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Research Article

Thrombocytopenia in newly diagnosed cases of liver cirrhosis

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Summary

Aim: The aim of this study was to determine the incidence of thrombocytopenia in cases with liver cirrhosis and its relationship with the severity of the disease. A retrospective study of cases with liver cirrhosis was conducted out from 2017 to 2021. The information was collected from the patient's hospital records at their first admission. The study group included 361 individuals over the age of 18 - 258 (71%) men and 103 (29%) women. A platelet count below 150 G/L was considered an indicator of thrombocytopenia. Results were analized using IBM SPSS 26 and Excel statistics. Results: Thrombocytopenia was found in 171 (47.4%) subjects. In 45 (26%) cases, accounting for 12.46% of the studied population with cirrhosis, thrombocytopenia was not accompanied by hematological abnormalities. There was no statistical relationship between the Child-Pough stage and the presence of thrombocytopenia (p = .400) and no statistically significant differences in platelet counts among the three Child-Pough stages (p = .205). The thrombocytopenia cases had a higher MELD Na than those without, with a statistically significant difference between the two groups (p = .002). Of the thrombocytopenia cases, 73.7% had oesophageal varices (p = 0.000). A cut-off value of 181G/L with 73% sensitivity and 54.5% specificity for predicting the occurrence of varices was established. There was no statistical association between thrombocytopenia and portosystemic encephalopathy (PSE); (p = .591). Thrombocytopenia is an important laboratory finding in the progression of portal hypertension in liver cirrhosis. An isolated finding also requires ruling out chronic liver disease and endoscopic examination to exclude oesophageal varices.

Key words: Child-Pough, MELD Na, oesophageal varices, platelet count, portosystemic encephalopathy

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Introduction

It has been shown that detecting cytopenia in the peripheral blood during bone marrow examination does not identify specific morphological changes in cases of cirrhosis, with thrombocytopenia being its first manifestation (Koschade et al. 2023). In 80.5% of cases with peripheral cytopenia, hypersplenism is present and is associated with liver cirrhosis. However, splenectomy is clinically ineffective (Lv et al. 2017) due to other pathophysiological mechanisms for its manifestation (Gallo et al. 2022). It has been found that decreased thrombopoietin production (Gallo et al. 2022), bone marrow suppression, and autoimmunity (Tajiri et al. 2023) are the main causes of developing thrombocytopenia. The

prevalence varies significantly from 6% to 78%, which has been associated with the transition from chronic liver disease to decompensated cirrhosis (Gallo et al. 2022). Chronic hepatitis C cases were found to have lower Plt (Pletelet) counts compared to healthy controls and further reduced progression to cirrhosis (Ali et al. 2015). A Plt count below 150 G/L is an important marker for cirrhosis progression and is inversely correlated with the severity of liver fibrosis, which is directly related to the onset of portal hypertension (Sigal et al. 2020). For isolated thrombocytopenia, the primary cause are believed to be alcohol-related liver cirrhosis, non-alcoholic fatty liver disease (NAFLD), and chronic hepatitis (Sheikh et al. 2012). In general, its presence is associated with worse prognosis, more complications, and more severe liver disease (Ahmed et al. 2021; Araji et al. 2023), as well as increased 90-day mortality in cases with acute-on-chronic liver failure (Ouyang et al. 2021). The decrease in leukocytes follows chronologically after thrombocytopenia (Qamar et al. 2009; Pierucka et al. 2016). Their combination is associated with advanced fibrosis (Pierucka et al. 2016) and poor prognosis, even in the compensated stage (Qamar et al. 2009).

Aim: To determine the incidence of thrombocytopenia in newly diagnosed cases with liver cirrhosis and its relationship with the stage of the disease.

