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Original Article

Platelet count to prothrombin (PLT/PT) ratio to predict esophageal varices in patients with hepatitis C related chronic liver disease

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Abstract:

Background: Variceal haemorrhage is a serious complication of portal hypertension in patients with chronic liver disease caused by various etiologies. In order to identify varices at earlier stages many non-invasive predictors have been studied to avoid unnecessary EGD and reduce bleeding related mortality.

Objective: To identify the relationship of PLT/PT ratio with presence of esophageal varices in patients with HCV-CLD.

Methods: In this cross-sectional study 140 patients with HCV related CLD were included. They distributed into those with and without esophageal varices. Variceal group was further subdivided into those low risk (Grade-I) and high-risk Varices (Grade-II/III). All patients were subjected to detailed history and examination. Laboratory tests. Ultrasound abdomen and EGD was performed.

Results: Median age of patients was 54+/- 10.18 years. 61.4% patients were male (n=86) and 38.6% were female (n=54). 86.4% (n=121) had EVs and 13.5%(n=19) had no varices. PLT/PT ratio at cut off value of ≤12384 predicted esophageal varices with sensitivity of 85.12%. Specificity of 73.68%, PPV of 95.37%, NPV of 43.74% and diagnostic accuracy of 83.57% with AUC of 0.817. PLT/PT ratio at cut-off value of ≤11145.03, with AUC of 0.707, sensitivity of 88.64%, specificity of 54.55%, PPV of 83.87%, NPV of 64.29% and diagnostic accuracy of 79.34%.

Conclusion: PLT/PT ratio has significant association with both the presence of esophageal varices and advanced grades of varices.

Keywords: Platelet count to prothrombin time (PLT/PT) ratio, Esophageal varices, HCV-related chronic liver disease**.**

How to Cite this article:

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Introduction:

Chronic liver disease (CLD) is characterized by progressive decline in liver functions which include production of clotting factors, detoxification and excretion of bile. It is a process of liver parenchymal inflammation, destruction and regeneration resulting in fibrosis and cirrhosis which consists of scarring and regenerative nodules. CLD is caused by different etiologies like Hepatitis B and C, alcohol and Steatosis. [(1)] The number of cases worldwide is estimated to be at 1.5 billion.[2] Around 1.32 billion people were reported to have died from CLD in 2017.[3] Amongst Asian countries Pakistan is noted to have the highest incidence of CLD.[4]

A grave consequence of this disease is portal hypertension(pHTN), which is a pathological rise in the venous pressure of the portal system.[5] Physiological adaptations of the body, result in the formation of collaterals that divert blood from the portal venous system to the inferior and superior vena cava such as, the gastro-esophageal collaterals that drain into the azygos vein and development of esophageal

varices(EVs).[6] Rupture of EVs, and bleeding is a significant complication of pHTN.[7] A less frequent complication to be considered is gastric variceal bleeding.[8] About half of these may resolve on their own.[9]

Esophagogastroduodenoscopy (EGD) is considered the gold standard for diagnosis of EVs.[10] Various imaging modalities such as contrast-enhanced MRI, CT with contrast, angiography, doppler ultrasonography, endoscopic ultrasound, and Fibroscan have been evaluated for use in diagnosing EVs.[11] However most of these modalities are not widely available and have financial implications. Liver stiffness measurement (LSM) along with platelet count has been utilized a predictor of low risk of EVs.[12,13] The Baveno VI/ VII guidelines recommended against screening EGD in patients with LSM < 20kPa or platelet counts >150x10^9. [14]

The high prevalence of CLD, but limited with the availability of invasive screening modalities for EVs, such as EGD in regions like Pakistan raises the need for further investigation into alternative non-invasive methods that can be employed in developing regions.

Materials and Methods:

This was a cross-sectional study, performed in the outpatient department of Hepato-gastroenterology at Shifa International Hospital Ltd. Islamabad, approved by the Ethical Review Committee (IRB). Non-probability consecutive sampling was used for recruitments of patients. Based on the previously studied sensitivity of 93.5% and specificity of 88.75% of platelet count to prothrombin time ratio (PLT/PT ratio) and 95% confidence level, a sample size of 97 patients was required.[15]

A written consent was obtained from all the patients. A total of 140 patients, aged > 18 years, both male and female, who had been suffering from HCV-related chronic liver disease (HCV-CLD) for a period of at least six months were included. They were classified in two groups (Variceal and Non-variceal), the variceal groups were sub grouped into those with low risk/non-advanced EVs (Grade-1) and those with high risk/ advanced varices (Grade-2/3 EVs).

