MEDICAL UNIVERSITY – PLEVEN

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"Epidemiological and clinico-laboratory characteristics in patients of liver cirrhosis in its different stages"

"AUTHOR'S ABSTRACT"

Of a Dissertation
For the Award of the Educational and Scientific Degree

"DOCTOR"

Field of Higher Education: 7. Healthcare and Sports
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Assoc. Prof. Dr. Ivan Anastasov Lalev, PhD

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The dissertation consists of 193 pages and is illustrated with 51 tables and 97 figures. It includes one appendix.

The bibliography contains 431 sources, of which 7 are in cyrillic and 424 in latin script.

The dissertation was reviewed and approved for public defense by the extended departmental council of the Department of Nephrology, Hematology, and Gastroenterology at the Medical University - Pleven, held on March 13, 2025.

The public defense of the dissertation will take place on ……, at …… hours, in room …….

The materials related to the defense are available to those interested at the Library of the Medical University - Pleven and on the university's website – www.mu-pleven.bg.

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ABBREVIATIONS USED:

AF – Alkaline Phosphatase
AH – Alcoholic Hepatitis
AKI – Acute Kidney Injury
ALAT – Alanine Aminotransferase
ALBI – Albumin/Bilirubin Ratio
ALC – Alcoholic Liver Cirrhosis
ALD – Alcoholic Liver Disease
ALF – Acute Liver Failure
ANOVA – Analysis of Variance
ASAT – Aspartate Aminotransferase
AT – Aminotransferases
EASL – European Association for the Study of the Liver
Er – Erythrocyte Count
GFR – Glomerular Filtration Rate
GGT – Gamma-Glutamyl Transpeptidase
Hb – Hemoglobin Level
HRS-AKI – Hepatorenal Syndrome - Acute Kidney Injury
HRS-non AKI – Hepatorenal Syndrome – Non-Acute Kidney Injury
INR – International Normalized Ratio
Maximal – Maximum Value
MCV – Mean Corpuscular Volume
Mean – Mean Value of the Examined Parameter
MELD Na – Model for End-Stage Liver Disease - Sodium
Minimal – Minimum Value
NAFLD – Non-Alcoholic Fatty Liver Disease
Plt – Platelet Count
Range – Range of the Examined Parameter
SD – Standard Deviation of the Examined Parameter
WBC – White Blood Cell Count

TABLE OF CONTENTS:

The numbering of figures and tables in the text does not correspond to that in the dissertation.

INTRODUCTION:

Liver diseases are the 11th leading cause of death worldwide, often associated with complications such as liver cirrhosis, hepatocellular carcinoma, and chronic viral hepatitis. The increasing global prevalence of alcohol dependence and related conditions, including liver damage and non-alcoholic fatty liver disease (NAFLD), represents a significant health and socioeconomic challenge. According to the WHO, alcohol ranks as the third most significant health-damaging risk factor, with the risk of disease development being genetically determined. It is responsible not only for liver damage but also for other socially significant diseases, such as hypertension, cerebrovascular diseases, malignancies, and mental and behavioral disorders. Long-term observations reveal that global alcohol consumption per capita has risen from 5.5 liters in 2005 to 6.4 liters in 2016, with projections suggesting a further increase to 7.6 liters by 2030. According to predictive models, by 2040, the prevalence of decompensated alcoholic cirrhosis is expected to reach 77%, with an associated mortality rate of 17.5 per 100,000. NAFLD is the most common chronic liver disease globally, with an estimated prevalence of 32.4%. It is recognized as the leading cause of cryptogenic cirrhosis, accounting for 75% of cases. Predictive models suggest that the prevalence of NAFLD will double by 2030 compared to the baseline level in 2016. In 2016, the WHO introduced a global strategy to eliminate hepatitis by 2030 through prevention, testing, and improved access to treatment, aiming for a 90% reduction in morbidity and a 65% reduction in mortality compared to the 2015 baseline. The declining prevalence of hepatitis B and C in recent years is attributed to improved treatment access, reducing their role as leading causes of cirrhosis. Cirrhosis represents the final stage of liver disease, characterized by severe complications, high mortality, and costly long-term treatment, particularly among individuals of working age. Clinical manifestations of liver failure typically occur after the loss of 80–90% of functioning liver parenchyma. Studies have shown a weak correlation between histopathological findings and clinical manifestations, leading to cirrhosis being termed the "silent disease," as most cases remain asymptomatic until decompensation occurs. Portal hypertension is responsible for the clinical complications, including esophageal varices, ascites, hypersplenism, hepatorenal syndrome, and jaundice. Acute-on-chronic liver failure can occur at any stage of the disease, often triggered by infection or severe alcoholic hepatitis. The prolonged asymptomatic nature of the disease, combined with the specific psychological profile of patients with alcohol dependence—often marked by a lack of awareness and criticality regarding their condition—makes diagnosis challenging and frequently delayed. The use of advanced but costly diagnostic methods for early fibrosis detection, such as FibroScan and elastography, is often inaccessible due to patients' poor socioeconomic status and lack of cooperation. Liver transplantation, the current definitive treatment for cirrhosis, remains a "panacea" in modern medicine. Despite advancements in

medical knowledge, better understanding of deviations in standard laboratory and biochemical tests is crucial for early identification and monitoring of these cases. Therefore, there is a growing need for a relatively simple and cost-effective approach for diagnosing and monitoring liver cirrhosis, utilizing standard clinical, laboratory, and instrumental tests applicable in routine daily practice.

AIM AND OBJECTIVES OF THE DISSERTATION:

AIM:

To study the epidemiological and clinico-laboratory characteristics of newly diagnosed hospitalized cases of liver cirrhosis in its different stages.

OBJECTIVES:

1.Analyze the demographic characteristics of the studied population:
-By gender, age, and etiology in the overall cirrhotic population and determine the relationship between these factors.
-By gender, age, and age groups in the population with pure alcoholic etiology.
2.Analyze the relationship between the etiological factor and the Child-Pugh stage at the time of diagnosis.
3.Analyze the prevalence of existing complications and their correlation with the Child-Pugh stage at the time of diagnosis.
4.Analyze the changes in key laboratory parameters and their correlation with the severity of liver disease.
5.Analyze cases of superimposed alcoholic hepatitis on cirrhosis with alcohol as an etiological facto-By their demographic characteristics.
-Analyze the values of laboratory parameters. -
Compare and evaluate the Child-Pugh, MELD-Na, and ALBI scores in cases of alcoholic cirrhosis and alcoholic hepatitis.

MATERIAL AND METHODS:

MATERIAL:

The study was conducted at the Gastroenterology Clinic of UMHAT "Georgi Stranski" – Pleven EAD, in accordance with ethical standards, with all data used being completely anonymous. A total of 361 newly diagnosed cases of liver cirrhosis were included, involving patients over 18 years of age who were hospitalized and treated during the period from January 1, 2017, to December 31,

2021. The study is a single-stage, entirely retrospective analysis, based solely on the first registered hospitalization at the time of diagnosis. All cases were clinically confirmed using standard routine diagnostic methods, without histological verification. The study excluded individuals with a history of previously documented liver disease, as well as cases with acute gastrointestinal bleeding treated in surgical departments, as they were not the focus of the current research.

METHODS:

1. Documentary Method: The necessary information was collected from the patients' medical records.

2. Anamnestic Data: Data were gathered regarding existing complaints, preceding and concomitant diseases, medications taken, and identified risk factors such as alcohol consumption and smoking.

3. Physical Examination: A thorough examination of organs and systems was performed to document the patient's objective condition at the time of diagnosis

4. Laboratory tests (Table 1).

Table.1 *Laboratory investigations*

Indicators	Measure	Reference limit
Hb Mild anemia Midle anemia Severe anemia	g/L	130–180 <130 for man <120 for women 100–80 < 80
Er	x10*12/L	4.4–5.9
MCV Microcytosis Normocytosis Macrocytosis	fl	82–96 <80 80–100 >100
Plt Mild thrombocytopenia Moderate thrombocytopenia Severe thrombocytopenia	x10*9/L	150–400 150–100 100–80 < 80
WBC Leucopenia Leucocytosis	x10*9/L	3.5–10.5 <3.5 >10.5
ASAT	UI/ml	0–40
ALAT	UI/ml	0–40
GGT	UI/ml	0–50

AP	UI/ml	40–130
Albumin No hypoalbuminemia Yes hypoalbuminemia	g/l	35–50 >35 <35
Total bilirubin Subicter Icter	μmol/l	< 21 21–50 >50
Direct bilirubin	μmol/l	до 5
Urea	mmol/l	2.8–8.1
Creatinin	μmol/l	53–115
INR		0.8–1.1
Sodium No hyponatriemia Mild hyponatriemia Severe hyponatriemia	mmol/l	135–145 >135 135–130 <130

Cases with anemia syndrome were categorized based on its severity and according toMCV
[StatPearls [Internet] https://www.ncbi.nlm.nih.gov/books/NBK545275/.]. All cases had no prior documentation of bleeding or blood transfusion within the past year. A baseline serum creatinine level above 130 μmol/l was considered a measure for identifying renal function impairment, due to the absence of previous data. Chronic kidney disease (CKD) was diagnosed in the presence of a prior history of renal disease unrelated to liver cirrhosis, as well as in cases without such history but with established changes in the renal ultrasound image and/or comorbidities and/or laboratory abnormalities suggesting its presence. Acute kidney injury (AKI) was defined as a reversible or irreversible acute impairment of renal function, without specifying the precipitating factor. Hepatorenal syndrome (HRS) was presumed in cases with a normal renal ultrasound image, without prior or current cause for renal pathology, in the presence of advanced liver disease, bland urinary sediment, and absence of proteinuria and hematuria in standard urine tests. Cases of HRS-AKI and HRS-nonAKI, according to the contemporary definition, were not analyzed separately due to the lack of GFR assessment in all patients (a limitation associated with the retrospective study design), as well as the absence of prior laboratory data clarifying renal function and subsequent chronological follow-up.

5. Serological Tests: HBsAg and Anti-HCV. For all positive results, an additional PCR test was performed to determine viral replication.

6. Immunological Tests: AMA testing was performed in cases of suspected primary biliary cirrhosis (PBC).

7. Additional Tests: Urinalysis.Standard cytological and biochemical analysis of ascitic fluid in cases of paracentesis.Microbiological tests when indicated.

8. Instrumental Examinations:

8.1. Abdominal Ultrasound: The evaluation was performed using a conventional method, based on the following criteria:Change in liver size.Restricted mobility.Alteration in echostructure.Irregular contours and shape deformation.Reduction in vascular network.Diameter of the *Vena portae* and *Vena lienalis*.Presence or absence of focal lesions.Double contouring and thickening of the gallbladder wall.Presence or absence of splenomegaly.Presence or absence of ascites.

8.2. Upper Gastrointestinal Endoscopy: Performed in 263 patients during their first hospitalization. The number of endoscopic examinations was lower than the total number of cases included in the study due to patient refusal or temporary contraindications.

The aim was to identify the presence and size of esophageal varices (EV) at the time of diagnosis. For statistical processing, the modified Poquet classification wasapplied.

Table 2. *Poquet classification*

I degree-small EV	Varicose veins extending just above all of the mucosa
II degree-midle EV	Varicose veins, prominent and occupying one-third of the lumen diameter, that cannot be compressed with air insufflation
IIIdegree-large EV	Varices, prominent and occupying up to 50% of the lumen diameter and in contact with each other

9. Analysis of Clinical and Laboratory Results:

9.1. Staging: The cases were staged using the *Child-Pugh* scoring system, categorized into Child A, B, and C.

Table 3. *Child-Pugh score system*

Indicators	1 point	2 point	3 point
Ascites	no	moderate	tense
PSE	no	I-II degre	III-IV degre
INR	<1.7	1.7–2.2	>2.2
Albumin g/l	>35	35–28	<28
Total bilirubin µmol/l	<34	34–50	>50
Child A:5–6p.- compensated illness Child B :7–9p.- moderate decompensation Child C:10–15p.- severe decompensation			

9.2. Ascites Assessment**:**Evaluated through physical examination and ultrasound, classified as absent, minimal, moderate, or tense.

9.3. Assessment of Portosystemic Encephalopathy (PSE): Based on the *West-Haven* classification:

Stage I: Patient oriented to time and place, with slightly slurred speech, ataxia, possible flapping tremor, slowed thought process, and sleep inversion.

Stage II: Presence of disorientation, somnolence, inability to perform mental tasks, understandable speech, and inappropriate behavior.

Stage III: Marked somnolence or psychomotor agitation, incomprehensible speech, and inability to perform mental tasks.

Stage IV: Coma, with or without response to painful stimuli (*Cordoba*).

No additional neurophysiological tests were performed. In some cases, a brain CT scan was conducted upon emergency admission to exclude cerebrovascular incidents or trauma as causes of unconsciousness.

10. MELD-NaScore: Calculated for all patients using an online calculator with the following formula: MELD-Na (https://www.mdcalc.com/calc/10437/model-end-stage-liver-disease-meld?):

11. ALBI Score: Calculated for all patients with alcohol-related cirrhosis and alcoholic hepatitis (AH) using a mathematical model. Based on the results, cases were categorized into three groups: *ALBI 1*: Low risk. *ALBI 2*: Moderate risk. *ALBI 3*: High risk. (https://www.wjgnet.com/10079327/full/v24/i39/4436.htm):

ALBI-score
$[\log_{10}$ bilirubin (μmol/L) × 0.66] + [albumin (g/L) × -0.085]
ALBI grade is defined by the resulting score:
Grade 1 ⩽ -2.60
Grade 2 > -2.60 to ⩽ -1.39
Grade 3 > -1.39

12. ASAT/ALAT (De Ritis Index): Calculated for all patients as an absolute value.

13. Diagnostic Criteria for Alcoholic Hepatitis (AH): Persistent alcohol consumption for more than 6 months, with a daily intake exceeding 50 g of ethanol.Onset of jaundice within less than 2 months of abstinence.ASAT levels between 50 and 400 U/l, with an ASAT/ALAT ratio > 1.5.Total bilirubin > 50 μmol/l.To identify cases of severe AH, a threshold MELD-Na score > 20 was applied.

STATISTICAL METHODS USED:

1. Descriptive Analysis:Frequency distribution of the examined variables presented in tabular form, showing counts and percentages, broken down by study groups.

2. Graphical Analysis:Used for visual representation of the obtained data.

3. Crosstabulation:Applied to identify relationships between categorical variables.

4. Fisher's Exact Test and Chi-Square Test (χ^2):Used to test hypotheses regarding the dependence between categorical variables.

5. Kolmogorov-Smirnov and Shapiro-Wilk Nonparametric Tests:Employed to assess the normality of the data distribution.

6. Mann-Whitney U Test:Used to compare quantitative differences between two independent categorical samples when the examined variables do not follow a normal distribution.

7. Kruskal-Wallis Test:Applied for comparing quantitative differences across two or more independent categorical samples of equal or different sizes, in the absence of normal distribution.

8. ANOVA (Analysis of Variance):Used to determine differences among three or more unrelated groups by calculating the mean and standard deviation of the examined variables, assuming a normal distribution. It also tests the relationship between an independent categorical variable and a dependent quantitative variable.

9. ROC Analysis (Receiver Operating Characteristic):Used to validate the diagnostic performance of the examined indicator by determining its cut-off value, sensitivity, and specificity.

10. Correlation Analysis (Pearson's and Spearman's Correlation):Applied to investigate the strength and direction of the potential relationship between two independent quantitative variables, without implying causation.