Material and methods

A retrospective study was conducted on newly diagnosed cases of liver cirrhosis treated at the Gastroenterology Clinic of Dr. Georgi Stranski University Hospital-Pleven from 2017 to 2021. A primary documentary method was used. The necessary information was collected from patients' records on their first admission. The study group included 361 individuals over the age of 18: 258 (71%) men and 103 (29%) women, and a mean age of 57.8 ± 11.4 years. Alcohol alone or in combination with other factors was identified as the major etiological factor in 262 (72.57%) of the cases. All patients were classified using the Child-Pough scoring system (https://www.mdcalc.com/calc/340/child-pugh-score-cirrhosis-mortality). There were 98 (27%) cases in Child A, 141(39%) in Child B, and 122 (34%) in Child C. The MELD Na score (Model For End-Stage Liver Disease) was calculated for each patient using an online calculator (https://www.mdcalc.com/calc/10437 model-end-stage-liver-disease-meld?). In our study, the reference limit for Plt was set between 150–400 G/L. Thrombocytopenia was defined as a Plt count below 150 G/L. Thrombocytopenia cases were divided into three groups: 150–100 (mild), 100–80 (moderate) and below 80 (severe) G/L. Upper gastrointestinal endoscopy (UGE) was performed on 263, of whom 164 (62.12%) had oesophagal varices (EV). A modified Pocket classification was used to categorize them as small, medium and large. Portosystemic encephalopathy (PSE) cases were graded using the West-Haven classification from grade I to IV. The results were analyzed using the Crosstabulation and Pearson-Chi Square test to test hypotheses about qualitative (categorical) data distribution; ANOVA - to compare variances between means and standard deviation (SD) of different groups; Kolmogorov-Smirnov test to check the normal distribution of the data, and Mann-Whitney and Kruskal-Wallis test to compare two or more samples or groups that were not normally distributed. A ROC analysis was performed to assess the diagnostic and predictive value of Plt counts for detecting EV. Data was processed using IBM SPSS 26 and Exel statistics. A value of $p < 0.05$ was accepted as a level of significance.

Results

Out of the people examined, 171 (47.4%) had thrombocytopenia, regardless of its severity and the stage of the disease. Cases with mild thrombocytopenia predominated (79; 46%). Pure thrombocytopenia was present in 45 cases (26% or 12.46% of the entire studied cirrhotic population) without other hematological abnormalities. The most common combination of thrombocytopenia was with anemia (Fig. 1).

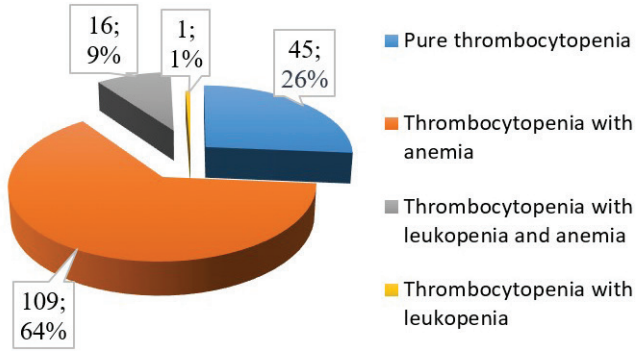

Figure 1. Thrombocytopenia alone and in combination with other hematological abnormalities: Legend: N = 171: Number of cases with thrombocytopenia present in the whole cirrhotic population

When evaluating the relationship between etiology and the occurrence of thrombocytopenia, it was found that the frequency was higher in cases with a non-alcoholic etiology. Despite the differences found, there was no statistical difference between the two groups: Pearson-Chi Square test 9.360 df3, p = .025 (Fig. 2).

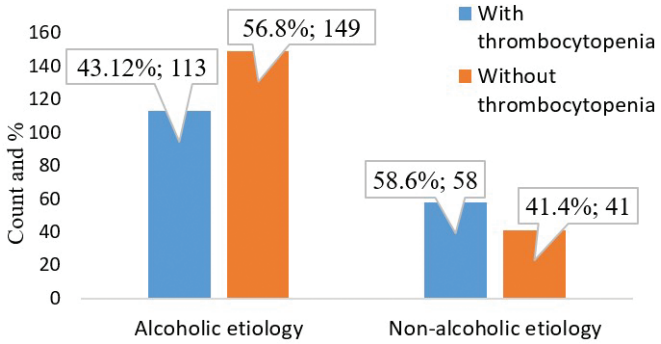

Figure 2. Frequency of thrombocytopenia depending on the etiology: Legend: N = 361: Number of cases with alcohol etiology is 262 (72.57%), and with non-alcoholic is 99 (27.43%)

The distribution of thrombocytopenia cases according to Child stage showed no statistical relationship: Pearson Chi-Square test 6.208 df 6 p = .400 (Table 1).

There were no significant differences in the Plt count in the three Child-Pough stages: Kruskal-Wallis test H df 2 F 1.592 p = .205 (Table 2).

Thrombocytopenia cases were found to have a higher MELD Na than those without, and there was a statistically significant difference between the two groups: Mann-Whitney test U p = .002 (Fig. 3).

UGE was performed on 263 (72.5%) of all the patients. The results demonstrated a statistically significant difference in the number of Plt in the cases

Table 1. Dependence on Child-Pough score and the presence of thrombocytopenia.