Patients with BMI>30, severe life-threatening comorbidities such as congestive heart failure (NYHA-III and IV), end-stage renal disease were excluded. Exclusion criteria also extended to patients who were of post-sclerotherapy status, or with a history of any previous intervention of EVs, hepatocellular carcinoma or portal vein thrombosis, patients already on a beta blocker or anticoagulation therapy, or patients having a haematological disorder affecting their platelet count.

All patients were subjected to a full medical history, while strictly following the inclusion and exclusion criteria, clinical assessment, and laboratory studies including complete blood count, HBsAg,Anti HCV, liver functions tests, Prothrombin time (PT), albumin, renal function tests. PLT/PT ratio was calculated and statistically analysed. Abdominal ultrasonography was performed by an experienced radiologist for measuring splenic diameter and assessing for features of CLD (Portal vein diameter, portal venous flow, Liver contour and echogenicity). Screening EGD was performed for EVs in endoscopy department.

Data analysis:

IBM SPSS Statistics, Version 26.0. (IBM, NY, USA) MedCalc version 19.4.1 was used for data entry and analysis. Qualitative data were reported as numbers and percentages. As the Kolmogorov-Smirnov test indicated that most variables were non-normally distributed, quantitative variables were expressed as median (IQR). The Chi-square test or the Fisher exact test as appropriate was used for the comparison of qualitative data between two groups and the Mann–Whitney U test was employed to assess differences in non-normally distributed quantitative data between the two groups. The receiver operating characteristic curve was used in assessing the diagnostic significance of significant predictors that had been associated with esophageal and advanced varices. A p-value of 0.05 or lower was regarded as statistically significant.

Results:

Amongst the total 140 patients, 86 (61.4%) were male and 54 (38.6%) females with overall median age of 54+/- 10.18 years. 86.4% (n=121) had EVs and 13.5 %(n=19) had no varices. Different clinical, laboratory and imaging features were compared between these two groups. (Table.1)

	Esophageal varices Yes (n=121 No (n=19)		
	n (%) Median (IQR)		p-value
Age	55 (50-60)	51 (49-65)	0.850
Gender			
Female	43 (35.5)	11 (57.9)	0.078
Male	78 (64.5)	8 (42.1)	
aspartate transaminase	47.0 (35.0-70.0)	37.0 (28.0-49.0)	0.084
Alanine transaminases	33.0 (23.0-48.0)	25.0 (20.0-48.0)	0.315
Total bilirubin	1.29 (.92-1.96)	.79 (.50-1.20)	0.002
Haemoglobin	10.20 (8.90-11.90)	12.80 (10.80-13.20)	0.001
Total leukocyte count	5470.0 (4120.0-8910.0)	5600.0 (4500.0-6600.0)	0.891
Platelets	101000.0 (70000.0-140000.0)	155000.0 (125000.0-183000.0)	0.000
Prothrombin time	13.00 (11.90-14.50)	10.50 (10.00-11.50)	0.000
International normalized ratio	1.25 (1.12-1.40)	1.09 (1.00-1.20)	0.000
Albumin	3.00 (2.70-3.50)	4.00 (3.50-4.00)	0.000
Sodium	135.0 (131.0-139.0)	136.0 (135.0-140.0)	0.235
Blood urea nitrogen	15.00 (12.00-23.54)	15.00 (11.00-20.00)	0.692
Creatinine	.92 (.70-1.20)	.72 (.50-1.00)	0.054
PV diameter	11.00 (10.00-13.00)	10.00 (10.00-11.00)	0.208
Spleen size	14.00 (12.80-16.10)	13.00 (12.00-13.40)	0.002
MELD sodium	13.0 (10.0-17.0)	10.0 (7.0-12.0)	0.001
AST to platelet ration index	1.10 (.70-1.90)	.60 (.30-1.20)	0.007
Fibrosis-4 score	4.90 (3.17-8.46)	2.40 (2.00-3.47)	0.001
Platelet to prothrombin time ratio	7342.50 (4797.29-10857.14)	15124.37 (9652.00-17700.00)	0.000
Platelet to splenic diameter ratio	7166.60 (4625.00-10160.00)	12500.00 (8141.59-15625.00)	0.000
Ascites			
Mild	44 (36.4)	1 (5.3)	0.009
Moderate	15 (12.4)	1 (5.3)	
Gross	4 (3.3)	0	
No ascites	58 (47.9)	17 (89.4)	
Child Pugh score			
Class A	46 (38.0)	16 (84.2)	0.001
Class B	62 (51.2)	3 (15.8)	
Class C	13 (10.7)	0	