RESULTS AND DISCUSSION:

I. Demographic Characteristics of the Studied Population:

1. Entire Group:

Among all participants (N=361), 29% (N=103) were women and 71% (N=258) were men. The average age at the time of diagnosis was 57.8±11.4 years, with no statistically significant difference between the sexes (Pearson Chi-Sqare: 29.127; df = 1; F = 0.224; Sig. p = 0.637). A wide age range was observed for both sexes:Women: 26–86 years (Median = 59.00), Men: 20–86 years (Median = 58.00). No significant difference was found between the sexes, and the studied indicator showed a normal distribution (Kolmogorov-Smirnov: men – statistic = 0.039; df = 258; p = 0.200; women – statistic = 0.079; df = 103; p = 0.117; Shapiro-Wilk: men – statistic = 0.994; df = 258; p = 0.437; women – statistic = 0.996; df = 103; p = 0.010) (Fig. 1).

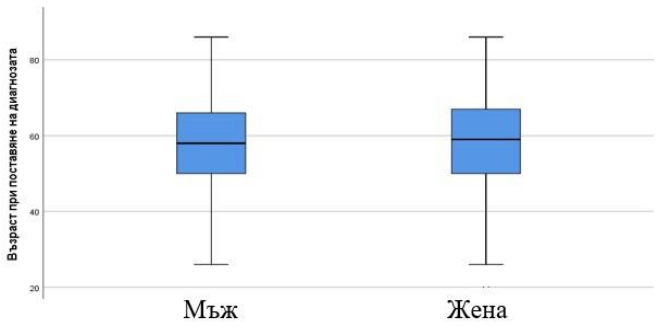


Figure 1. *Age in man and woman*

The distribution of cases by age groups showed a predominant involvement of the active age group 40–60 years (50%; N=181) and those over 60 years (45%; N=162), with the total share of all cases over 40 years comprising 95% of the entire studied group. Among all men, 96.8% were over this age, while among women, the share was 90.2%. The distribution by age groups, depending on gender, revealed a significant predominance of men in the age groups over 40 and over 60 years. In the smallest group under 40 years (N=18), there was a slight predominance of women (N=10; 55.6%), without a significant difference between the sexes (Pearson Chi-Square test: 9.657, df 2, sig. p=0.008) (Fig. 2).

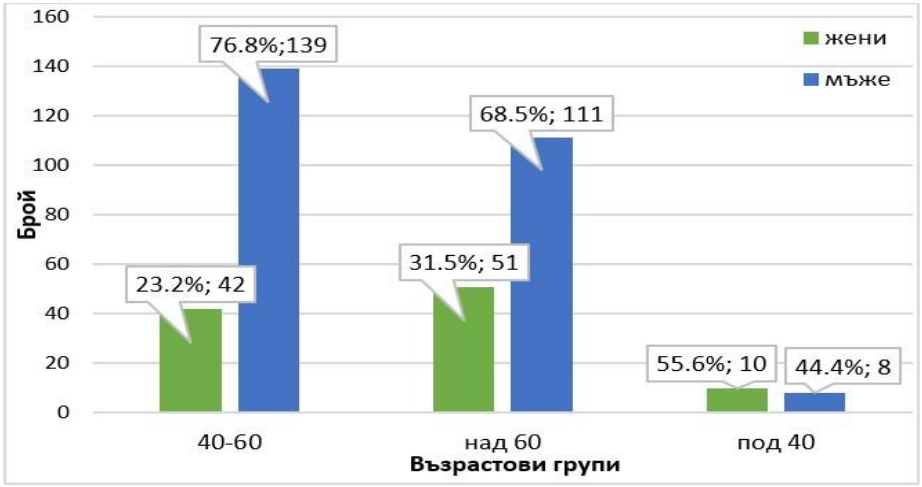


***Figure 2**. Distribution by age group (blue-man, green-women)*

Alcohol, as an independent etiological factor, accounts for the largest share—67.59% of all studied cases. When combined with HBV and HCV, the total share of alcohol involvement in the etiology of the studied population reaches 72.57% (N=262) (Fig. 3).

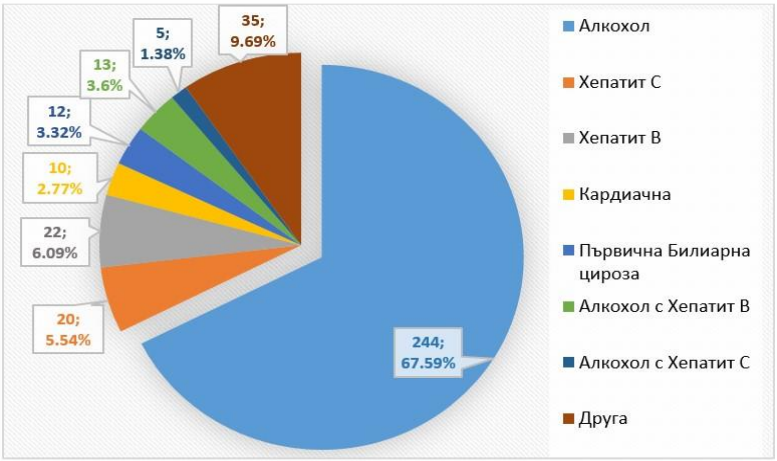


Figure.3 *Distribution by etiology in studied group*

The distribution of cases by etiology and gender showed a significant association with the male gender and alcohol-related etiology. Among all cases with pure alcohol etiology (N=244), 80.3% were men. In cases involving a combination with hepatitis B or C, men also predominated. In cases with pure viral etiology, there was no significant gender difference. Absolute significance associated with the female gender was found in PBC—100% (N=12). No gender difference was observed in cases with cardiac or other etiologies (Pearson Chi-Square test: 53.634, df 7, sig. p=.000) (Fig. 4).

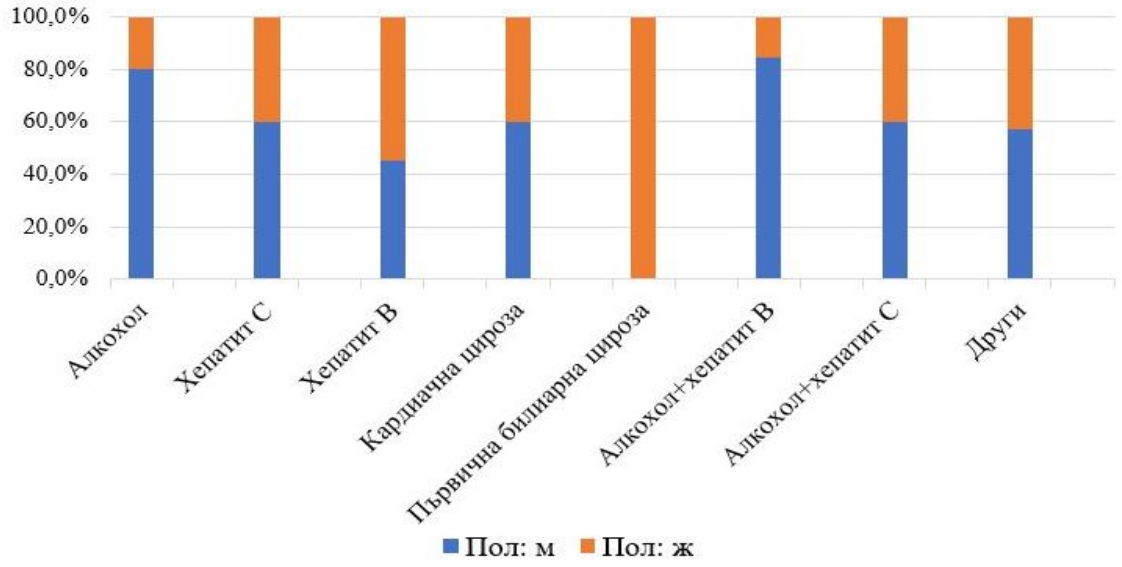


Figure.4 *Distribution by gender and etiology*

Alcohol etiology predominated across all three age groups, mainly affecting the active age group of 40–60 years and, to a lesser extent, those over 60 years. In cases with pure viral etiology, the disease primarily debuted after the age of 60 and significantly less frequently between 40 and 60 years, unlike the combined etiology with alcohol, where onset occurred at a younger age. Patients with PBC were mainly over 60 years old and, to a lesser extent, over 40 years old, with no cases reported under 40 years. Patients with cardiac cirrhosis were predominantly over 60 years, while those with so-called "other cirrhosis" showed some heterogeneity, with a predominance of cases over 60 years. The results confirmed a significant association between. The results confirmed a significant association between the etiological factors and the age of disease manifestation (fig.5).

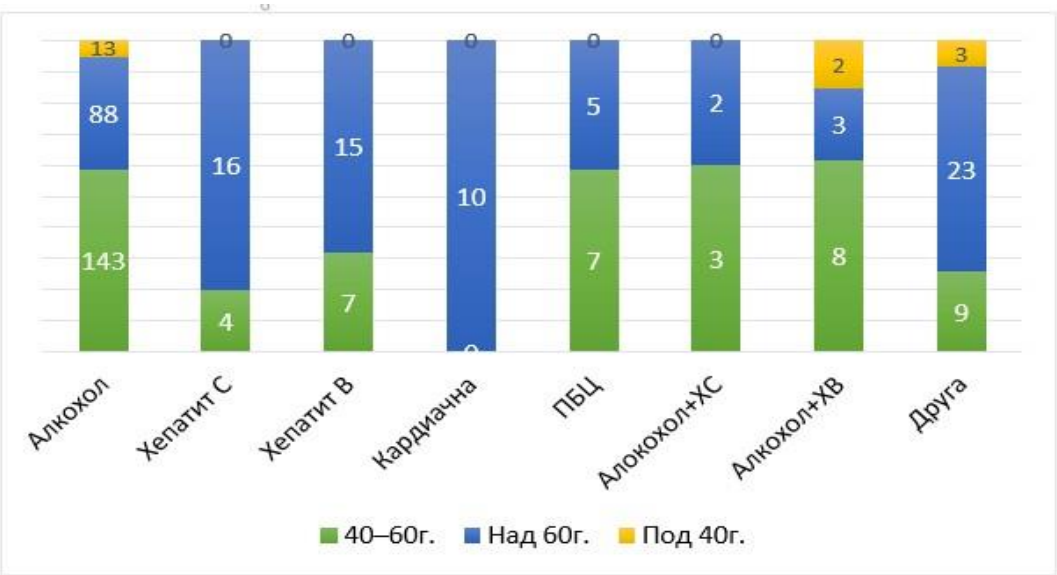


Figure 5*. Distribution by age and etiology*

Discussion:

Globally, the incidence and mortality rates of liver cirrhosis are higher in men, with an approximate male-to-female ratio of 2:1, though regional variations exist. Our results confirmed the predominance of males in 71% of all cases, regardless of the etiological factor, consistent with data from other countries. The mean age of the studied group was 57.8 ± 11.4 years, with a wide age range and no statistically significant gender difference. Our findings align with a global study that reported an age range of 19 to 94 years, with our cohort's mean age being higher than the global average (51.5 ± 10.7 years). Age distribution indicated that the most affected individuals were aged 40–60 years (50%) and over 60 years (45%), consistent with other studies. In our study, 96.8% of men and 90.2% of women were over 40 years old, matching findings from an American study, where these values were 90% and 87%, respectively. The high incidence in working-age adults is associated with frequent alcohol abuse among men. The low incidence under 40 years of age (5%) aligned with Swedish data. Despite the small number of young patients, women predominated, mainly in alcohol-related cases, consistent with findings from China. Our results differ significantly from other studies reporting higher rates under 40 years (20.22% and 14.28%), primarily among men with alcohol-related etiology. Alcohol-related cirrhosis is the leading cause in Europe, followed by chronic viral infection. Among our patients, 67.59% (N=244) had pure alcohol-related etiology, followed by hepatitis B (6.09%, N=22) and hepatitis C (5.54%, N=20). Including cases with combined alcohol and viral etiology, the overall share of viral cirrhosis reached 16.61%, lower than the

2016 data for Bulgaria, where hepatitis B-related cirrhosis was 18% and hepatitis C-related was 16%. As of 2019, the global prevalence of hepatitis B-related cirrhosis was 19.8% and hepatitis C-related was 22.9%, with significant geographic differences. The low prevalence of viral etiology in our group aligns with the declining trend in Europe, explained by expanded hepatitis B vaccination and antiviral programs. In the Americas, the prevalence of hepatitis B is 5%, matching our findings, while hepatitis C prevalence is significantly higher at 32%. Our results differ significantly from Asia and Africa, where viral etiology predominates. We observed a low prevalence of primary biliary cirrhosis (PBC), consistent with other studies. The small number of patients in our study prevents accurate determination of its true prevalence. The low incidence of cardiac cirrhosis likely reflects the fact that these patients are typically treated by cardiologists, while gastrointestinal symptoms often remain secondary.

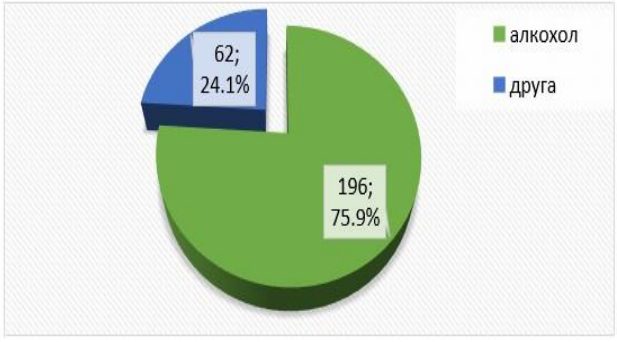
Globally, the prevalence of cardiac cirrhosis is 1–2% in developing countries and over 10% in developed countries. Combined etiology (alcohol and hepatitis B or C) was identified in a small proportion of our patients, consistent with the low prevalence of viral hepatitis in our region. We did not identify any cases of liver cirrhosis with combined viral etiology. The high proportion of patients with unknown etiology (9.6%) corresponds to findings from Brazil, where 9.6% of cases are cryptogenic. This proportion differs from studies in Sweden (14.5%), Iceland (6%), and the Americas (4%). We hypothesized that some cryptogenic cases might be associated with non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome, which were not thoroughly investigated due to the retrospective study design. According to the literature, cryptogenic cirrhosis accounts for 10%–30% of cases worldwide, primarily linked to NAFLD. Among alcohol-related cases, 80.3% were men, consistent with global data. We found no significant gender difference for hepatitis B and C, though men were more frequently affected by hepatitis C. In contrast, other studies report higher hepatitis C prevalence in women and higher hepatitis B prevalence in men. In the Americas, lower viral etiology prevalence has been observed among women.

For combined alcohol and viral etiology, men predominated, consistent with other studies. An absolute female predominance was observed in PBC, with no male cases in our cohort. This aligns with global data, where the gender ratio always favors women despite regional differences. A Chinese study reported that 14.2% of PBC patients were men, but the small number of cases in our study prevents accurate prevalence estimation. In cardiac cirrhosis, gender distribution was proportional, despite literature suggesting a higher male association. Other

etiologies also showed equal gender distribution, unlike a Swedish study reporting male predominance. Age distribution analysis showed that alcohol-related etiology predominated among those aged 40–60 years, with a lower prevalence over 60 years. Viral etiology most commonly appeared after the age of 60, less frequently between 40 and 60 years, and was absent under 40 years, with no statistically significant gender difference. This contrasts with other studies reporting earlier onset for hepatitis B. Hepatitis C cases had a late disease onset, consistent with findings from other researchers indicating most patients are aged 50–70 years. This correlates with the long latency period and late diagnosis. When combined with alcohol, onset occurred at a younger age, more pronounced in women, consistent with foreign data, likely due to the synergistic effect of etiological factors. PBC predominantly affected individuals over 60 years, with a smaller proportion over 40 years and no cases under 40 years, unlike a Chinese study where 5.4% of patients were younger. Cardiac cirrhosis patients were over 60 years old, consistent with literature linking long-term cardiac pathology to decompensation and subsequent liver involvement. Cases with other etiologies showed heterogeneous age distribution, with predominance over 60 years, consistent with findings that this etiology is more common in older patients.

2.Epidemiological structure of the group with pure alcohol-related etiology:

Among all men in the studied population (N=258), 75.9% (N=196) had pure alcohol-related etiology. Among all women (N=103), 46.6% also had pure alcohol-related etiology (Fig. 6, Fig. 7).



