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The ratio of platelet count / spleen diameter is an easy, accurate and affordable way to detect esophageal varices caused by chronic liver diseases

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Abstract
Variceal bleeding is one of the most serious consequences of liver cirrhosis due to its attendant high mortality. The prevalence of varices in patients with cirrhosis is approximately 60- 80% and the risk of hemorrhage is 25-35%. The incidence of first variceal hemorrhage ranges from 20 to 40% within 2 years. Recurrent bleedings occur in 30% to 40% of patients within the next 2 to 3 days and in up to 60 % within 1 week. Therefore, the prevention of esophageal varietal (OV) bleeding remains one of important long-term management lines of cirrhotic patients. The objective of the study is to assess the reliability of platelet count/spleen diameter (PC/SD) ratio for the noninvasive detection of OV in cirrhotic patients. One hundred twenty-five patients with history of chronic liver disease (CLD) were recruited from the GIT Hospital in The Medical City in Baghdad, Iraq. These patients had blood tests for platelet count, ultrasound examination to measure spleen diameter, and gastrostomy. Platelet count/spleen diameter ratio was calculated and compared with the presence/absence of oesophagealvarices. There was a high statistically significant correlation with high diagnostic accuracy of PC/SD ratio in detection esophageal varices and it was correlated well with size of varices. The platelet count/ bipolar spleen diameter ratio is a highly accurate noninvasive test to assess the OV in patients with CLD. It is easy to calculate and can lower the financial and sanitary burdens of endoscopy units, especially in developing countries.

Keywords: Chronic liver diseases, Oesophagealvarices, Platelet count, Spleen diameter.

Introduction

Liver cirrhosis causes disturbed liver function due to damage and replacement of liver parenchyma by fibrosis which developed from liver injury (1). Liver cirrhosis also causes portal hypertension which leads to OV which is the one of dangerous complications of portal hypertension (2). The first bleeding attacks usually happen in the first year of the diagnosis of varices (3), and carry a mortality rate of 5-10% (4-6). Therefore, screening for esophageal varices is an important part of the diagnostic steps in work up in patients with cirrhosis, in addition to its prognostic utility (7-8). Thrombocytopenia resulted from the chronic liver disease and OV is presumably related to the degree of portal hypertension and few other factors. The main cause behind thrombocytopenia in chronic liver disease is understandably due to platelet pooling in the spleen and antibody mediated destruction (9). In addition, the reduced production of thrombocytopenic protein from the liver (thrombopotien), the rapid degradation of the platelets and the inhibitory influence of the viruses on bone marrow may also play a role in development of the thrombocytopenia in patients with cirrhosis (10). Studies also showed there were antithrombic antibodies and thrombolytic associated immunoglobulins in the sera of patients with cirrhosis (11-12). Platelet count lower than 100,000 can be used as a predictor of OV (10). Two advantages are gained from using splenic diameter (SD) to predict the development of OV. The first one is that it can be performed in outpatient setting and second is that it can be done concomitantly during the 6-monthly screening for hepatocellular carcinoma by abdominal ultrasound (13). The current guidelines recommend a screening gastro copy at the diagnosis of cirrhosis and to be repeated every 1-2 years according to the findings of first gastro copy and on the severity of liver disease (14-17). Researchers have tried to find out noninvasive tests to predict esophageal varices instead of the usual invasive test (gastro copy) and thereby reducing the harm on patients and the burden on endoscopy units. Increasing burden on endoscopy units and prevent unnecessary harm to patients (18-19). Several studies have shown a number of noninvasive markers to predict OV and their bleeding risk such as hyopoalbuminemia, the Child-Pugh score, an increased SD, a low PC, the PC/SD ratio, and the aspartate aminotransferase-to-platelet ratio index (20-23). The use of PC/SD ratio is an important easy tool to predict OV. This hypothesis is supported

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by several reasons. Firstly, the platelet count may be reduced by several causes in patients with chronic liver disease (24-25). secondly, the PC/SD ratio was the only parameter independently correlated with the presence of OV.[26]thirdly, the ratio is easy to calculate and can be used at the bedside. Biannual measurement of the ratio will not add extra cost to the management cost of patients with cirrhosis. This is because the platelet count measurement is estimated routinely and the abdominal ultrasound is usually performed at least two times a year to monitor hepatocellular carcinoma (27). In fact, spleen diameter calculation usually show high reproducibility and low intra- and inter observer variability (28). For this aim, the PC/SD ratio was investigated to predict the presence of OV in adult patients with cirrhosis (29-31).