In patients with varices the median age was found to be 55 years and in those without it was 51 years. The varices group contained 35.5% females and 64.5% males, in the non-varices group 57.9% were females and 42.1% males(p=0.078). No significance was found in AST, ALT and renal function tests between the two groups (p> 0.05). However, bilirubin levels, PT and albumin were statistically significant(p<0.05), along with haematological parameters such as haemoglobin levels(p=0.001) and platelet count(P=0.000). PT and INR were higher while the albumin levels were found to be lower in the variceal group as compared to those without varices (p=0.000). In imaging parameters, PV diameter showed no significance(p=0.208) however, patients with varices were found to have a larger splenic size which proved to be significant(p=0.002).

MELD (model for end stage liver disease) scoring, which involves the use of INR, renal function tests and albumin levels for assessment of need for the liver transplant in patients with CLD, was found to be significantly higher in the variceal group (p=0.001). Similarly, the AST to Platelet ratio index (APRI) (p=0.007) and the Fibrosis-4 score(p=0.001) were both also significant.

PLT/PT ratio was significantly lower in the varices group in comparison with non-variceal group (7342.50 vs 15124.37, p=0.000). Moreover, platelet to spleen diameter ratio (PLT/SD ratio) and the presence of mild ascites were both significant (P=0.000) and (p=0.009) respectively. 51.2% patients in variceal group had CTP Class-B while most of the patients in Non-variceal group had CTP-A, indicating increased rate of development of EVs with progressive stages of CLD. Higher values of PT, INR, and MELD score, APRI, FIB-4 and CTP Score while lower platelet count, albumin and PLT/PT were observed in patients with advanced high-risk varices. (Table.2).

Variceal Subgroups			
Nonadvanced/Low risk Grade-I (n=33)		Advanced/High risk varices Grade-II &Grade-III (n=88)	
n (%) Median (IQR)			p-value
Age	54 (48-57)	55 (50-62)	0.189
Gender			
Female	12 (36.4)	31 (35.2)	1.00
Male	21 (63.6)	57 (64.8)	
aspartate transaminase	42.0(30.0-64.0)	48.0 (38.5-70.5)	0.127
Alanine transaminases	32.0 (21.0-39.0)	34.0 (24.0-49.0)	0.356
total bilirubin	1.30 (.69-1.80)	1.29 (.92-2.07)	0.313
Hemoglobin	11.00 (9.60-12.70)	10.00 (8.85-11.55)	0.112
Total leukocyte count	5200.0 (4570.0-9240.0)	5520.0 (3875.0-8910.0)	0.528
Platelets	135000.0 (81000.0-151000.0)	97000.0 (65100.0-128000.0)	0.005
Prothrombin time	11.90 (11.01-13.60)	13.05 (12.20-14.75)	0.001
international normalized ratio	1.12 (1.05-1.28)	1.27 (1.15-1.44)	0.001
Albumin	3.30 (3.00-3.50)	3.00 (2.60-3.35)	0.009
Sodium	134.0 (130.0-136.0)	137.0(132.5-139.5)	0.027
Blood urea nitrogen	15.00 (10.00-18.00)	16.00 (12.00-25.00)	0.051
Creatinine	.96 (.65-1.07)	.91 (.70-1.23)	0.641
PV diameter	10.20 (10.00-12.00)	12.00 (10.00-13.00)	0.137
spleen size	13.50 (12.60-15.00)	14.20 (12.95-16.50)	0.144
MELD sodium	11.0 (10.0-15.0)	13.5(11.0-18.5)	0.035
AST to platelet ration index	.80 (.50-1.40)	1.30 (.75-2.00)	0.004
Fibrosis-4 score	3.30 (2.20-5.29)	5.28 (3.57-8.84)	0.002
Platelet to prothrombin time ratio	11200.00 (6330.11-13589.00)	6769.93(4218.17-9761.90)	0.000
platelet to splenic diameter ratio	9806.45(6000.00-12230.00)	6607.66(4394.97-9026.15)	0.015
Ascites			
Mild	8 (24.2)	36 (40.9)	0.070
Moderate	3 (9.1)	12 (13.6)	
Gross	0	4 (4.5)	
No ascites	22 (66.7)	36 (40.9)	
Child Pugh score			
Class A	22 (66.7)	24 (27.3)	0.000
Class B	9 (27.3)	53 (60.2)	
Class C	2 (6.1)	11 (12.5)	