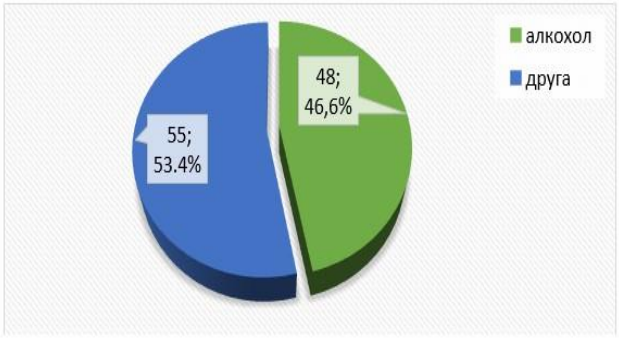


Figure 6. *Proportion of people with pure alcohol* ***Alcohol-green, without alcohol-blue***

Figure 7*. Proportion of women with pure alcohol*

Of all patients with pure alcohol-related etiology (N=244), 80.32% (N=196) were men and 19.67% (N=48) were women, with a male-to-female ratio of 4:1 (Fig. 8).

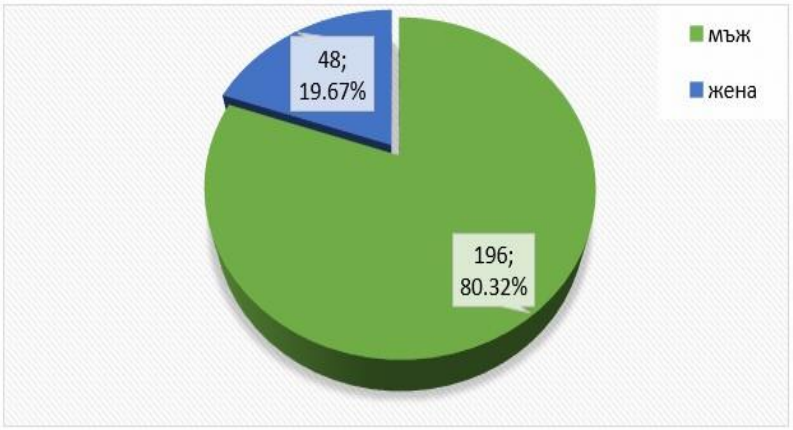


***Figure 8**. Male-female ratio (men-green, female-blue)*

The mean age of the studied group was 55.69 ± 10.418 years (range: 26–83 years), with no statistically significant difference between the sexes, comparable to the overall population (Pearson Chi-square test: 298.300, df = 1, F = 2.768, p = 0.097). Age group distribution revealed a significant predominance of men among cases over 40 years. There was no gender difference among those under 40 years. Among all men (N=196), 58.7% (N=115) were aged 40–60 years, 37.8% (N=74) were over 60 years, and 3.6% (N=7) were under 40 years. Among all women (N=48), 58.3% (N=28) were aged 40–60 years, 29.2% (N=14) were over 60 years, and 12.5% (N=6) were under 40 years (Pearson Chi-square test: 6.559, df = 2, p = 0.038) (Fig. 9).

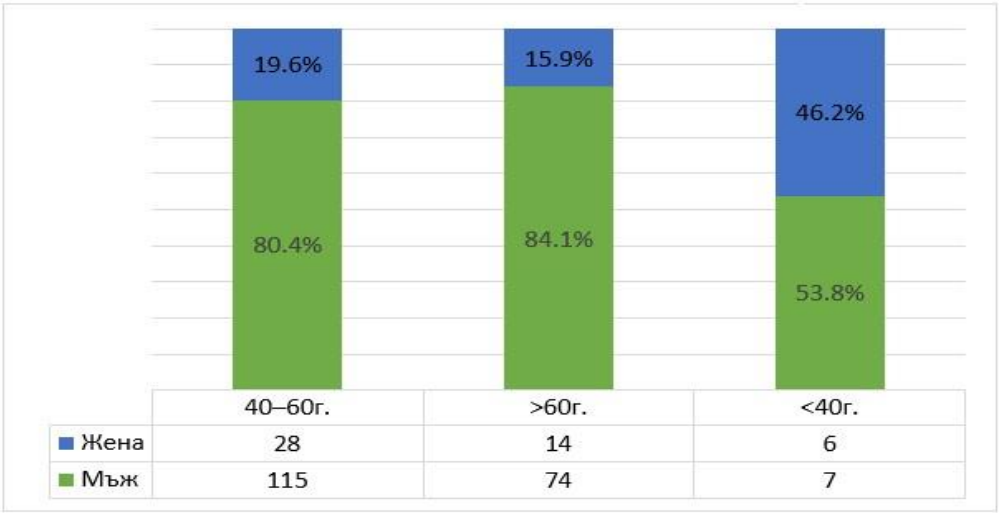


***Figure 9.** Distribution by age groups (men-green, female-blue)*

Discussion:

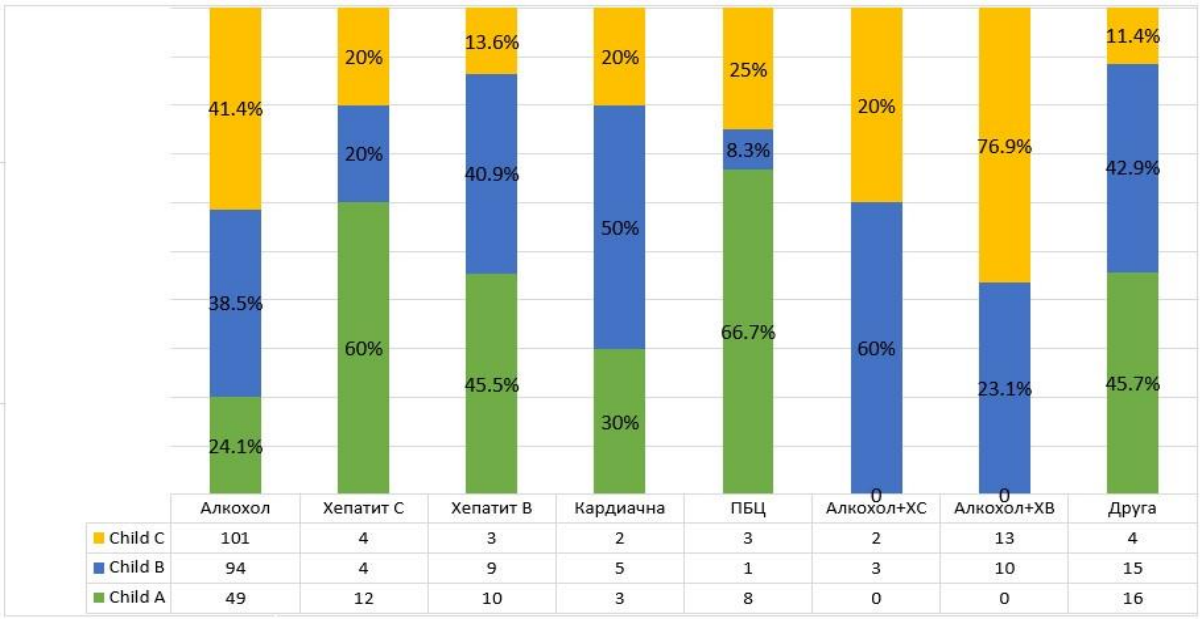
Our study demonstrated that the majority of the examined patients had a pure alcohol etiology—68%. These findings are consistent with results from other European countries, the USA, Latin America, as well as India and China. They

differ significantly from regions with a lower prevalence, which can be explained by geographical and cultural-religious factors. Compared to older data from Bulgaria in 2009, when the proportion of alcohol etiology was around 43%, current results reveal a concerning trend of increasing alcohol-related cirrhosis in the population. In our study group, pure alcohol etiology was identified in 75.9% of men and 46.6% of women. According to WHO data from 2018, 77.8% of cirrhosis cases among men and 57.3% among women worldwide are attributed to alcohol. Our results align with European trends, though the proportion of affected women in our group is lower. Global studies show that the male-to-female ratio varies across regions, always with a male predominance—ranging from 1.5:1 to 5.2:1. The highest ratio is observed in Tropical Latin America, Oceania, and East Asia, while the lowest is reported in Africa, North America, and Indigenous Latin America. In Europe, the ratio ranges from 1.9:1 to 2.9:1. In our study population, the ratio was approximately 4:1, exceeding the European average. A similar result was found in a study of the cirrhotic population in Serbia, where 89.45% were men and 10.55% were women. The age distribution for alcohol etiology in Europe and America typically falls between 45 and 64 years, with an average age of around 53 years. Our findings are consistent with this trend, showing an average age of 55.69 ± 10.41 years. This age distribution is comparable to the general population and reflects a wide age range. No significant difference in age distribution between men and women was observed, consistent with other studies. Our results align with findings from Serbia and Romania, while patients in countries such as Sweden, Italy, and Germany tend to be older. Similarly, the Japanese population with alcohol-related cirrhosis has an average age of 68.1 years. In contrast, our findings significantly differ from those reported in China (38–48 years) and India (47.75 years), where the disease tends to manifest at a younger age.The majority of our cases were aged over 40 years for both sexes, with a predominance among men, a trend confirmed by other studies. Most cases in our group were aged 40–60 years, while only 5.3% were under 40 years, of whom 53.8% were men and 46.2% women. This finding highlights a relatively high proportion of young women affected.In another study, 6.3% of cases were under 40 years, with 48.7% being women, which is comparable to our results. Studies from China also report an increasing proportion of young women affected by alcohol-related conditions. Our study revealed a low prevalence of combined alcohol and hepatitis C (1.9%) or hepatitis B (4.96%) etiology, which can be explained by the overall low prevalence of viral hepatitis in the region. Globally, hepatitis C prevalence in the general population ranges from 0.5% to 2%, but

among alcohol abusers, the prevalence is significantly higher—between 2.1% and 51%, with a global average of 16.32%. This prevalence is notably lower among non-intravenous drug users (6.6%). In the United States, 10%–14% of cirrhosis cases are associated with combined alcohol and hepatitis C etiology, making them a leading indication for liver transplantationAccording to a systematic meta-analysis, the global prevalence of hepatitis B ranges from 0.7% to 6.2%, with the lowest rates in North and South America and the highest in the Western Pacific region (WHO, 2018). Among alcohol abusers, hepatitis B prevalence can reach 20%, significantly higher than in the general population. In Europe, the prevalence of the Australian antigen is around 0.9%, while among patients with alcohol-related cirrhosis, hepatitis B infection varies between 9% and 47%, with an average of 32%. Our results are consistent with findings from other researchers but differ from regions reporting significantly higher prevalence rates. These variations can be attributed to differences in alcohol consumption patterns and the endemic profile of viral hepatitis in the compared populations

II. Relationship between Etiology and Child-Pugh stage at diagnosis:

The distribution of patients in the entire study population (N=361) showed that 27% (N=98) were classified as Child A, 39% (N=141) as Child B, and 34% (N=122) as Child C. Overall, 73% of all examined patients were in Child B and C stages. With the progression of the Child-Pugh stage, the proportion of cases with pure alcohol etiology increased within each group. Among all Child B patients (N=144), 66.7% (N=94) had pure alcohol etiology, while in the Child C group (N=122), this proportion rose to 82.8% (N=101). (Pearson Chi-Square test 56.444, df=14, p=.000) (Fig. 10).



	Алкохол	Хепатит С	Хепатит В	Кардиачна	ПБЦ	Алкохол+ХС	Алкохол+ХВ	Друга
Child C	101	4	3	2	3	2	13	4
Child B	94	4	9	5	1	3	10	15
Child A	49	12	10	3	8	0	0	16

***Figure 10**: Distribution of cases per child depending on etiology:*

Among all patients with alcohol as an etiological factor (N=262, 72.6%), 40.5% (N=106) were classified as Child C. In comparison, among patients without alcohol in the etiology (N=99, 27.4%), only 16.2% (N=16) were in Child C. The overall prevalence of cases in Child B and C stages reached 81.3% in the alcohol group, while it was significantly lower in the non-alcohol group—50.5%. These results confirm a statistically significant correlation between alcohol as an etiological factor and a higher Child-Pugh class at the time of diagnosis in our patients (Pearson Chi-Square test: 38.423, df=2, p=.000) (Fig. 11).

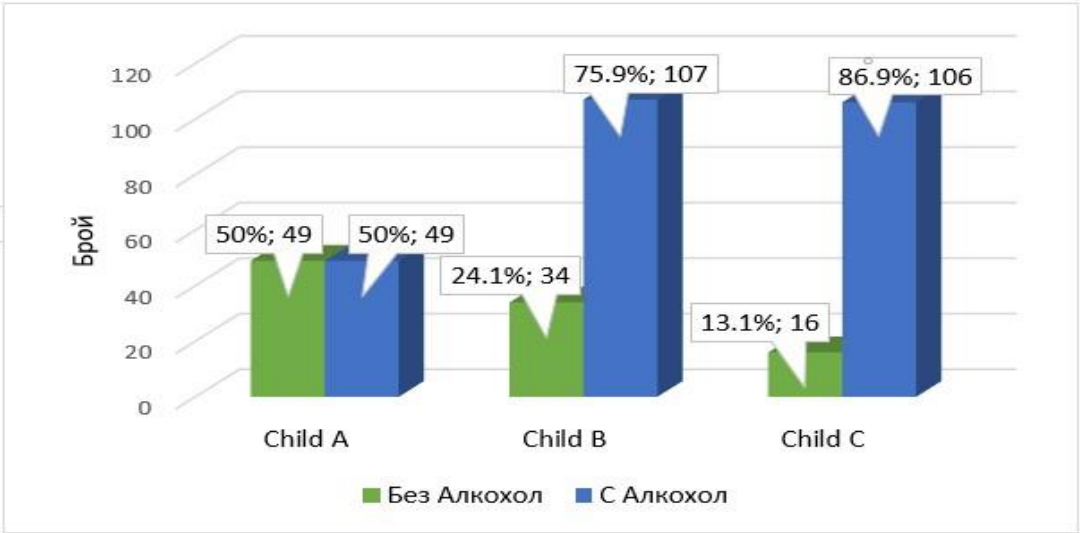


***Figure 11.** Distribution of cases by Child in the population with and without alcohol in the etiology (without alcohol-green, with alcohol-blue)*

Discussion:

Our study revealed a relatively high proportion of decompensated cases within the overall cirrhotic population, with 34% of all examined individuals classified as Child C and a combined 73% in Child B and C. Among the population with pure alcohol etiology, the proportion of Child C cases was higher, which is associated with late diagnosis. Studies show that Child C cases are linked to high rates of 30-day rehospitalization, future decompensations, and mortality. An American study found that 43% of hospitalizations with a liver cirrhosis diagnosis were emergency admissions due to decompensating events. A Scandinavian study reported that 71% of cases presented with decompensation at the time of diagnosis, primarily associated with alcohol etiology. Our findings align with another study, where 37% and 45.6% of patients were in Child B and C stages, respectively, with pure alcohol etiology confirmed in 85.5% of cases. According to Schwarz M et al., in a cohort of 476 patients, 50% of cirrhosis cases were decompensated at diagnosis, with alcohol etiology present in 44.3% of them. This differs from our results, which showed a higher frequency of decompensation and a higher share of alcohol etiology (72.6%). Our data also significantly contrast with a study of the cirrhotic population in Korea, where viral etiology prevailed, and only 9.4% of cases were classified as Child C. However, the majority of those were associated with alcohol etiology. Another large-scale American study involving 9,261 patients showed that 34% of newly diagnosed cirrhosis cases were decompensated, with alcohol etiology accounting for 40.2%. Similar findings were reported by other authors (40.4%, 42%, and 47%), aligning with our results. When examining the population with alcohol etiology alone or combined with HBV and HCV, among the 262 patients (72.6%), the decompensation rate was significantly higher, reaching 81.3%. This corresponds with the findings of the UK Biobank global study, where 83% of cases with alcohol involvement were diagnosed late. Of all patients classified as Child C (N=122; 34%) within the general cirrhotic population (N=361), 86.9% had alcohol involvement in their etiology. Stage distribution showed that as the Child stage increased, the share of alcohol etiology grew accordingly: 18.7% in Child A, 40.8% in Child B, and 40.5% in Child C. These findings are somewhat consistent with other researchers, who reported that 60% of Child C cases were alcohol-related, with a distribution of 15% for Child A, 25% for Child B, and 60% for Child C. A comparison between pure viral etiology and its combination with alcohol revealed that pure viral cases were predominantly compensated, unlike

the combined cases, which were mostly decompensated. In the combined group, no cases were classified as Child A, a finding consistent with other studies. Among those diagnosed with primary biliary cholangitis (PBC), the majority had compensated disease (66.7%), consistent with a Swedish study reporting 84%. Another study on the autoimmune cirrhotic population in China also demonstrated a low frequency of hepatic decompensation at diagnosis. No significant findings were established for cardiac cirrhosis due to the small sample size. Among cases classified under "other etiology," most were compensated, with a possibility that some were associated with non-alcoholic steatohepatitis (NASH), which was insufficiently explored in our study.

