PT and APTT variables showed non- significant relationship ($p > 0.05$) while for stage F3 and F4, significant relationship with found with $p=0.022$ and $p=0.01$ respectively

Conclusion: PT, APTT can be used as prognostic markers efficiently only at stages of advanced fibrosis and cirrhosiswhile initial stages of fibrosis don't affect PT, APTT significantly. Implication of study can be limited by pathological factors other than liver disease in individual cases.

INTRODUCTION

Have you heard the term "Serial Killer"? Yes! Right? Then you will be amazed to know that hepatitis C is "Silent Serial Killer". Death from hepatitis C is due to liver cirrhosis and hepatocellular carcinoma[1]. According to the report of 2015, 167000 deaths occurred from liver cancer while 326000 from cirrhosis in hepatitis C patients. More than 700000 people die from hepatitis C related diseases every year[2].

HCV can cause both acute and chronic hepatitis. It is spread from blood to blood contact involving intravenous drug users, blood transfusions, needles stick injuries or vertical transmission. Its envelope proteins often vary their antigenic structure and our immune system can't keep up rendering the vaccine obsolete immediately. Hep C causes inflammation of liver which leads to jaundice, right upper quadrant pain and hepatomegaly. 60-80% become chronic. Lymphocytes infiltrate the portal tract and with chronic inflammation and infection, hepatocytes die. Liver cells and parenchyma are irritated and liver quickly needs to replace them. Some come to fibrosis and cirrhosis or alternatively hepatocytes go into frenzy and reproducing cells become malignant leading to hepatocellular carcinoma. Hep C infection leads to development of cryoglobulins or serum proteins containing IgM that precipitate and cool our temperature[3,4].

Globally 71 million people are estimated to be chronically infected. A significant number of those will develop cirrhosis or hepatocellular carcinoma. Pakistan has the world's second highest prevalence of the hepatitis C, second only to Egypt. (WHO, n.d.). HCV is "Silent Serial Killer" because the infected person remains symptomless unless a great amount of damage has occurred. According to a research conducted by U.S Department of Health and Human Services(HHS), 51% of persons living with hepatitis C infection do not know they have the virus. Especially in Pakistan, more than 60% of the population lives in rural areas. They do not have access to quality health facilities. Another huge problem is lack of awareness to get themselves screened for such infections periodically. Also, they are not financially that strong to afford tests like PCR,ELISA and Fibroscan[6].

As DAAs have made it possible to achieve 95% cure rate. So the major hurdle today in our way to achieve HCV free world is the timely diagnosis of the infection. This research was carried out to assess how effective are AST and ALT in predicting different stages of fibrosis[1].

As liver forms various pro- and anticoagulant factors as well as pro- and antifibrinolytic components, soin chronic hepatitis C infection and cirrhosis coagulopathy make it more fatal because lymphocyticinfiltration of the portal tract leading to chronic inflammation and infection due to exposure to HCV virus, hepatocytes die. Liver cells and parenchyma are irritated and liver quickly needs to replace them. Some come to fibrosis and cirrhosis or alternatively hepatocytes go into frenzy and reproducing cells become malignant leading to hepatocellular carcinoma and alternatively, decreased concentration of all those clotting factors and essential proteins causing abnormally prolonged PT and APTT. This prolonged PT and APTT is a one of the serious complication of chronic hepatitis C infection and cirrhosis[8].

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METHODS AND MATERIALS

This retrospective cross sectional study was conducted at Hepatitis Clinic,Lahore General Hospital, Lahore. HCV positive patients were identified. Later,we threw light on our study plan for clarification of patient's conceptsabout the whole process and informed consent was obtained from patients who were willing to be involved in research. The analytical study was carried out from February 14, 2018 to January 14, 2019. It was made sure that Patients having bleeding disorders or having disrupted coagulation system hemostasislike on anticoagulation drugsdon't get includedin our study. Also patients who had received a immunosuppressive therapy or had clinically diagnosed HBV or HIV or any type of liver cancer were not included in the study.

Blood samples were collected and PT,APTT tests were performed at Pathology Lab, Lahore General Hospital,the diagnostic performance was then compared with fibroscan score, which determined fibrosis stage, using statistical analysis.The study was approved by Institutional Ethical Review Board (IERB), LGH.