Among the different non-invasive scores calculated in this study PLT/PT ratio at cut off value **≤12384** had the highest AUC (0.817) for prediction of EVs with increased sensitivity, specificity, PPV and diagnostic accuracy after FiB-4 score. (85.12%, 73.68%, 95.37%, and 83.57% respectively) as shown in table. Moreover, PLT/PT ratio also showed significant association with advanced grades of varices with sensitivity of 88.64% and diagnostic accuracy of 79.34%.

Discussion:

In this study PLT/PT ratio at cut off value of **≤12384** predicted EVs with sensitivity of 85.12%. Specificity of 73.68%, PPV of 95.37%, NPV of 43.74% and diagnostic accuracy of 83.57% with AUC of 0.817. Further PLT/PT ratio at the cut-off value of ≤11145.03, with AUC of 0.707, sensitivity of 88.64%, specificity of 54.55%, PPV of 83.87%, NPV of 64.29% and diagnostic accuracy of 79.34%.

Although PV diameter, PLT/SD, Fib-4. APRI was found to be significant for the prediction of EVs but PLT/PT ratio had the highest AUC, i.e. 0.817 and 0.707 for the presence of EVs and high-risk varices respectively. Further PLT/PT ratio had the highest diagnostic accuracy for detecting varices assessment of high-risk varices.

Moreover, a great variability has been observed between variceal and non-variceal group in terms of various prognostic scores such as MELD, CTP score, APRI, FiB-4 which indicate synthetic functions of liver as well as parenchymal and structural outline and similar changes were noticed in PLT/PT ratio, which reflects both the hepatic synthetic function (prothrombin time) and outcomes of portal hypertension (Low platelet count).

PHTN is a serious complication of CLD which is the main reason for the development of EVs, gastric varices and portal hypertensive gastropathy.[16] The American Association for the Study of Liver Diseases guidelines advise that EGD be carried out every 2 to 3 years minimum for the screening of varices.[17] However, due to the limited nature of such resources in developing countries, a need was felt to explore further non-invasive techniques, such as laboratory testing for biochemical markers etc for screening of EVs in patients with CLD.

Although the role of PLT/SD ratio has been studied in different populations for non-invasively predicting EVs but a systemic review by Chawla et al concluded it as inadequate parameter for the assessment of varices.[18] Our study also agreed with this statement because both Platelet count and splenic size only indicate PHTN which could be

secondary to causes other than liver cirrhosis such as isolated PV thrombosis or splenic vein thrombosis. Therefore, the PLT/PT ratio could be a better alternative which reflects both the liver function and portal hypertension.[18]

A study of MN Islam et al showed a positive correlation of prolonged PT with presence EVs with sensitivity of 56.67% and specificity of 73.33%. This study also reported association between Child Pugh score and presence EVs but no relationship with advanced grades of esophageal varices. Our study endorsed these results but the sensitivity and specificity could have been increased even more, if these variables could have been combined with Platelet count.[19]

Similarly, in another Indian study by Cherian et al, Low platelet count, CTP-B/C, splenic diameter (SD) and portal vein (PV) diameter were found significantly as independent variables in prediction of EVs and presence of high-risk varices. These variables were comparable with the present results in terms of sensitivity and specificity.[20]

Recently combined platelet count and albumin were compared with Baveno-VI and Transient Elastography (TE) in patients with HCV-CLD who were cured with direct acting antivirals (DAAs) and created HCV-RESIST criteria for prediction of high-risk varices. These criteria included platelet count and plasma albumin level. The Negative predictive value (NPV) of platelet count more than 120 x 10^9/L and Albumin level > 3.6g/dl for prediction of High-risk varices were 97.2% and 94.7%, respectively. The performance of these combined variables was almost similar to that of Elastography based algorithm and hence avoided unnecessary EGD in many patients. (21)