III. Frequency of Complications in the Studied Population and Their Dependence on the Child-Pugh Stage:

1. Ascites:

Among all 361 patients at the time of diagnosis, ascites was detected in 64.5% (N=232), while 35.5% (N=127) had no ascites. Of those with ascites (N=232), tense ascites was present in 63% (N=146), moderate in 22% (N=51), and minimal in 15% (N=35) of cases. With the progression of the Child-Pugh stage, the frequency of ascites increased within the studied population. Among patients in Child C (N=122), 88.5% (N=108) had ascites (Fig. 12).

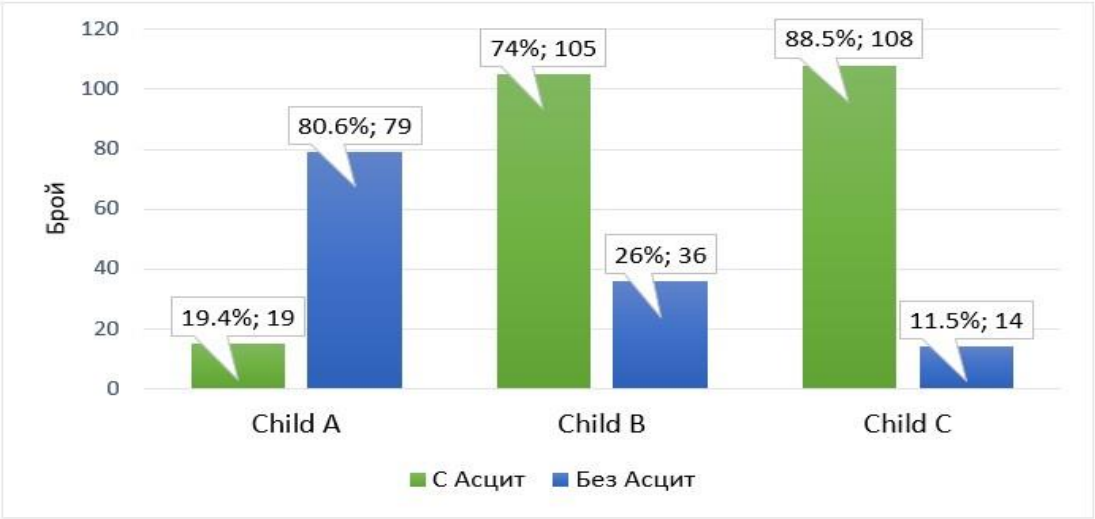


Figure 12. *Distribution of cases with ascites in three stages according to Child (with ascites-green, withouth ascites-blue)*

The distribution based on the occurrence and amount of ascites showed a significant increase in both the frequency and volume of ascites with the progression of the Child-Pugh stage. Tense ascites predominated, affecting 40.4% of the entire study group, with 63.1% (N=77) of those classified as Child C

presenting with tense ascites (Pearson Chi-square test 139.724, df = 8, p = .000) (Fig. 13).

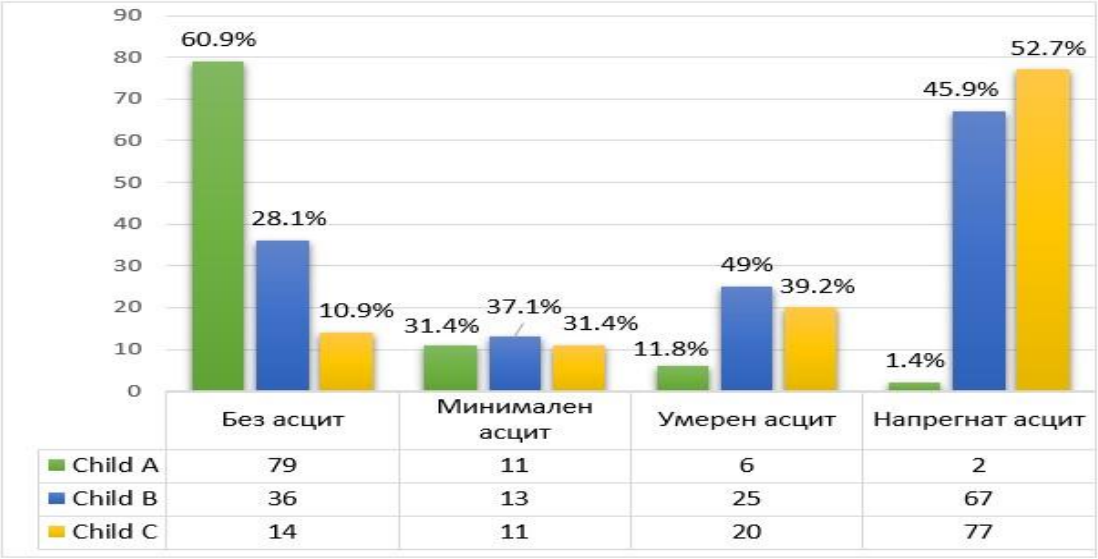
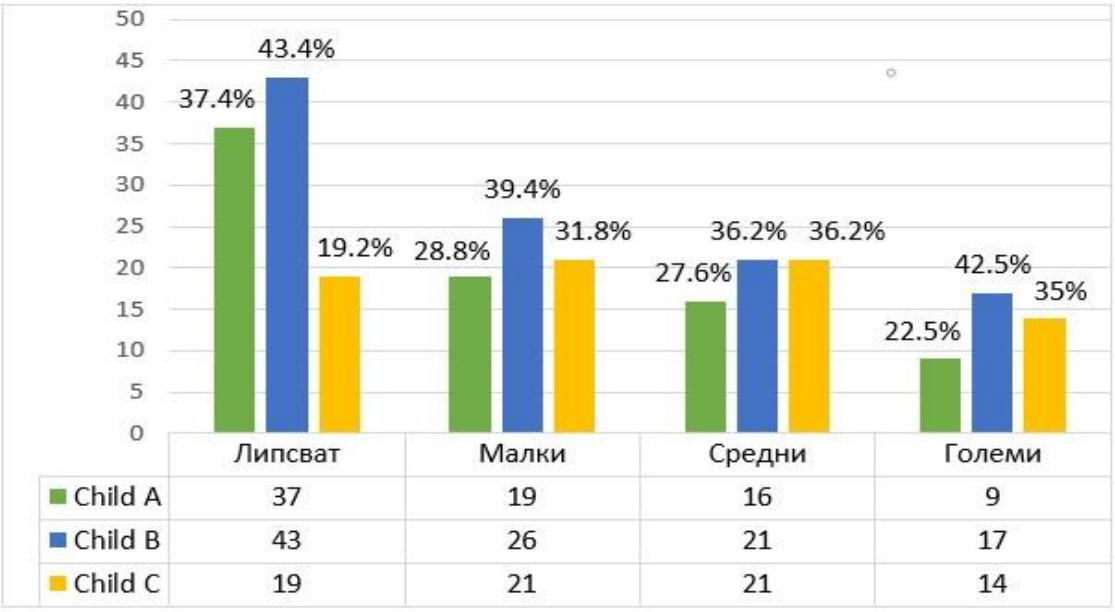


Figure 13. *Distribution of ascites cases depending on your amount in the three Child stages*

2. Esophageal Varices:

Among all patients who underwent FGS (N=263), esophageal varices were detected in 62.4% (N=164), regardless of their size and Child-Pugh stage. Small varices predominated (N=66; 42.4%), with no significant correlation with the stage, while large varices were primarily associated with Child B and C. Esophageal varices were found in 74.7% (N=56) of those classified as Child C, compared to 54.3% (N=44) in Child A. Despite the observed differences, there was no statistically significant association between the presence, size of varices, and Child-Pugh stage (Pearson Chi-Square test 8.158, df = 6, p = 0.22) (Fig. 14).

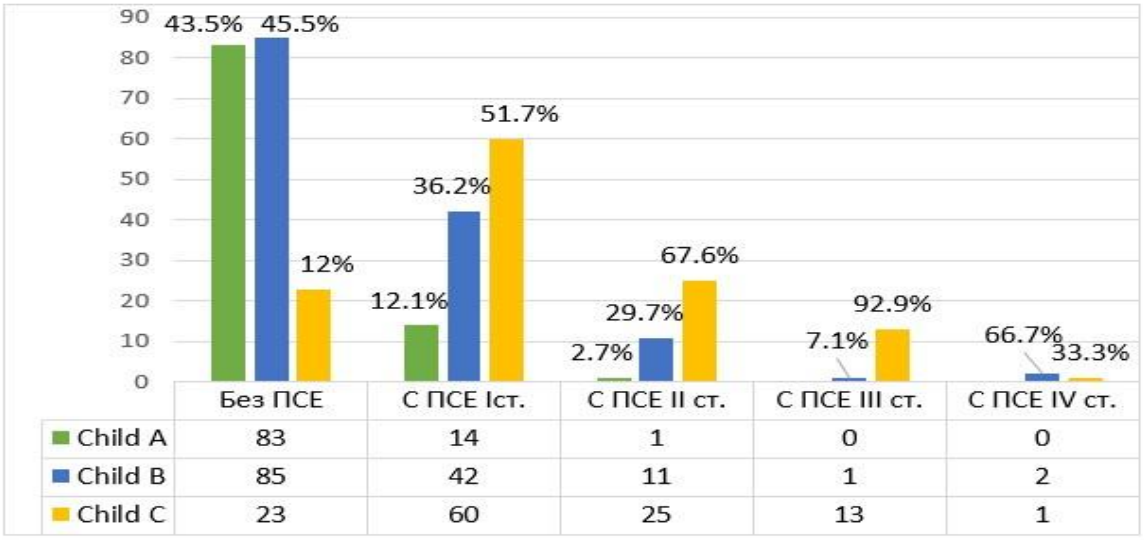


	Липсват	Малки	Средни	Големи
Child A	37	19	16	9
Child B	43	26	21	17
Child C	19	21	21	14

Figure 14*. Distribution of cases with varices in three stages according to Child*

3. Portal Encephalopathy:

Among all 361 studied patients, 47% (N=170) exhibited signs of PSE, regardless of its severity and disease stage. PSE Grade I was the most prevalent in the studied population, accounting for 32.1% or 68.23% (N=116) of all cases with PSE (N=170), with the highest proportion found in Child C (N=60; 51.7%). No cases of hepatic precoma or coma were identified in Child A. A significant correlation was confirmed between the occurrence and severity of PSE and the Child-Pugh stage (Pearson Chi-square test 112.655, df = 8, p = .000) (Fig. 15)



	Без ПСЕ	С ПСЕ Iст.	С ПСЕ II ст.	С ПСЕ III ст.	С ПСЕ IV ст.
Child A	83	14	1	0	0
Child B	85	42	11	1	2
Child C	23	60	25	13	1

Figure 15. *Distribution of cases with PSE in the three stages according to Child*

4. Jaundice in the Studied Population:

Among all studied patients (N=361), jaundice was observed in 34.3% (N=124) of cases. The frequency of jaundice increased with the progression of the Child-Pugh stage, reaching 75.4% in Child C. The results confirmed a significant correlation between elevated total bilirubin levels and the Child-Pugh stage (Pearson Chi-square test 176.968, df = 4, p = .000) (Fig. 16).

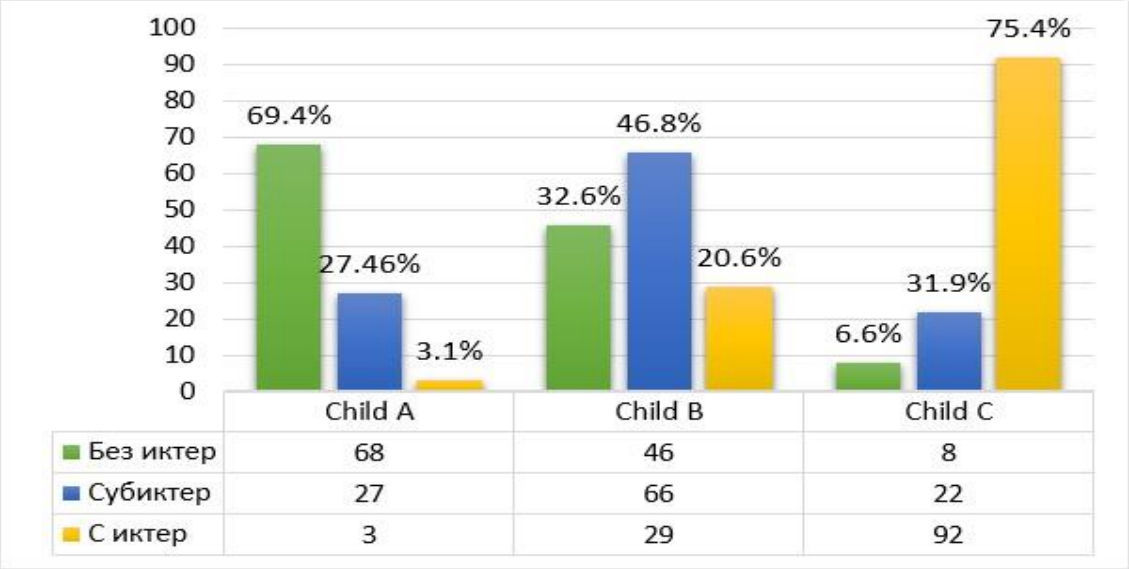


***Figure 16**. Distribution of jaundice cases by Child*

5. Renal Function Abnormalities:

Among all 361 studied patients, 82% (N=296) had no renal function abnormalities, while 18% (N=65) showed deviations, regardless of their type or disease stage. The distribution based on the presence and type of renal dysfunction across Child-Pugh stages revealed a statistically significant difference between the studied groups. Hepatorenal syndrome (HRS) was the most common abnormality (N=29; 8%), with the highest proportion of cases (N=19; 65.5%) in Child C and none in Child A. Among those with acute kidney injury (AKI) (N=16; 4.4%), the majority (N=11; 68.8%) were in Child C, with no cases in Child A. Chronic kidney disease (CKD) was found in 5.5% (N=20) of the studied population, evenly distributed across all Child-Pugh stages. The results confirmed a significant association between renal dysfunction and disease decompensation (Pearson Chi-square test 31.142, df = 6, p = .000) (Fig. 17).