Methods and Materials

In this cross-sectional study, one hundred twenty-five patients with history of CLD were recruited from a tertiary GIT center (the GIT Hospital at the Medical City in Baghdad, Iraq. The study was conducted from April 2018 to January 2019. The history and physical examination were performed for these patients and classified according to etiology of chronic liver diseases. These patients also had measurement of platelet count, ultrasonography examination and gastro copy. The platelet count was measured by the machine of Celtac MEK-6510K by NIHON KOHDEN Company (automated analyzer). The ultrasonic-graphic Examination was performed by the machine of Phillips HD-11, to detect splenic diameter expressed by millimeters (mm). In this study we used the 110 mm measurement as upper normal limit for splenic size (32) while the gastro copy was accomplished with machine of EPK-i 5000 of PENTAX Company to detect the presence of OV. The study population was divided into two groups: the first group who had no varices and another group who had varices.

Esophageal varices were categorized into 4 grades as follows (33):

Grade (I): Varices at the level of mucosa.

Grade (II): Varices smaller than 5mm & filling less than 1/3 of the esophageal lumen.

Grade (III): Varices larger than 5mm & filling more than 1/3 of the oesophageallumen.

Grade (IV): Varices occupying more than 2/3 of esophageal lumen.

Then we used the following ratio:

Ratio =platelet count /spleen diameter (23)

We used this ratio to assess its reliability in prediction of OV in patients with history of chronic liver disease in patients referred to our hospital. Accordingly, we divided the patients into two groups:

- Those who had platelet count /spleen diameter ≤ 909.
- Those who had platelet count / spleen diameter >909.

Where the ratio ≤ 909 indicates presence of esophageal varices and when the ratio >909 indicates absence of OV.

Exclusion Criteria: Acute upper GIT bleeding, hepatic encephalopathy, Tran jugular intrahepatic port systemic shunt, Hepatocellular carcinoma, unstable general condition.

Statistical analysis: categorical variables were assessed using chi square using interactive chi-square software. The p value lower than 0.05 was used to measure statistical significance**,** validity tests by calculating sensitivity, specificity, accuracy rate, and negative and positive predictive values had been applied. All statistical tests were analyzed using the SPSS program version 24.

Results

The total number of patients was 125 patients, 66(52.8%) patients were male, and 59(47.2%) patients are female, and their ages were ranging between 16-80 years. The patients enrolled in this study had the following etiologies for the CLD: HCV infection 39 patients (31.2%); HBV infection 29 patients (23.2%), alcoholic liver disease 17 patients (13.6%); cryptogenic 13 (10.4%); autoimmune hepatitis 9 patients (7.2%); Wilson disease 7 patients (5.6%); primary sclerosing cholangitis 4 patients (3.2%); primary biliary cirrhosis 3 patients (2.4%); combined HCV infection and alcoholic liver disease 1 patient (0.8%), Methotrexate-induced liver disease 1 patient (0.8%); and glycogen storage disease 1 patient (0.8%). The patients were classified according to the presence or absence of esophageal varices and the grade of varices as follow: 57 patients (45.6%) had no varices, 68 patients (54.4%) had varices that were also classified into: 19 patients (15.2%) had grade I, 32 patients (25.6%) had grade II, and 17 patients had grade III (13.6%). In this study, we found that 45 patients (36%) had platelet count ≤ 100000 /ml and 80 patients (64%) had platelet count > 100000 /ml. One hundred three patients (82.4%) had spleen diameter ≥ 120 mm and 22 patients (17.6%) had spleen diameter < 120 mm. Men had statistically higher percentage (p-value =0.02) to have OV than the

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female (Table 1). The esophageal varices occur most frequently with advanced age where they occur in 48 (60%) patients out of 80 patients that their age more than 40 years old while the varices occur only in 17 (53.1%) patients out of 32 patients in those that their age range between 20-40 years old, and the varices occur only in 3 (23.1%) patients out of 13 patients that have their age less than 20 years old (table 2).

Table 1: The correlation between sex distribution and presence and absence of esophageal varices

Gender	With O.V.	Without O.V.	Total
Male	42(63.6%)	24(36.4%)	66(100%)
Female	26(44.1%)	33(55.9%)	59(100%)
Total	68(54.4%)	57(45.6%)	125(100%)

P-value = 0.02

Table 2: The association between age groups and presence and absence of oesophagealvarices

There is no significant statistical correlation p-value = 0.7

Age (in years)	With O.V.	Without O.V.	Total
<20	3(23.1%)	10(76.9%)	13(100%)
20-40	17(53.1%)	15(46.9%)	32(100%)
>40	48(60%)	32(40%)	80(100%)
Total	68(54.4%)	57(45.6%)	125(100%)

P-value: 0.7

In this study, we detected that the patients with low platelet count (≤ 100000/ml) had higher rate to have esophageal varices than patients with higher platelet count (>100000/ml), with statistical significance (p-value =0.0001) as shown in the table 3.