Thrombocytopenia	Child A N = 98	Child B N = 144	Child C N = 122
No	57 (58.2%)	73 (51.8%)	60 (49.2%)
% in Child	30%	38.4%	31.6%
Mild	15 (15.3%)	37 (26.2%)	27 (16.4%)
% in Child	19%	46.8%	34.2%
Moderate	13 (13.3%)	14 (9.9%)	20 (16.4%)
% in Child	27.7%	29.8%	42.6%
Severe	13 (13.3%)	17 (12.1%)	15 (12.3%)
% in Child	28.9%	37.8%	33.3%

Table 2. Platelet count in the Child stage.

Plt G/L	Child A N = 98	Child B N = 144	Child C N = 122
Mean ± SD	186.44 ± 115.23	177.87 ± 94.81	163.31 ± 86.03
Min-Max	(14–796)	(45–499)	(41–393)
Mean Rank	190.73	184.73	168.87

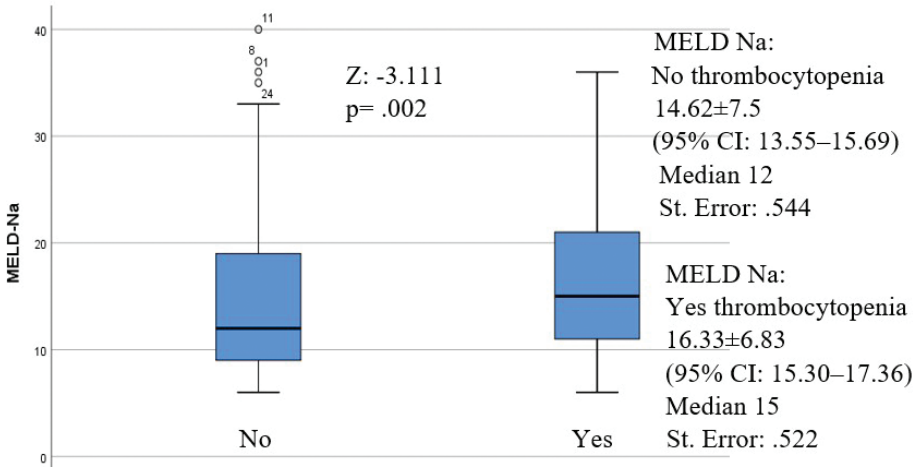

Figure 3. MELD Na in cases with and without thrombocytopenia: Legend: N = 361: Number of cases; Yes:171(47.4%) with thrombocytopenia; No:190 (52.6%) without thrombocytopenia

without and with varices, regardless of their size. When comparing cases with existing varices, it was found that as the size increases, the number of Plt counts significantly decreases (Table 3).

Of all those with thrombocytopenia, a total of 137, 101 (73.7%) had varices. Of all 126 without thrombocytopenia, 63 (50%) had varices. The obtained result confirmed that establishing thrombocytopenia was significantly associated with the presence of varices: Pearson-Chi Square test 27.414 df 3 p = .000 (Fig. 4).

ROC analysis revealed a cut-off of 181G/L with 73% sensitivity and 54.5% specificity for predicting the appearance of EV (AUR .632, SE .037, 95% CI 560–704). Examining the relationship between the presence of thrombocytopenia and the occurrence and severity of PSE did not reveal statistical dependence: Pearson Chi-Square test 2.806 df4 p = .591 (Table 4).

Table 3. Dependence on platelet count and presence of EV.

EV:	Plt G/L:	Significance:
Without EV:	Mean:193.12	df 1 F 9.406 p = .002
N = 99	SD ± 98.836	
With EV total:	Mean:154.70	
N = 164	SD ± 98.203	
Small:	Mean:186.50	df 3 F 7.398 p = .000
N = 66	SD ± 121.621	
Moderate:	Mean:138.55	
N = 58	SD ± 82.351	
Large:	Mean:125.63	
N = 40	SD ± 52.628	

Table 4. Dependence on PSE and the presence of thrombocytopenia.

PSE	Without Thrombocytopenia	With Thrombocytopenia	Total (N)
No	101(52.9%)	90 (47.2%)	191
I	60 (51.7%)	56 (48.3%)	116
II	19 (51.4%)	18 (48.6%)	37
III	7 (50%)	7 (50%)	14
IV	3 (100%)	0 (0%)	3

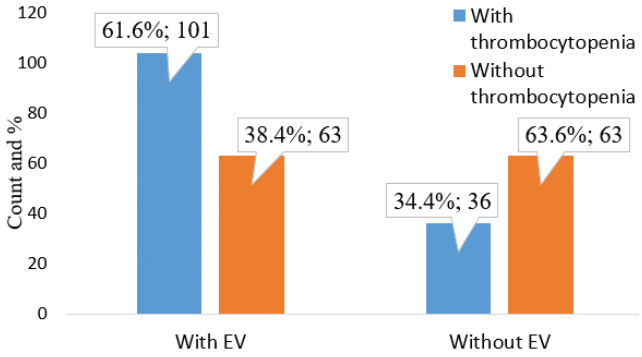

Figure 4. Dependence between Presence of EV and thrombocytopenia: Legend: N = 263 cases with performed endoscopy examination; Shows the incidence of thrombocytopenia in cases with 164 (62.35%) and without 99 (37.64%) EV