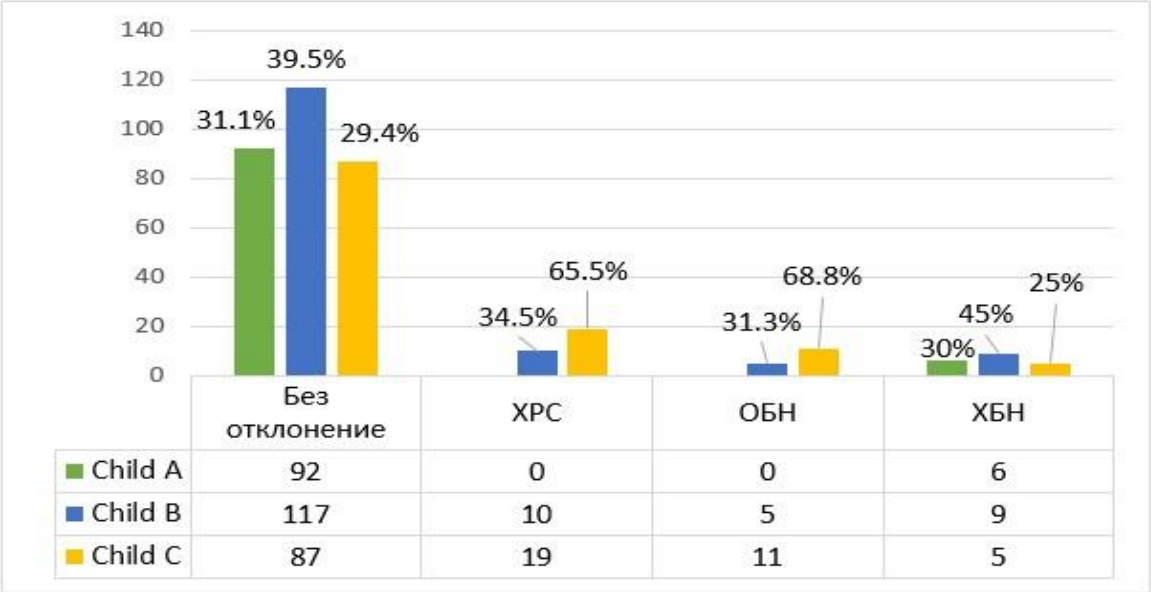


Figure 17. *Child distribution according to renal function*

Discussion:

The occurrence of ascites is the most common complication of liver cirrhosis, confirmed in our study in 64.5% of cases. Our findings align with other researchers, who report varying frequencies in their studied populations (50.5%, 54.8%, 64.18% to 72.3%). Annually, 5% to 10% of compensated cirrhosis cases develop ascites, associated with reduced life expectancy—50% of affected individuals die within the next two years, and 80% within five years of its onset. Our study confirmed the correlation between the presence and severity of ascites and the Child-Pugh stage, consistent with other studies. Tense ascites cases predominate, associated with a high Child score, indicating late decompensation and poor prognosis. According to other studies, the presence of ascites itself, rather than its volume, correlates with an increasing Child-Pugh score. Esophageal varices, as a marker of portal hypertension progression, clinically manifest with upper gastrointestinal bleeding. In our study group, 62.4% had esophageal varices, with 74.6% of them in Child C. The established average prevalence is around 50%, with variability ranging from 40% to 85%, correlating with advancing stages from Child A to Child C. Various studies report different prevalence rates of esophageal varices (39.5%, 57.4%, 77.7% to 90.6%). The observed differences are related to the characteristics of the compared groups—lower prevalence dominates in groups with compensated disease, while higher rates appear in Child B and C patients, with statistical significance regarding their occurrence and disease stage. Small varices predominate in our study group

(40.2%) without significant differences by Child stage, consistent with another study reporting 42.3%. Large varices were identified in only 24.4% of cases, primarily in Child B and C. This significantly differs from other studies reporting higher prevalence rates (41.1%, 61.4%, 82.22%) associated with high Child class. These discrepancies likely stem from differences in study populations and variceal staging classifications. PSE was found in 47% of examined patients, with minimal PSE predominating (68.24%). Studies show that 50% to 80% of all cirrhotic patients develop PSE over time, with minimal PSE accounting for up to 80% of cases. It is more common in alcohol-related cirrhosis, often accompanied by other neurological deficits. The high prevalence in our patients may also be explained by the predominant alcohol-related etiology in our population. A correlation between PSE occurrence, severity, and Child stage was confirmed, consistent with other studies identifying PSE as a leading cause of rehospitalization in cirrhotic patients. Advanced encephalopathy (grades III and IV) was observed in only 10% of cases, primarily in Child C and B, consistent with another study reporting a 9% prevalence. Studies confirm that its occurrence relates to other organ complications and often signifies acute-on-chronic liver failure. Minimal PSE predominated in our cirrhotic population (32.1%), with its significance validated by other authors. Our results show a lower overall prevalence compared to other studies (34%, 43.8%, 50.9%, and 52.2%). These differences likely result from variations in study populations and classification methodologies. Insufficient diagnosis due to a lack of additional psychometric tests and neurological evaluations might also explain the discrepancies. Nonetheless, a correlation was found, with predominance in cases with a high Child score. The appearance of jaundice is a laboratory marker of hepatocellular insufficiency, typically occurring late in liver cirrhosis progression and indicating poor prognosis. Elevated total and direct bilirubin fractions serve as crucial prognostic markers for six-month survival in cirrhotic patients and for recognizing acute decompensation and acute-on-chronic liver failure. This condition often coincides with complications such as ascites, coagulopathy, encephalopathy, and renal dysfunction. Our study revealed jaundice in 34.34% of cases, with 75.4% of them in Child C and an overall decompensation rate of 73%. Another study reported jaundice in 22.8% of cases, with 69.2% decompensated, using a bilirubin threshold of 60 µmol/L compared to our 50 µmol/L threshold, demonstrating partial alignment. The results confirmed that jaundice correlates with hepatic decompensation. It is established that 18% to 39% of cirrhotic patients develop renal dysfunction within five years of follow-up. In our study, 82% had no renal

abnormalities, with an incident rate of 18% in the studied population. This result contrasts with a large-scale American study where 66% had no renal abnormalities and 35% had dysfunction, as well as other studies reporting higher prevalence rates of 29.1% and 43%. Acute kidney dysfunction is among the most common life-threatening complications in cirrhosis, with a 50% mortality rate within the first month, rising to 65% within a year. It correlates with high Child scores and poor survival outcomes, confirmed by various studies. Our findings indicated a low incidence of acute renal dysfunction (12.4%), aligning with other studies (12.9% and 14%). A significant correlation was confirmed, with 67.15% of our cases in Child C, consistent with other studies (58% and 78%). No cases were recorded in Child A, aligning with external findings. Only 5.5% of patients had chronic kidney disease (CKD), unrelated to the Child stage. CKD prevalence varies across studies (4% to 43%), often linked to comorbidities like hypertension and diabetes. These conditions further exacerbate liver disease and acute-on-chronic kidney failure. The divergent results across studies likely reflect differences in study populations, cirrhosis etiologies, staging criteria, and definitions of renal dysfunction. Insufficient diagnosis due to limited laboratory resources for case categorization, stemming from the retrospective study design, may also account for our study's limitations.

IV. Analysis of Laboratory Results in the Studied Population and Their Dependence on Disease Severity:

1.Analysis of Aminotransferases and Their Dependence on Child-Pugh and MELD Na:

The measured mean value of ALT did not show statistical significance concerning the Child-Pugh stage and MELD Na score (ALT/Child-Pugh: df = 2, F = 0.435, p = 0.647; ALT/MELD Na: df = 32, F = 1.623, p = 0.020), unlike the AST values (AST/Child-Pugh: df = 2, F = 5.740, p = 0.004; AST/MELD Na: df = 32, F = 1.623, p = 0.036). In 61.77% (N = 223) of all cases, ALT values were within the reference range, regardless of the severity of liver disease. In all three Child-Pugh groups, cases with normal ALT values predominated (Pearson Chi-Square test: 7.098, df = 2, p = 0.29) (Fig. 18).

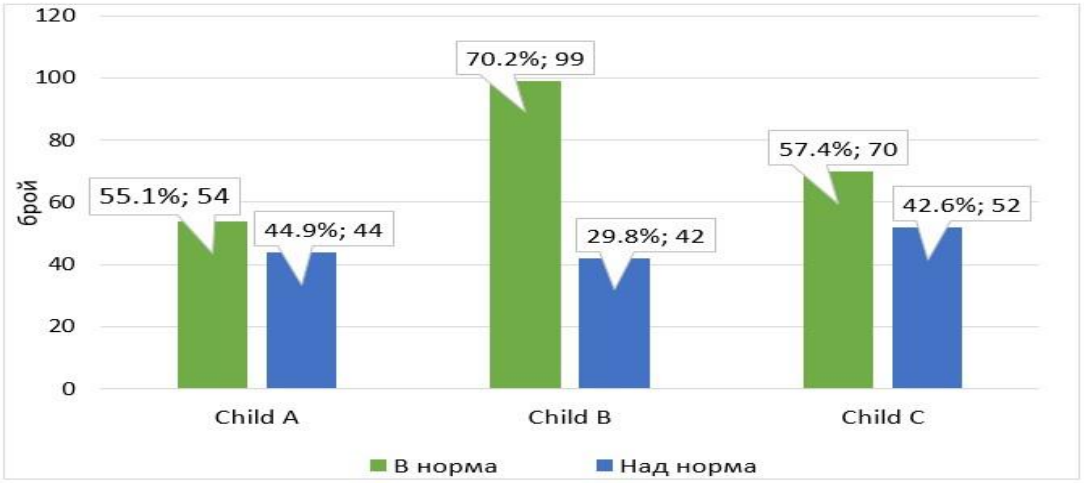


***Figure. 18**. Distribution of cases with normal and elevated ALT in Child (normal--green, elevated-blue)*

In 25.76% (N = 93) of cases, AST values were within the normal range, with a significant decrease in the number of cases with normal values as the Child-Pugh stage increased (Pearson Chi-Square test: 25.140, df = 2, p = 0.000) (Fig. 19).

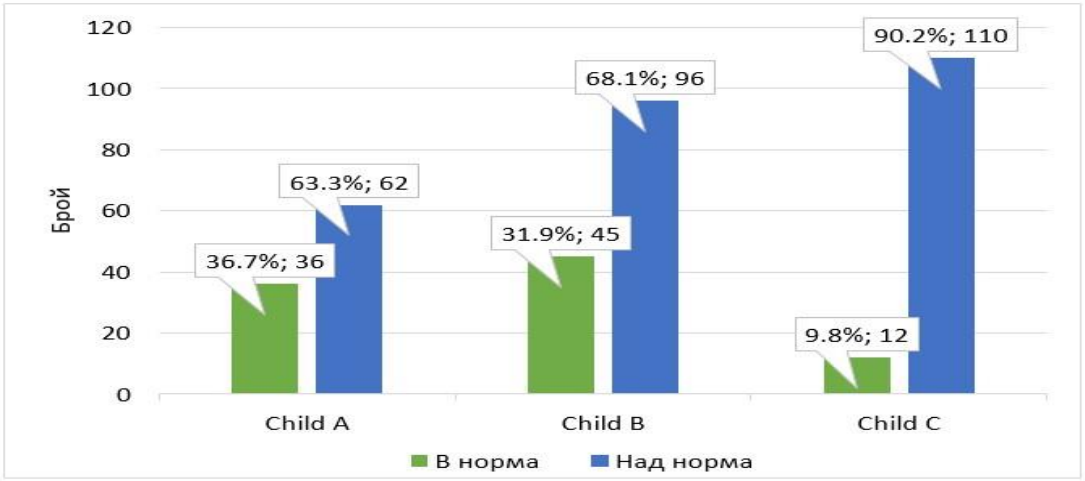


***Figure. 19.** Distribution of cases with normal and elevated ASAT (normal--green, elevated-blue)*

In 27.7% (N = 89) of cases, both enzymes were within the normal range, with only 9.8% (N = 12) in the Child C group (Pearson Chi-Square test: 21.971, df = 2, p = 0.000) In 9.97% (N = 36) of all cases, the AST/ALT ratio was < 1, in 36.28% (N = 131) it was > 1, and in 53.7% (N = 194) it was > 2. Among those classified as Child C, 75.4% (N = 92) had a value > 2. The distribution of cases based on the ratio and Child-Pugh stage showed a significant association (Pearson Chi-Square test: 77.141, df = 4, p = 0.000) (Fig. 20).

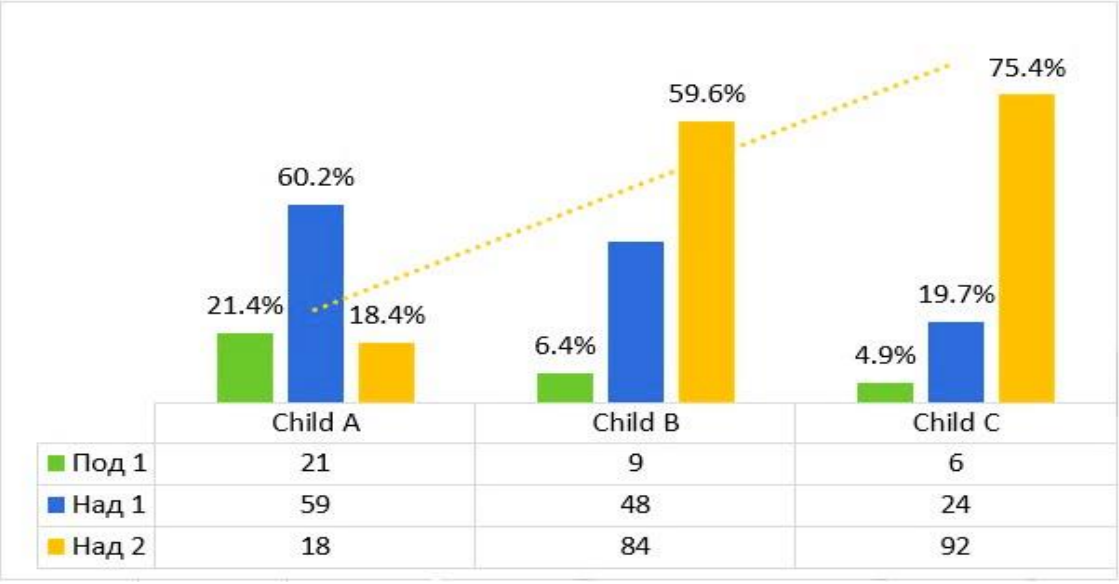


***Figure 20**. Distribution of cases depending on the ASAT/ALT ratio and Child stage*

With an increase in the AST/ALT ratio, both the Child-Pugh and MELD Na scores also increased, confirming that its elevation is associated with worsening liver function, regardless of the absolute aminotransferase values. A statistically significant difference was found when comparing the two groups with values >1 and >2 in terms of the calculated Child-Pugh score (Median 8; H = 57.011; df = 1; p = 0.000) and MELD Na score (Median 14; H = 15.857; df = 1; p = 0.000) (Table 4).