Table 3: The association between the platelet count and presence and absence of esophageal varices

PC	With O.V.	Without O. V	Total	Odds ratio (95% CI)
≤ 100000/ml	41(91.1%)	4(8.9%)	45(100%)	20.12 (6.52-62.06)
> 100000/ml	27(33.8%)	53(66.2%)	80(100%)	
Total	68(54.4%)	57(45.6%)	125(100%)	

There is highly significant statistical correlation p-value is 0.0001, odds ratio is 20.12, sensitivity is 60.29%, specificity is 92.98%, accuracy rate is 75.2 %, PPV is 91.1% and, NPV is 66.25%.

There was direct correlation between low platelet count (≤100000/ml) and the grade of esophageal varices with significant statistical correlation (table 4).

Table 4: The association between the platelet count and the grade of esophageal varices

Platelet count	Without O.V.	O.V. Grade I	O.V. Grade II	O.V. Grade III	Total
≤100000/ml	4(8.9%)	8(17.8%)	22(48.9%)	11(24.4%)	45(100%)
>100000/ml	53(66.2%)	10(12.5%)	12(15%)	5(6.3%)	80(100%)
Total	57(45.6%)	18(14.4%)	34(27.2%)	16(12.8%)	125(100%)

P-value: 0.00001

There was statistically significant correlation (p = 0.0001) between the spleen size and OV (table 5). In addition, we found a direct correlation between splenomegaly and the grade of OV as shown in table 6.

Table 5: The association between the spleen diameter and presence and absence of esophageal varices

Spleen diameter	With O.V.	Without O.V.	Total	Odds ratio(95% CI)
≥ 120 mm	66(64.1%)	37(35.9%)	103(100%)	17.83 (3.94-80.61)
< 120 mm	2(9.1%)	20(90.9%)	22(100%)	
Total	68(54.4%)	57(45.6%)	125(100%)	

There is highly significant statistical correlation p-value is 0.0001, odds ratio is 17.83, sensitivity is 97.05%, specificity is 35.08%, accuracy rate 68.8%, PPV is 64.07%, and NPV is 90.90%.

Table 6: The association between the spleen diameter and the grade of oesophagealvarices

Spleen diameter	Without O.V.	O.V. Grade I	O.V. Grade II	O.V. Grade III	Total
≥120mm	37(35.9%)	18(17.5%)	32(31.1%)	16(15.5%)	103(100%)
<120mm	20(90.9%)	0(0%)	2(9.1%)	0(0%)	22(100%)
Total	57(45.6%)	18(14.4%)	34(27.2%)	16(12.8%)	125(100%)

P-value = 0.001

The patients with a ratio of platelet count / spleen diameter ≤ 909 had higher rate of OV compared with patients with a ratio of >909 (Table 7).

Table 7: The association between platelet count /spleen diameter (PC/SD) ratio and esophageal varices

PC/SD	With O.V.	Without O.V.	Total	Odds ratio(95% CI)
≤ 909	63(86.3%)	10(13.7%)	73(100%)	59.22 (18.97-184.80)
> 909	5(9.6%)	47(90.4%)	52(100%)	

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Total	68(54.4%)	57(45.6%)	125(100%)	

There was highly significant statistical correlation p-value is 0.0001, odds ratio 59.2, sensitivity is 92.6%, specificity is 82.5%, accuracy rate is 88%, PPV is 86.3% and NPV is 90.4.

We also found that there is direct correlation between low platelet count / spleen diameter ratio and the grade of OV with a high statistical significance as shown in the table 8.

Table 8: The correlation between platelet count /spleen diameter (PC/SD) ratio and the grade of oesophagealvarices

PC/SD ratio	Without O.V.	O.V. Grade I	O.V. Grade II	O.V. Grade III	Total
≤ 909	10(13.7%)	18(24.7%)	29(39.7%)	16(21.9%)	73(100%)
> 909	47(90.4%)	1(1.9%)	3(5.8%)	1(1.9%)	52(100%)
Total	57(45.6%)	19(15.2%)	32(25.6%)	17(13.6%)	125(100%)

There is highly significant statistical correlation p-value 0.00001.