Statistical analysis: The data was analyzed using statistical package SPSS windows version 22. A p value of less than 0.05 was considered statistically significant. To determine the significant association between continuous variables and liver fibrosis stages, Spearman's rank correlation was used. The One Way ANOVA and student t-test was used to compare arithmetic means and parameters. The univariate analysis was done for PT and APTT.

RESULTS

Frequencies: Total patients taken were 260, out of which 108 (41.5%) were male and 152 (58.5%) were female. Fibrosis stage demographics wereF0-F1 =144 (55.4%), F2=20 (7.7%), F3= 28 (10.8%),F4=68 (26.2%).

Descriptive Statistics: The minimum and maximum values of PT andAPTT were 13.7 & 17.5 and26.0& 46.2 respectively. The mean values and standard deviationvalues of patient age, baseline viral load, fibroscan score, Hb were 41.83 ± 12.95,984797.38 ± 2377269.10,11.42 ± 9.65 and 12.92 ± 3.62 respectively as shown in table (1)

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Patient Age	256	14	71	41.83	12.954
Baseline Viral Load	260	221	13129102	984797.38	2377269.104
FibroScan Score	260	3.3	46.4	11.422	9.6488
Hb	136	7.0	30.3	12.929	3.6202

The mean values and standard deviationvalues of platelet count, ALT, AST, Alkaline Phosphatase, Albumin,**PT,APTT**were242123.20 ±93279.70,, 60.09 ± 40.36, 57.82 ± 40.31, 317.95 ± 136.44, 2.59 ± 1.84, 15.01 ±1.02, 35.24 ± 2.48 respectively as shown in table (2) which is also describing statistical values stage wise.

Table 2:

Fibrosis Stage		Platelet Count	ALT	AST	Alkaline Phosphatase	Bilirubin	Albumin	PT	APTT
F0-F1	Mean	288611.333	49.800	47.882	322.559		2.7525	14.864	35.103
	N	144	140	136	136	144	144	144	144
	Std. Deviation	80861.9997	33.4163	31.6928	141.8181		1.91158	.9115	3.0944
F2	Mean	161200.000	79.000	59.600	337.667		1.6600	14.840	35.400
	N	20	20	20	12	20	20	20	20
	Std. Deviation	56588.6356	44.6224	15.9552	121.5695		1.76826	1.1975	2.0105
F3	Mean	257428.571	74.714	67.286	252.500		2.3543	14.871	34.571
	N	28	28	28	24	28	28	28	28
	Std. Deviation	82391.7600	42.5300	47.6895	65.4583		1.77103	.9884	.7418
F4	Mean	161176.471	71.786	76.571	330.571		2.5982	15.429	35.765
	N	68	56	56	56	68	68	68	68
	Std. Deviation	51850.8024	46.3711	52.3759	143.3519		1.66260	1.0970	1.2231
Total	Mean	242123.200	60.098	57.817	317.947		2.5852	15.011	35.242
	N	260	244	240	228	260	260	260	260
	Std. Deviation	93279.7019	40.3571	40.3132	136.4401		1.83750	1.0195	2.4821

Analysis of variances (ANOVA) for PT and APTTshowed a statistically significant relationship ($p<0.05$) with fibroscan score-determined fibrosis stage

Table 3:

		Sum of squares	dF	Mean square	F	Sig.
PT	Between Groups	233.410	49	4.763	27.942	.000
	Within Groups	35.800	210	.170		
	Total	269.210	259			
APTT	Between Groups	1322.091	49	26.981	20.717	.000
	Within Groups	273.500	210	1.302		
	Total	1595.591	259			

Independent samples T-test: The independent samplet-test results for stage F0-F1 and F2,PT and APTT variables showed non-significant relationship of PT and APTTwith fibroscan score-determined fibrosis stage with p=0.932andp=0.677) respectively.

The independent t- test results for stage F3 and F4,PT and APTT variables showed astatisticallysignificant relationship of PT and APTTwith fibroscan score-determined fibrosis stage withp=0.022 andp=0.01respectively.