***Table 4.** Value of Child-Pough and MELD Na in АСАТ/АЛАТ Ratio <1,>1 u >2*

AST/ALT	Child-Pough	MELD Na
< 1 (N=36)	6.92±1.87	12.22±5.10
> 1 (N=131)	7.31±2.32	13.92±6.60
> 2 (N=194)	9.38±2.22	17.05±7.57
N=361;ANOVA-test Child-Pough/АСАТ/АЛАТ: df 2 F 42.524 p=.000 MELD Na/АСАТ/АЛАТ: df 2 F 11.906 p=.000		

Discussion:

The evaluation of aminotransferase (AT) levels is a simple, accessible, and widely used method for detecting liver function impairment. Our results demonstrated

that deviations from normal liver enzyme levels could indicate an underlying serious condition. Elevated enzyme levels, particularly when combined with other laboratory markers such as decreased albumin and increased bilirubin, are significant indicators of progression toward fibrosis and cirrhosis, especially in cases of chronic hepatitis. Cohort studies involving patients with chronic hepatitis B (CHB) and chronic hepatitis C (CHC) confirm that enzyme levels are significantly higher in cirrhotic patients compared to healthy controls. Similarly, when comparing CHB patients with and without cirrhosis, the group with cirrhosis exhibited higher enzyme levels. Interestingly, no significant differences were found in enzyme levels among cirrhotic patients of varying etiologies. In our study, the mean ASAT value showed a significant association with the Child-Pugh and MELD Na scores, despite considerable variability across different disease stages. Only 25.76% of all patients had ASAT levels within the normal range, with just 9.8% of them classified as Child C. This finding confirmed that deviations from normal values, rather than the absolute enzyme levels, correlate more strongly with the presence of chronic liver disease. MStudies on CHB patients have demonstrated that persistent ASAT elevation, even with normal or near-normal ALAT levels, is associated with severe inflammatory activity and an increased risk of cirrhosis progression. Another study based on liver biopsies revealed that elevated ASAT levels were linked to advanced fibrosis (grades 3 and 4) compared to cases with no fibrosis. Among our patients, the mean ALAT value did not show a significant difference across the three Child-Pugh stages, with 61.77% having ALAT levels within the normal range. No association was found between ALAT levels and either the Child-Pugh or MELD Na scores. This finding confirmed that ALAT measurement alone is not indicative of the presence or severity of liver cirrhosis. This conclusion aligns with histological studies indicating that ALAT levels do not correlate with fibrosis severity, as normal or near-normal levels can be observed even in advanced liver disease. It has been established that an ALAT threshold below 20 UI/ml can effectively exclude significant underlying disease, while higher values, even within the normal range, cannot distinguish between mild and significant inflammation in patients with CHB and CHC. In our study population, a relatively high proportion of patients had normal levels of both enzymes (24.7%), with many exhibiting normal ALAT values regardless of ASAT levels. This further supports the notion that absolute AT values have low specificity and sensitivity for diagnosing cirrhosis, as ALAT can remain normal even in advanced cirrhotic stages. A study on alcoholic cirrhosis similarly found no correlation between enzyme levels and the presence

of complications or mortality, with many patients showing normal or near-normal AT values. Among 90% of all patients in our study, the ASAT/ALAT ratio was >1, regardless of the absolute enzyme values. This ratio increased significantly with higher Child-Pugh and MELD Na scores, indicating a strong association with the severity of liver damage. Other studies have shown that dynamic monitoring of the ASAT/ALAT ratio can predict cirrhosis progression, even when enzyme levels are near normal and may mask disease severity. Combined assessment of this ratio with the MELD score has been used to predict survival in patients with severe liver dysfunction. In our study, an ASAT/ALAT ratio >2 was observed in 53.7% of patients, with 75.4% of them classified as Child C. This finding was associated with the predominant alcohol-related etiology in our study group and cirrhosis decompensation in many patients, consistent with previous findings by other authors.

2. Analysis of Biochemical Indicators and Their Relationship with Child-Pugh and MELD Na:

With the progression of the Child-Pugh stage and an increase in the MELD Na score, the mean albumin level decreases, while total bilirubin increases. This trend reflects the progressive deterioration of liver function, with both indicators showing absolute significance in relation to both scoring systems. A similar pattern is observed for INR values, although the detected variations are smaller, and the levels are lower than those typically associated with the corresponding Child stage (Tables 5 and 6).

Table. 5*. Values of research indicators in the three stages according to Child*

Child-Pough:	Albumin mean±sd	Total bilirubin mean±sd	INR mean±sd	MELD Na mean±sd
Child A N=98	40.17±4.87 (23.60–55) 95% CI: 39.20–41.13	19.23±13.57 (3.07–101) 95% CI: 16.55–21.92	1.15±0.183 (0.86–1.93) 95% CI: 1.11–1.18	9.54±2.75 (6–19)
Child B N=141	31.89±6.05 (11.40–54) 95%CI: 30.89–32.88	47.97±61.07 (4.32–433) 95% CI: 37.89–58.05	1.26±0.189 (0.91–1.99) 95% CI: 1.22–1.29	13.6±4.88 (6–30)
Child C N=122	25.32±3.44 (17–35.20) 95% CI: 24.71–25.93	126±116.72 (4.40–568) 95%CI: 105.28–146.71	1.66±0.456 (1.01–3.65) 95% CI: 1.57–1.74	22.3±6.5 (9–40)

***Table 6**: Relationship between the studied indicators with Child and MELD Na with ANOVA*

Significance:	df	F:	P value (p<0.05)
Albumin/ MELD Na	32	5.669	.000
Total bilirubin/ MELD Na	32	17.365	.000
INR/ MELD Na	32	12.063	.000
Albumin/ Child-Pugh	2	241.505	.000
Total bilirubin/ Child-Pugh	2	58.38	.000
INR/ Child-Pugh	2	88.864	.000

Hypoalbuminemia was found in 63.4% (N=229) of cases, with these patients having a significantly higher MELD Na score (18.32±7.23, median 18) compared to those without hypoalbuminemia (10.42±3.59, median 9). The results demonstrated absolute statistical significance (Mann-Whitney test: U = 4798.500, Wilcoxon W = 13576.500, Z = -10.819, Asymp. Sig. (2-sided) = .000). The mean serum albumin level in patients with ascites was significantly lower (N=233; 29.43±6.48 g/l; median 29.0) compared to those without ascites (N=128; 36.42±7.46 g/l; median 37.0) (ANOVA: df = 1, F = 86.049, p = .000; Mann-Whitney U: 7242.500, Wilcoxon W = 34503.500, Z = -8.086, Asymp. Sig. (2-sided) = .000) (Fig. 21). Among patients with hypoalbuminemia, the prevalence of ascites was significantly higher, observed in 77.7% (N=178) of cases (Fisher Exact test, p = .000) (Fig. 22).

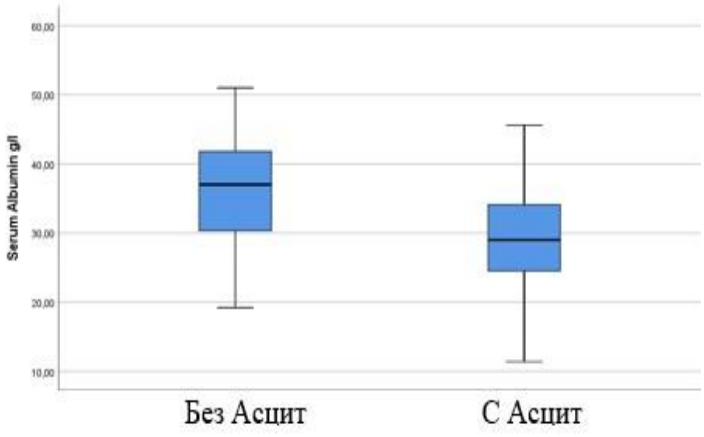


***Figure. 21**. Serum albumin value in cases without and with ascites*

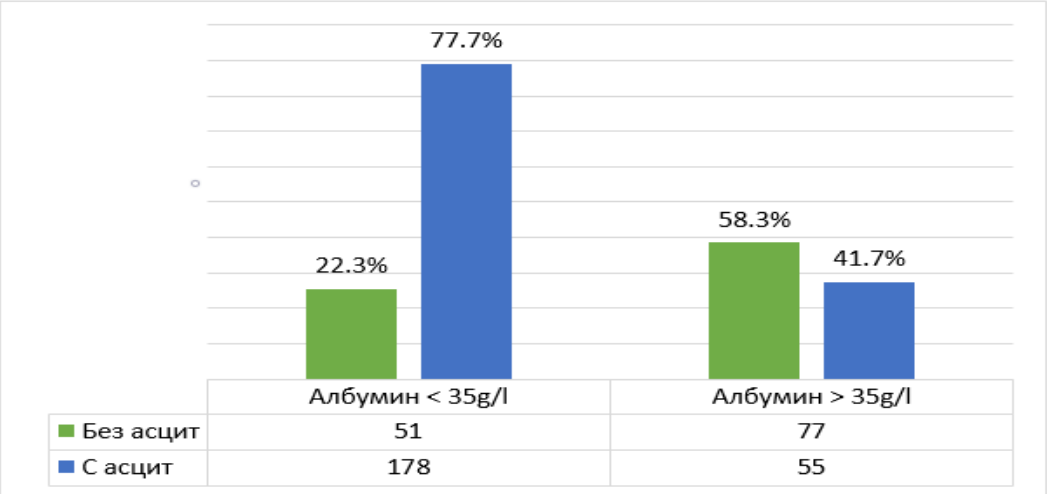


***Figure 22**. Distribution of cases depending on the value of serum albumin and the presence of ascites (without ascites--green, with ascites-blue)*

When comparing cases with ascites based on its volume, it was found that the mean serum albumin level significantly decreased as the amount of ascitic fluid increased, despite minimal differences between the individual groups (Kruskal-Wallis test: H = 10.727, df = 2, Asymp. Sig. (2-sided) = .005).

Using an ROC curve (Area under ROC = .757; 95% CI: LB .704 - UB .810), a cutoff value of 31.850 g/l was determined, with a sensitivity of 82% and specificity of 66% for predicting the presence of ascites.

The mean serum albumin level in cases with hepatic encephalopathy (HE) was significantly lower (N = 170; 28.6±6.37 g/l; median 27.00) compared to those without HE (N = 191; 34.83±7.44 g/l; median 35.90), showing a statistically significant difference between the two groups (Mann-Whitney U = 8268.500, Wilcoxon W = 22803.500, Z = -8.050, Asymp. Sig. (2-sided) = .000) (Fig. 23).

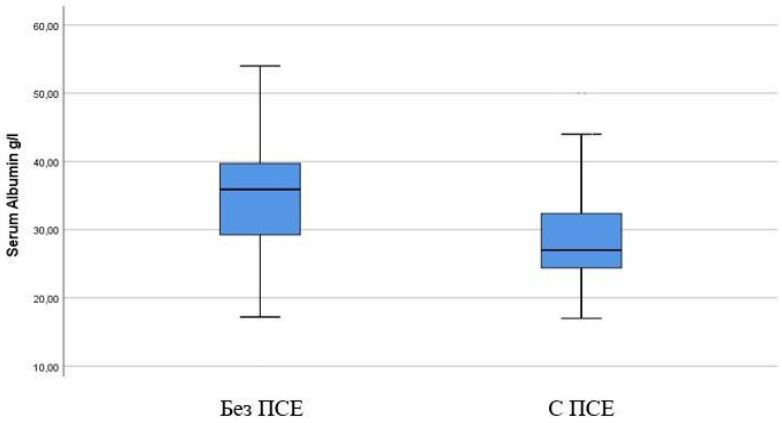


***Figure. 23**. Serum albumin persistence in cases with and without PSE*

An ROC curve (Area under ROC = .745; 95% CI: LB .694 - UB .796) identified a cutoff value of 34.32 g/l with a sensitivity of 63% and specificity of 83%, associated with the occurrence of HE.In cases of hypoalbuminemia, the incidence of portosystemic encephalopathy (PSE) is significantly higher—62.4% (N=143) (Fisher's Exact test, p=.000) (Fig. 24).

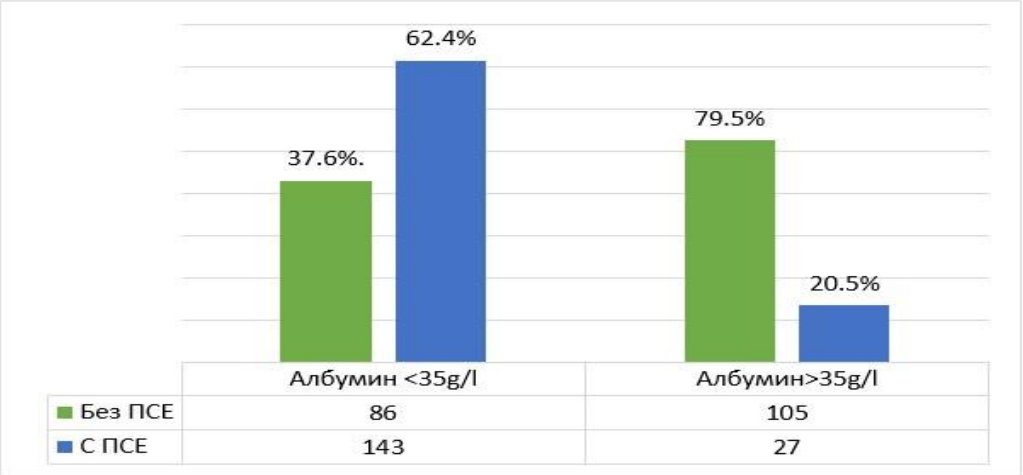


Figure 24*. Distribution of cases according to serum albumin value and presence of PSE (without PSE--green, with PSE-blue)*

In cases of impaired renal function, the incidence of hypoalbuminemia is significantly higher—89.7% (N=26) among all cases with hepatorenal syndrome (HRS) and 93.8% (N=15) among those with acute kidney injury (AKI) (Pearson Chi-Square test: 17.333, df 3, p=.000) (Fig. 25). The mean serum albumin level in cases with HRS (N=29; 26.81±6.23 g/L, median 26.00) and AKI (N=16; 27.22±5.54 g/L, median 27.70) was significantly lower compared to those with normal renal function (N=296; 32.65±7.47 g/L, median 32.00) (Mann-Whitney U: 2429.000, Wilcoxon W: 2864.000, Z: -3.858, Asymp. sig. 2-tailed p=.000 for HRS; Mann-Whitney U: 1369.500, Wilcoxon W: 1505.500, Z: -2.841, Asymp. sig. 2-tailed p=.004 for AKI). Using an ROC curve (Area under ROC: 0.706, 95% CI: LB 0.614 - UB 0.798), a cutoff value of 27 g/L was determined, with a sensitivity of 59% and a specificity of 70%, associated with the occurrence of HRS and AKI.

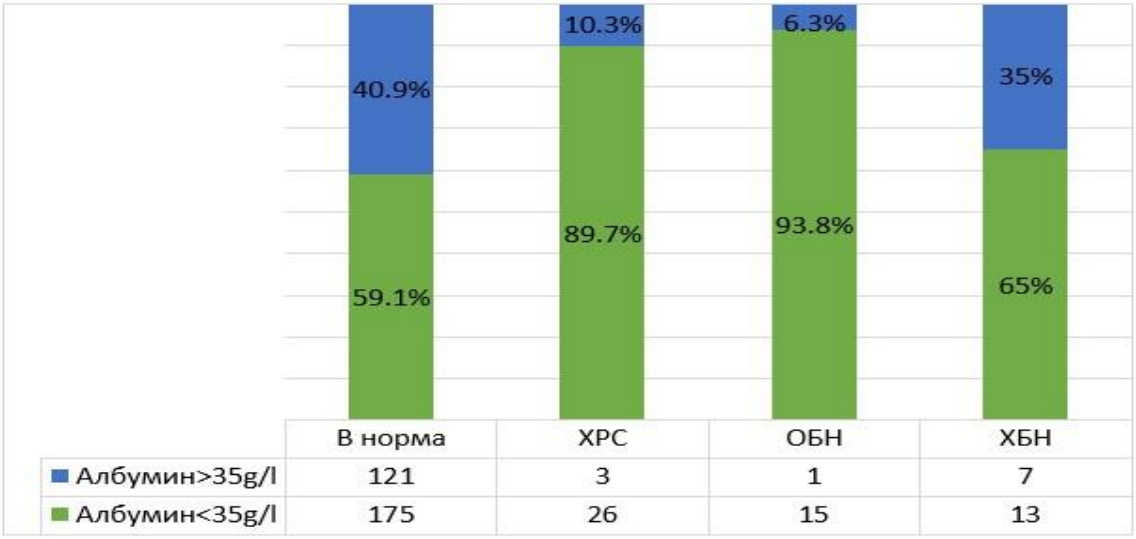


Figure 25. *Distribution of cases according to serum albumin value and renal function abnormalities (with hypoalbuminemia--green, without hypoalbuminemia-blue)*

In cases of hepatic encephalopathy (HE), regardless of its severity, the measured mean value of total bilirubin was higher (95.40±112.49 µmol/L, median 48.55) compared to those without HE (41.48±51.4 µmol/L, median 24.23) (Mann-Whitney U: 10329.000, Wilcoxon W: 28665.000, Z: -5.967, Asymp. sig. 2-tailed p=.000). Despite the established correlation, elevated bilirubin levels are not necessarily associated with the occurrence of HE, as a significant number of cases with high bilirubin levels were observed without HE manifestations (Fig. 26).