Discussion

Although there was a big advancement in management of patients with liver cirrhosis, bleeding from ruptured varices is still the leading cause of mortality (34). Using noninvasive way to diagnose OV has attractive potential. This is through reducing the number of screening gastro copy for patients with at high risk of varices (35). In addition, it reduces the risk of sedation to cirrhotic patients which regarded as high risky patients for anesthesia. Moreover, performing endoscopy may lead to disruption of the natural barriers which contribute to bacterial infection in patients with liver cirrhosis (36). Our study demonstrated that the esophageal varices occur more commonly in males (63.6%). This is consistent with the results of the study by Fook Hong et al. (37), who found 38 males (66%) and 15 females (34%), and the study by Schepis et al. (38), who found 94 males (66%) and 49 females (34%) have esophageal varices. We found that the esophageal varices occurring more frequently with advancing age. This is consistent with Monkez M. Yousif et al. (39), where they found the varices occur most frequently with advanced age. We study the association between platelet count and presence and absence of esophageal varices and we found that there is high significant correlation. Hamdy M. Mostafa et al. (40), and G. Chandra Shekar et al. (41), found that patients with OV demonstrated a significant reduction in platelet count than the patients who do not OV and this equivalent with our study result. Similarly, the study accomplished by Gue et al., revealed a correlation between size of varices and lower platelet and leukocyte counts (42). This is also true for BC Kaji et al. (43), showed similar correlation. Our data also showed that there is association between the spleen size and presence and absence of OV. Like our result, Esmatet al. (44), found a high statistically significant correlation between the presence and grade of OV with the SD ($p<0.001$). In addition, Watanabe and colleagues,[45]measured the splenic index (length X width X height of the spleen) on CT-Scan and revealed that patients having an index higher than 963 have esophageal varices, and this in turn can predict OV bleeding in patients with liver cirrhosis. Amarapurkaret al. (46), argued that splenomegaly alone is a significant predicting sign for the development of large esophageal varices. However Mahassadiet al. (47), demonstrated that SD has a lower predicting ability in diagnosis of OV in African patients with liver cirrhosis. This may be due to a high prevalence of chronic parasitism and anemia in African patients which can contribute to splenomegaly (48). However, Rasheid, S.A. et al. (49), found that correlation between degree esophageal varices and splenomegaly detected by ultrasound was insignificant. These differences could signify that it is actually difficult to predict the grading of OV only by the interpretation of the bipolar diameter of the spleen but they can also be the result of an interpretation bias because of different methodologies used in different studies and the lack of standardization in the study protocols. The most accurate evaluation is obtained when measurements are performed in an identical setting in all patients: the same plane of ultrasonography section, the same phase of respiration, same etiology of cirrhosis, same race and phenotype for all patients (50). Our study also confirmed the association between PC/SD ratio and presence and absence of OV. Similarly, Giannini et al. (23) utilized the PC/SD ratio in the prediction of OV in patients with cirrhosis as it estimates the level of thrombocytopenia which usually depends on hypersplenism. Giannini et al. (27), revealed in 2003 in a study of 145 cirrhotic patients that PC/SD ratio is independent and high accurate diagnostic tool to predict the presence of OV at a cut off value of 909 (the negative predictive value was 100%, sensitivity 100% and specificity 71%).[24]This was confirmed by Agha et al. (50), using the same cut off of 909 while Esmat& Rashid (51), showed that the PC/SD ratio yielded the

highest accuracy (94%) at a cut-off value of 1326.MonkezM.Yousif (39), found that analysis of the cut-off of the platelet count/spleen diameter ratio (750) was the optimal value for accurate prediction of OV with a resulting 81% sensitivity, 81% specificity and 81% accuracy. The differences between the best cut-off values, sensitivity, specificity, and accuracy in our study and other studies may be attributed to several factors influencing the platelet count including infection, drugs, and lower thrombopoietin levels in patients with liver cirrhosis. In addition, the absence of Interobserver agreement between the sonographers and endoscopists of the different studies which can affect the results (48), we found an association between the PC/SD ratio and the grade of OV. Saranagapani A. et al. (52), found that the platelet count/spleen diameter ratio is also useful in the discrimination of large versus small varices and in their study a platelet spleen diameter ratio of less than 909 was statistically significant in predicting large varices. Elshazly Abd Elhady Sheta et al. (53), found a statistically significant relation to the presence and grade of OV (p. value<0.001).On the other hand Ozdil et al. found that PC/SD ratio was not significantly different between large and small gastric varices (p>0.05) (54).

Conclusion

The use of the PC/SD ratio is effective tool to detect many patients with OV. Measuring the PC/SD ratio could be proposed in clinical practice as part of the diagnostic workup of patients with chronic liver disease in order to reduce the financial and sanitary burden of the endoscopy unit as well extra medical costs related to OV screening.

Conflicts of interest: The authors have no conflicts to declare.

Author Contributions: Ali Naji Musa wrote the paper. Mahmoud Alchlaihawi, Manal F. AL-Khakani and Jasim Al Malki designed the idea and collected the literatures. The authors reviewed and approved the final manuscript.

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