Tijana Glisic et al in another study in Serbia assessed various non-invasive scores such MELD score, AST to ALT ratio (AST/ALT), APRI, fibrosis-4-index (FIB-4), albumin-bilirubin (ALBI) score, and platelet-albumin-bilirubin (PALBI). This study concluded that ALBI and PALBI could be utilized for predicting presence of EVs with AUC of 0.603, and 0.606, respectively whereas APRI and MELD for high risk varices and variceal bleeding with AUC of 0.662 and 0.637 respectively which also endorse the results of our study but still the PLT/PT ratio had the highest AUC (0.817 and 0.707)[22]

PLT/PT ratio is easy to calculate which require simple blood test with no associated potential complications related to invasive procedures and imagine modalities. Still no data is available to find out its association with LSM. So further studies are required to focus at the association of PLT/PT ratio with LSM with hope that we can cooperate it into the algorithm for evaluation of portal hypertension and hence avoid unnecessary EGDs in these patients.

The main limitations of this study include single centre and cross-sectional study.

Conclusion:

PLT/PT ratio has significant association with both the presence of EVs and advanced grades of EVs.

Table 3. Diagnostic value of significant factors associated with E. varices (EVs)

Parameters	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
PV Diameter	>11	0.589	49.59	78.95	93.75	19.74	53.57
Fibrosis-4 score	>2.5	0.732	88.43	68.42	94.69	48.14	85.71
APRI	>0.7	0.692	68.60	63.16	92.22	24.00	67.86
PLT/SD ratio	≤10714	0.779	80.99	73.68	95.14	37.83	80.00
PLT/PT ratio	≤12384	0.817	85.12	73.68	95.37	43.74	83.57

Table 4. Diagnostic value of significant factors associated with advanced varices

Parameters	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
PV Diameter	>12.5	0.587	32.95	87.88	87.88	32.95	47.93
Fibrosis-4 score	>3.39	0.682	76.14	60.61	83.75	48.78	71.90
APRI	>0.5	0.669	93.18	39.39	80.39	68.41	78.51
PLT/SD ratio	≤9618.32	0.643	79.55	54.55	82.36	50.00	55.23
PLT/PT ratio	≤11145.03	0.707	88.64	54.55	83.87	64.29	79.34

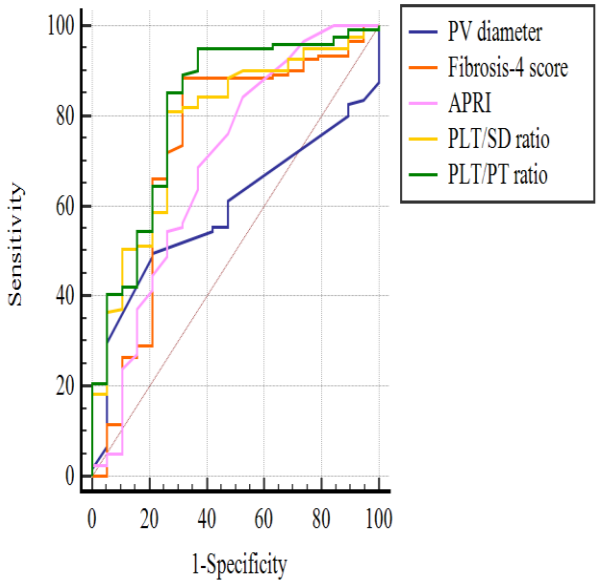
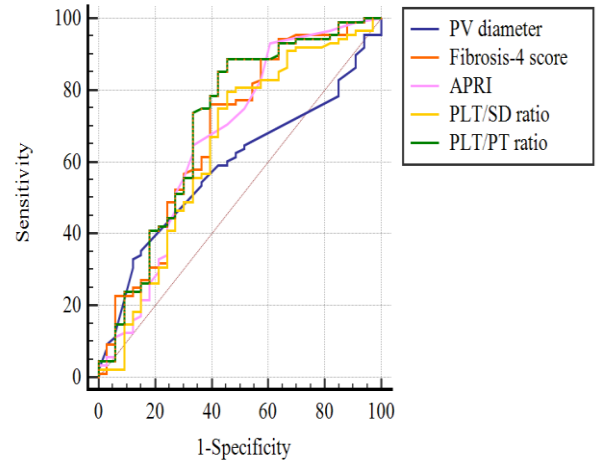


Figure: 2



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Author's Contribution:

MA: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
MA, SR, MS, AK, MBB: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.