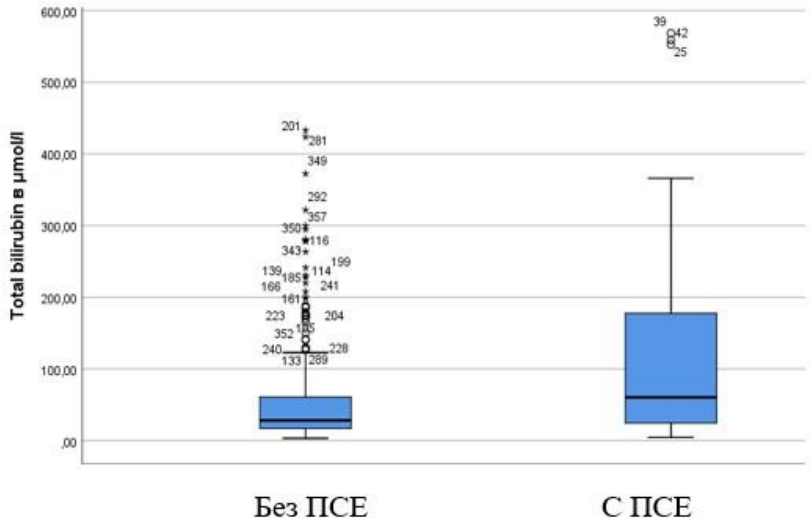


Figure 26*. Total bilirubin persistence in cases with and without PSE*

The frequency of jaundice is significantly higher in cases with psychosocial and emotional factors (PSE) (N=83; 66.9%) (Pearson Chi-Square test 30.823 df 2 p=.000) (Fig. 27).

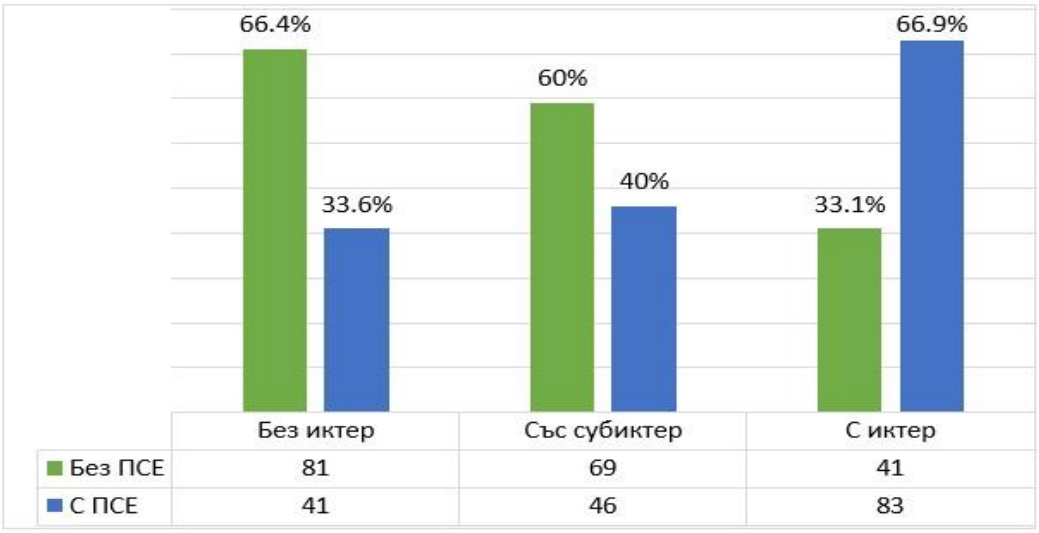
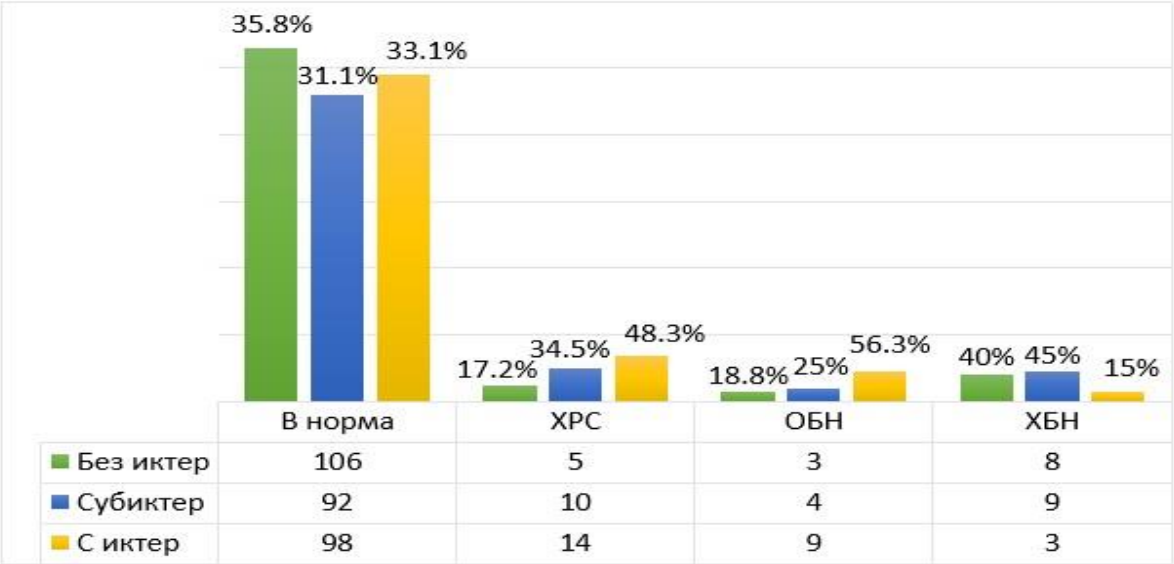


***Figure 27**. Distribution of cases depending on the presence of jaundice and PSE (without PSE--green, with PSE -blue)*

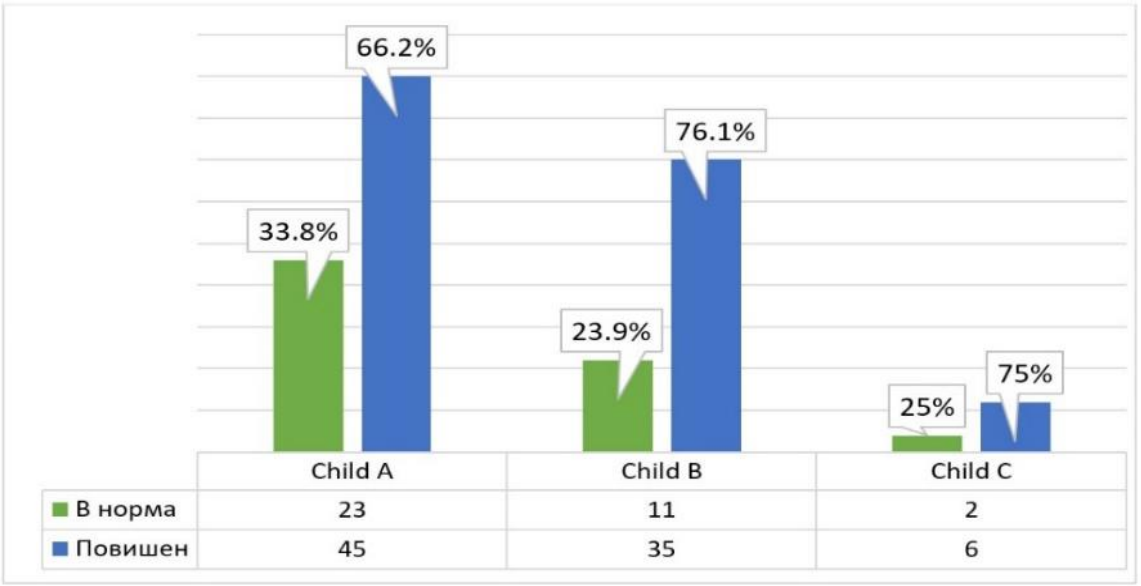
Jaundice is more common in cases of chronic renal syndrome (CRS) (N=14; 48.3%) and obstructive biliary disease (OBD) (N=9; 56.3%), despite the lack of absolute significance (Pearson Chi-Square test 11.631 df 6 p=.071) (Fig. 28). Cases with CRS (N=29) and OBD (N=16) have significantly higher mean total bilirubin levels (130.45±147.25, median 47.50 for CRS; 117.79±146.93, median 59.95 for OBD), compared to those without kidney function abnormalities (N=296; 60.46±77.23, median 28.62). (For CRS: Mann Whitney U 2803.000, Wilcoxon W 46759.000, Z=-3.083, Asymp. Sig. 2-tailed p=.002; For OBD: Mann Whitney U 1586.500, Wilcoxon W 45542.500, Z=-2.224, Asymp. Sig. p=.026).



	В норма	ХРС	ОБН	ХБН
Без иктер	106	5	3	8
Субиктер	92	10	4	9
С иктер	98	14	9	3

Figure. 28*. Distribution of cases according to renal function*

In 70.49% (N=86) of all cases without jaundice (N=122; 33.8%), there is an elevation of only the direct bilirubin fraction. Only 9.97% (N=36) of the entire study population have normal direct bilirubin levels, and in all three Child groups, cases with elevated direct bilirubin significantly predominate (Pearson Chi-Square test: 13.258 df 2 p=.001) (Fig. 29).



	Child A	Child B	Child C
В норма	23	11	2
Повишен	45	35	6

Figure 29*. Distribution of cases with normal and elevated direct bilirubin in the population with normal total bilirubin in Child*

Discussion:

Serum albumin and prothrombin time (PT) values do not change even in advanced fibrosis, making them unreliable for its assessment. Changes in their levels are

observed when cirrhosis develops, as a result of the liver's limited functional capacity on one hand, and on the other hand, they are directly related to the hemodynamic changes associated with portal hypertension. A study on chronic viral hepatitis cases has proven that any decrease in serum albumin, combined with an increase in serum bilirubin, serves as a laboratory marker for the progression to liver cirrhosis. Other studies have shown that in cirrhosis, albumin levels are lower compared to cases of chronic hepatitis. Its increase after antiviral treatment in cirrhosis due to hepatitis C is associated with an improvement in liver functional capacity and a reduction in non-inflammatory activity. It has been established that with alcoholic etiology of the disease, hypoalbuminemia is more frequently observed. Albumin levels are an important predictor of mortality, both in compensated and decompensated liver cirrhosis, with a decrease below 40g/l, even within the reference range, being a significant prognostic marker for future decompensation. In our study, it was found that serum albumin progressively decreases, while total bilirubin increases with the rise of Child-Pugh and MELD Na scores, which is associated with the onset of hepatic decompensation. Hypoalbuminemia was present in 63.4% of the examined cases, and it was significantly associated with both the appearance and the quantity of ascites, which was the most frequently observed decompensating event in the study population. This result is comparable with data from another study showing this relationship, despite the lack of statistical significance. ROC analysis identified a cutoff value of 31.85g/l, predicting its appearance, which corresponds to findings from another study of cases with newly developed ascites after TIPS (30.8g/l). It has been proven that worsening hypoalbuminemia and hyperbilirubinemia, along with accompanying thrombocytopenia, are linked to a higher frequency of spontaneous bacterial peritonitis (SBP) in cirrhotic ascites and worsening cognitive dysfunction. Our cases with psychosocial and emotional (PSE) factors also showed significantly lower mean albumin levels, compared to others without. ROC analysis established a cutoff value of 34.32g/l as a boundary for PSE. The relationship between the onset of hypoalbuminemia and the development of cognitive dysfunction has also been proven in other studies, with cutoff values of 31.6g/l and 30.5g/l, respectively, and values below 22.8g/l predicting early in-hospital mortality. Our results also showed a connection between the worsening hypoalbuminemia and kidney function deviations, which have previously been documented. In all cases with chronic renal syndrome (CRS) and obstructive biliary disease (OBD), the mean albumin level was significantly lower compared to others with normal kidney function. A study has shown that 85.3% of cases

with CRS have concomitant hypoalbuminemia, supporting our findings. ROC analysis identified a cutoff value of 27g/l predicting its appearance, which is identical to that found in another study. An increase in total bilirubin with the progression of Child-Pugh and MELD Na scores was linked to the onset of hepatic decompensation. Total bilirubin is a key indicator for determining the severity of liver damage in both scoring systems. In our study, 70.5% (N=86) of cases with normal total bilirubin levels (N=122; 33.4%) showed an elevation in its direct fraction only. The results suggest that early elevation of direct bilirubin, despite normal total bilirubin levels, may be a marker for advanced liver disease, even with compensated liver function. A histological study on an animal model has shown that elevated direct bilirubin is associated with advanced fibrosis and is a poor prognostic sign for a fatal outcome, regardless of its stage. Another study demonstrated that direct bilirubin is a better indicator for six-month prognosis in cirrhosis when combined with other laboratory markers such as prothrombin time and serum creatinine. Measuring the ratio between total and direct bilirubin has been used to evaluate cases with acute-on-chronic liver failure, with a value above 0.8 being considered a good prognostic outcome. Hyperbilirubinemia combined with elevated leukocytes is associated with increased in-hospital mortality in decompensated cases. A sharp rise in bilirubin, accompanied by prolonged prothrombin time, is a laboratory marker of acute liver failure. In our study, a significant link was found between elevated total bilirubin levels and the appearance of PSE, even though many cases of hyperbilirubinemia did not show symptoms, a relationship previously confirmed in other studies. Prolongation of prothrombin time is an important indicator for assessing the progression of liver cirrhosis but does not reflect the hemorrhagic risk in these patients. No differences were found in its value when comparing cases of chronic hepatitis and cirrhosis, and it is considered an unreliable prognostic marker in the compensated stage of the disease. Its measurement is an important element in the two most widely used scoring systems for evaluating liver cirrhosis: Child-Pugh and MELD/MELD Na scores. It is important to note that there are large differences in the determination of prothrombin time between different laboratories, as well as variations in its value influenced by other factors. In this regard, the obtained result may not have real diagnostic value in all cases. In our study, we found that INR increases with the progression of liver damage, showing significance in relation to both Child-Pugh and MELD Na scores. This result is consistent with another study, where a close correlation with the rising Child-Pugh score was also established. Measuring INR, together with other coagulation indices, fibrinogen, and platelet parameters,

has 80% sensitivity for early detection of cirrhosis. A significant deviation in prothrombin time, associated with an increase in serum bilirubin, is an important prognostic sign of acute liver failure, along with other laboratory markers, and is closely related to a high MELD score. Increasing INR, accompanied by encephalopathy and infection, is independently associated with a high three-month mortality in 90% of cases of acute-on-chronic liver failure.

3. Analysis of Serum Sodium Values:

In 71% (N=256) of cases, serum sodium levels are within the normal range, 20.5% (N=74) exhibit mild hyponatremia, and 8.5% (N=31) have severe hyponatremia. The distribution across the three groups showed that as the Child-Pugh stage increases, the frequency of hyponatremia cases also rises, as well as the severity of the condition. Among all cases in Child C, 50.8% (N=62) have hyponatremia, while 91.8% (N=90) of cases in Child A do not have it (Pearson Chi-Square test: 53.154 df 4 p=.000) (Fig. 30).