Univariate analysis of Variance: The relationship of PT and APTT with fibro scan score in univariate analysis was found to be statistically significant (p values <0.05) with R squared values of 0.886, 0.886 respectively.

DISCUSSION

Most cases of hepatitis C progress to chronic liverdisease[3]and most frequentlythe disease keeps onprogressinggradually over the year,even decades[3,9] with patients being unalarmed esp. witnessedin developing countries due to poor prognification of liver fibrosis and subsequently less accurate treatment approach in overburdened healthcare system as prevalence of hepatitis is coincidingly higher in developing countries[1]. Several Non-invasive tests particularly transient elastography i-e fibroscan and combination of biomarkers are replacing invasive liver biopsy which has almost become obsolete owing to both healthcare burden and inconveniences and repercussions for patient,can even be mortal [1.6% mortality rate observed in a study[10], also inter-observer variability and sampling error upto 30%[11] included in drawbacks[9,11]. EASL recommendation also approve the preferential use of NITs over invasive biopsy[9]. Fibroscan inducted recently[first machine inaugurated in 2011 in Karachi, Pakistan]has been most preferred choice for prognosis of liver fibrosisif available and affordable to patient,it is quite convenient and reliable but expensive and most importantly its availability is problematic in developing countries where burden is also higher in curbing prevalent hepatitis.

Hepatitis is more prevalent in females than males[1] and we got this consistent result in our study. Fibrosis stages F0-F1 and F4 stages were most commonly encountered with percentages 55.4% and 26.2% respectively. There was significant relationship of progressed liver disease and age of patient as consistent with results of all other studies. Previously many studies made use of the combination of biomarkers in developing fibrosis serum indices, like ALT / AST ratio (AAR) fibro test (FT),fibrosis index (FI),AST platelet ratio (APRI) and FIB-4, all proclaimed to be predicting the prognosis with significant sensitivity and specificity. However final stage cirrhosis and mild fibrosis cannot be determined accurately by applying justone NIT, also all the readily available indiceshave some limitations likeinabilityto differentiate all fibrosis stages individually and some have beendeveloped primarily for co-infected patients[12]

Blood markers have been used especiallyto predict cirrhosis andadvanced stages of fibrosis and have been integral part of comprehensive assessment of patients presenting with liver impairment. Clotting Profile i-e PT,APTTare still in used as prognostic factors among LFTs[13]. There has beenno study publishedso far comparing diagnostic performance of fibroscan and coagulation parameters. According to a study published(14) PT, APTT wasfound derangedin most of chronic liver disease patients, APTT was prolonged in 71% and PT was raised in 88% in cases of chronic liver disease[14].Coherently, Our results also indicate significant prolongation of PT,APTT in chronic cases. The minimum and maximum values of PT and APTT were 13.7 & 17.5 and26.0& 46.2 respectively in our study.

According to our results, for stage F0-F1 and F2,PT and APTT variables showed non-significant relationship of PT and APTTwith fibroscan score-determined fibrosis stage with p=0.932andp=0.677) respectively. for stage F3 and F4, PT and APTT variables showed astatisticallysignificant relationship of PT and APTTwith fibroscan score-determined fibrosis stage withp=0.022 andp=0.01respectively which means that PT, APTT, simplest to performamong other lab NITs,can be used as prognostic markers efficiently at stages of advanced fibrosis and cirrhosis while initial stages of fibrosis don't affect PT, APTT significantly because patients with chronic liver diseasefail to synthesizepro- and anticoagulant factors as well as pro- and antifibrinolytic components made by normal liver.

Limitation for implication of our study in individual casescan be patientfactors like hypocalcemia, Vitamin K deficiency,endothelial dysfunction/damage, hypertension, infection and renal failure that may disrupt coagulation system hemostasis in cirrhotic patients andtrigger factors like use of certain drugs inhibiting coagulationgiving false positiveresults.

CONCLUSION

PT and APTTare severely affected and prolonged in F3 and F4 but F0-F1 and F2 stages does not affect them significantly because various pro- and anticoagulant factors as well as pro- and antifibrinolytic components made by liver are affected greatly in chronic hepatitis C infection and cirrhosis leading to coagulopathy. Limitation of studycan be some pathologicalfactors other thanliver disease disrupting coagulation mechanism in individual cases.

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