Discussion

Thrombocytopenia was found in 171 (47.4%) of the cases examined, regardless of its severity and stage of the disease. The obtained result is consistent with data from other studies: 48.7% (Sambyal and Bharti 2019), 50% (Solomon et al. 2017), 51% (Rahman et al. 2022) and accordingly differs from the authors who reported a higher frequency: 56% (Tomar et al. 2023), 58.9% (Kaur et al. 2021), 60% (Al-Dholae et al. 2023), 61.4% (Abbas et al. 2022), and 64% (Sohail et al. 2023). These differences are likely due to varying proportions of decompensated patients in the study populations. In cases with thrombocytopenia (171; 47.4%) in 45 (26%) or 12.46% of the cirrhotic population being isolated without concomitant anemia and leukopenia. The obtained result shows that establishing isolated thrombocytopenia

may be a reason to exclude chronic liver disease in the differential diagnosis. A study found that 35% of cases with thrombocytopenia on bone marrow biopsy had previously unrecognized liver cirrhosis (Sheikh et al. 2012). When examining the dependence on the etiology, we found that out of 99 cases with a non-alcoholic etiology, 58 (58.6%) had thrombocytopenia, and of those 262 with an alcoholic, thrombocytopenia was detected in 113 (43.12%). The obtained result showed no statistical dependence, despite the greater frequency in non-alcoholic etiology, which also corresponds with results reported by other authors (Koo et al. 2000; Nadinskaia et al. 2023). Evaluation with Plt count and Child-Pough stage did not show a statistically significant difference. Another study found a relationship close to significant (Tomar et al. 2023). According to other authors, the progression to Child B and C is associated with a decrease in the number of Plt in an inverse relationship (Yang et al. 2020). A possible reason for the reported differences can be attributed to the different etiological profiles of the studied groups, with alcohol etiology taking the majority in our study and viral etiology prevailing in the groups compared. One other research found that the severity of thrombocytopenia correlates well with the severity of cirrhosis in viral etiology but does not correspond to the severity in alcohol etiology (Koo et al. 2000). Cases with thrombocytopenia had a significantly higher MELD Na than those without it. The mean value was 16.33, consistent with findings from other researchers' results (Ismail et al. 2008; Jain et al. 2016). Other studies reported values of 16.89 (Sohail et al. 2023), respectively (Al-Dholae et al. 2023) and 19.7, which are in close to ours. For the same MELD Na value, thrombocytopenia cases have a threefold higher mortality (Moore et al. 2019). EVs were found in 73.3% of cases with thrombocytopenia and underwent UGE. Out of 164 patients with existing EV, thrombocytopenia was present in 61.6% of them. The obtained result confirmed the statistical dependence between them. These results are consistent with previous studies (Sigal et al. 2020; Uong et al. 2023). With their appearance and progression, the number of Plt significantly decreases, which is consistent with finding from other authors (Ismail et al. 2008; Afsar et al. 2021; Uong et al. 2023). Our established Plt cut-off value for manifestations of EV was 181G/L with a sensitivity of 73% and a specificity of 54.5%, which differs from another study that sat a cut-of value of 123 G/L with a sensitivity of 75% and a specificity of 65% (Uong P et al. 2023). Although thrombocytopenia predicts the presence of varices, the method's sensitivity is not reliable enough for clinical practice (Sigal et al. 2020). Despite this fact, the severity of thrombocytopenia has been shown not to be directly related to hemorrhagic risk in patients with high-grade varices after TIPS (Transjugular intrahepatic portosystemic shunt) (Chen et al. 2023). In our study, no association was found between the presence of thrombocytopenia and PSE. Our result significantly differs from another study where a low Plt count combined with lower albumin and prolonged INR (International Normalized Ratio) was associated with PSE (Eid et al. 2021).

Conclusion

The appearance of thrombocytopenia is an important laboratory finding in the progression of portal hypertension in liver cirrhosis. It is often associated with other hematological manifestations. However, its detection as an isolated finding also requires the exclusion of chronic liver disease and performing an endoscopic examination to rule out oesophageal varices.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.
The authors declared that no experiments on humans or human tissues were performed for the present study.
The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
The authors declared that no experiments on animals were performed for the present study.
The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

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Data availability

All of the data that support the findings of this study are available in the main text.

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