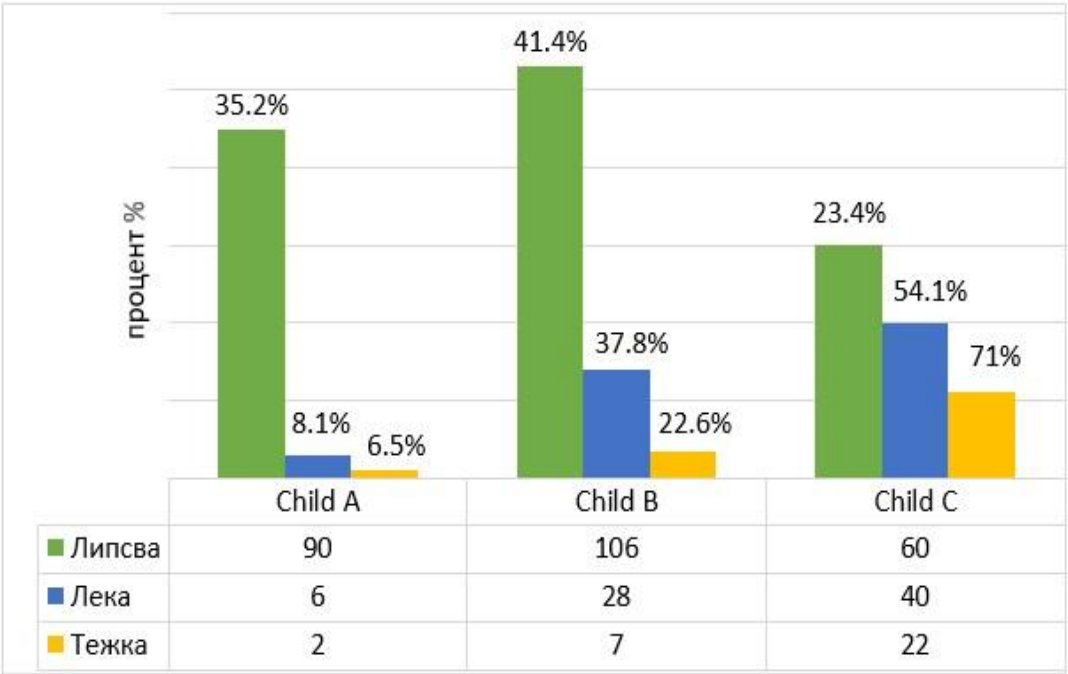


***Figure 30**. Child distribution in cases with and without hyponatremia (green–without, blue–with mild, yellow–severe hyponatriemia)*

Cases with serum sodium levels <135 mmol/l have a significantly higher Child-Pugh score (9.85±2.31, median 10) compared to those with levels >135 mmol/l (7.78±2.28, median 7) (Mann Whitney U 7057.00, Wilcoxon W: Z -7.144; Asimp. sig. 2-tailed: p=.000) (Fig. 31).

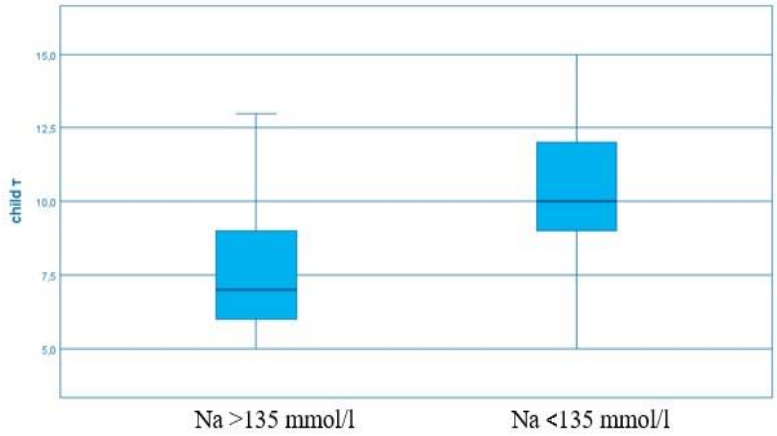


***Figure. 31**. Child scores in cases without and with hyponatremia*

Hyponatremia is more commonly associated with ascites (Pearson Chi-Square test: 8.854 df 2 p=.012) and PSE (Pearson Chi-Square test: 13.805 df 2 p=.001) (Fig. 32, 33).

***Figure. 32**. Distribution of cases depending on the presence of ascites (green–without ascites, blue – with ascites)*

***Figure. 33**. Distribution of cases depending on the presence of PSE (green–without PSE, blue– with PSE)*

The frequency of hyponatremia is significantly higher in cases of HRS (N=16; 55.1%), AKI (N=7; 44.8%), and CKD (N=8; 40%). In 75% (N=222) of all cases with normal kidney function, hyponatremia is absent (Pearson Chi-Square test: 20.361 df 6, p=.002) (Fig. 34).

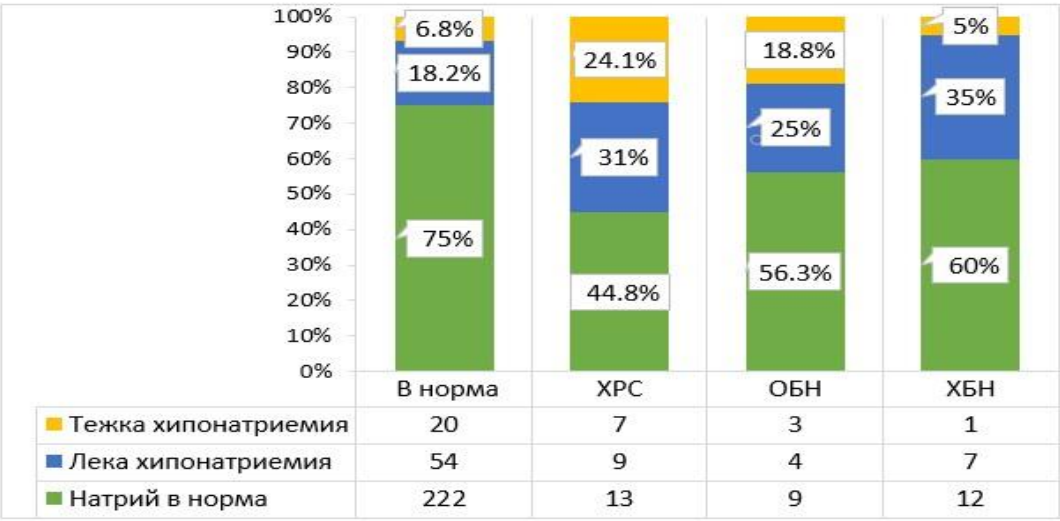


Figure. 34*. Distribution of cases depending on sodium value and renal function abnormalities (yellow– severe hyponatriemia, blue–mild, green–without hyponatriemia; first column - normal renal function, second column -HRS, third column - AKD, fourth column - CKD)*

Discussion:

According to the 2018 EASL report, a serum sodium value <135 mmol/l is considered the threshold for hyponatremia. Even a drop of just 1 mmol/l is associated with a 12% decrease in three-month survival. Prognostically, 12-month survival is better in cases with mild hyponatremia, compared to those with severe hyponatremia. In our study, we found a low frequency of hyponatremia in the studied cirrhotic population. This result significantly differs from other studies, which report a significantly higher prevalence (36.9%, 32.99%). Most authors consider a threshold of <130 mmol/l, and the prevalence they report is significantly higher than the figures from our study (21.6%, 30%, 37%, 42%, 45.5%). It has been proven that the onset of hyponatremia during liver cirrhosis is directly linked to its severity. Along with the MELD score, it predicts survival more accurately in patients waiting for a transplant. It has been established that even with a lower MELD score, the presence of hyponatremia results in a worse prognosis. In our study, we found that hyponatremia is closely associated with a high Child-Pugh class, with 71% of our patients with severe hyponatremia being in Child C, which is comparable to another study that reports a 79% frequency, a

relationship also confirmed by other authors. A connection was found between the severity of hyponatremia and the presence of ascites, which corresponds with findings from other studies, while also being differentiated from another study that found no such correlation. In our study, 55.1% of the cases with HRS and 44.8% of those with AKI had accompanying hyponatremia, confirming that it is significantly associated with renal function abnormalities. The threshold values for sodium reported by other authors are <130.5 mmol/l – 130 mmol/l for its manifestation. In 41.76% (N=71) of our cases with PSE, regardless of its severity, hyponatremia is also present, compared to 17.8% (N=34) in those without PSE. On the other hand, 62.2% of those with mild hyponatremia have PSE, and 80.6% of those with severe hyponatremia. The results showed a significant correlation between hyponatremia and PSE, which has also been confirmed by previous studies. The relationship between decreased serum sodium levels and the onset of PSE is associated with changes in osmotic pressure and subsequent cerebral edema, which leads to alterations in various neurological functions. In this context, the high frequency of PSE in hyponatremic patients observed in our study could be explained.

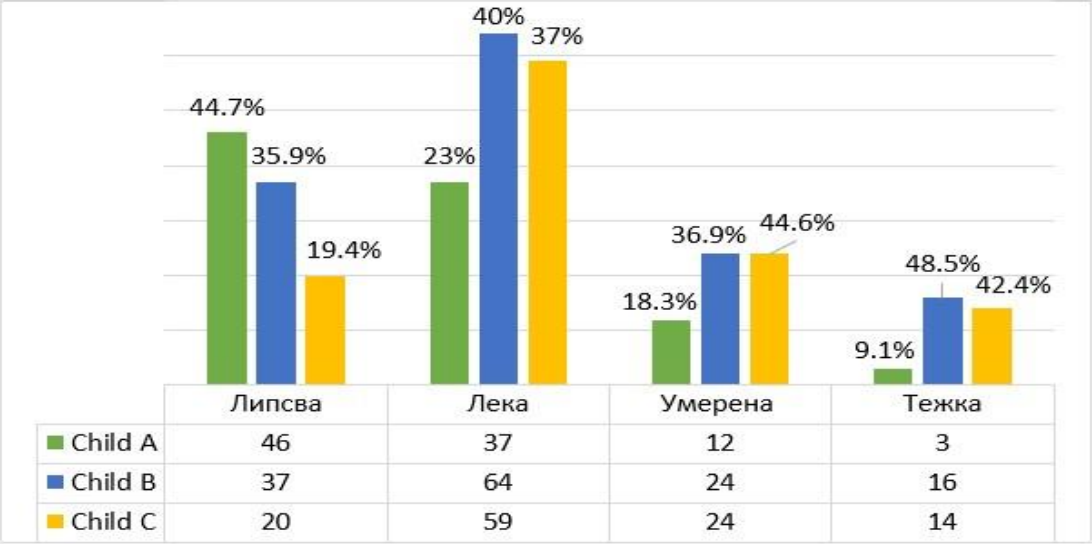
4. Hematological Parameter Analysis:

4.1 Anemia Syndrome Analysis:

An anemia syndrome was found in 71% (N=258) of all cases, regardless of its severity and disease stage. The majority were mild cases, accounting for 62% (N=160) of all cases with anemia syndrome (N=258) (fig. 35).

Figure. 35. *Ratio between cases of anemia syndrome depending on its severity (green–mild, blue– moderate, yellow–severe)*

The distribution of cases across the three Child groups showed that with the progression of the stage, both the frequency and the severity of the anemia syndrome increase. (Pearson Chi-Square test: 29.211 df 6 p=.000) (fig. 36).



	Липсва	Лека	Умерена	Тежка
Child A	46	37	12	3
Child B	37	64	24	16
Child C	20	59	24	14

Figure. 36*. Distribution by Child according to the severity of anemia (first column-no anemia, second column-mild, third column-moderate, fourth column-severe)*

The distribution based on the type of anemia according to MCV and its severity showed that in the studied population, normocytic anemia predominates (N=135; 52.3%), which is mostly mild to moderate in severity. Macrocytic anemia is the second most frequent (N=88; 34.1%), also predominantly mild to moderate in degree. The smallest group (N=35; 13.56%) with microcytic anemia consists mainly of severe and moderate cases (Pearson Chi-Square test: 63.595 df 9 p=.000). When determining the relationship between MCV (regardless of the presence or absence of anemia) and the etiological factor, it was found that the frequency of macrocytosis was significantly higher when alcohol was present as the etiology (72.57%; N=262): 39.7% (N=104) compared to 12.1% (N=12) for all other etiologies (N=99; 27.42%). In both groups, normocytosis predominates, while microcytosis is more common in non-alcoholic etiologies. Of all macrocytic cases (N=116), alcohol-related etiology was found in 89.7% (N=104), and non-alcoholic in only 10.3% (N=12). The result showed a statistically significant difference between the two groups (Pearson Chi-Square test: F 47.129 df 3 p=.000) (fig. 37).

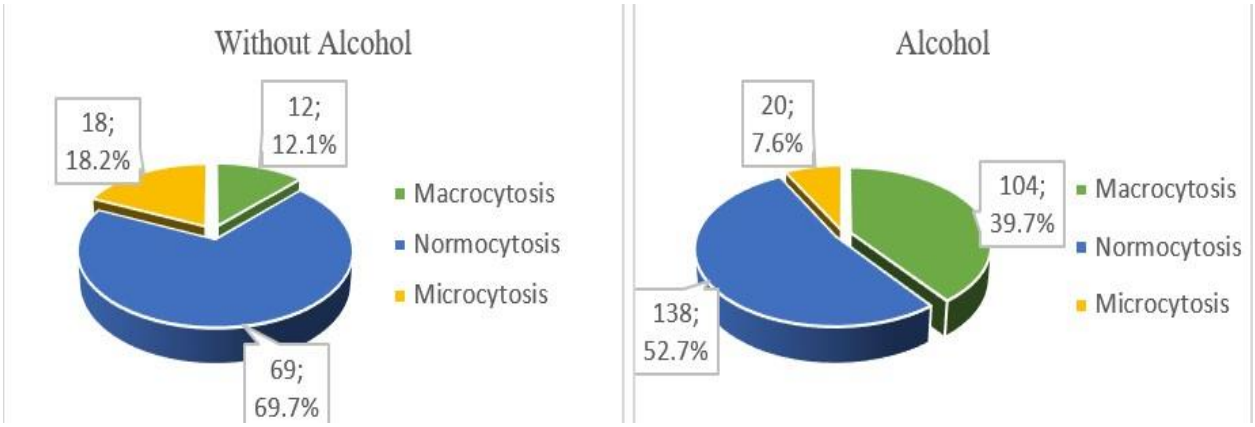


Figure 37*. Distribution of cases according to MCV in non-alcoholic and alcoholic etiology*

Table. 7*. Research indicator values with ANOVA:*

Стадий	Стойност	Hb g/L	Er 10*12/L	MCV fl	MELD Na
Child A (N=98)	Mean±sd	121.27±21.66	3.96±.716	91.77±10.66	9.54±2.75
	Minimal	56	2.1	62	6
	Maximal	164	6.16	114.5	19
	95% CI:	116.98–125.55	3.81–4.10	89.65–93.88	8.99–10.08
		±4.28 (±3.5%)	±0.14 (±3.6%)	±2.11 (±2.3%)	±0.54 (±5.7%)
Child B (N=141)	Mean±sd	109.90±23.09	3.48±.740	94.45±12.02	13.6±4.88
	Minimal	46	1.37	59.5	6
	Maximal	170	5.46	129	30
	95% CI:	106.29–113.67	3.35–3.60	92.48–96.41	12.80–14.39
		±3.77 (±3.4%)	±0.12 (±3.5%)	±1.96 (±2.1%)	±0.79 (±5.9%)
Child C (N=122)	Mean±sd	105.25±20.72	3.14±.702	98.65±9.70	22.3±6.5
	Minimal	51	1.25	68	9
	Maximal	144	5.23	126	40
	95% CI:	101.57–108.92	3.01–3.26	96.92–100.37	21.14–23.45
		±3.67 (±3.7%)	±0.12 (±4.0%)	±1.72 (1.7%)	±1.15 (±5.2%)

A statistically significant difference was found regarding the calculated Child-Pugh scores in cases with (7.44±2.41) and without (8.76±2.39) anemia (Mann-Whitney: Z -4.799; Asimp. sign. 2-tailed: p=.000) (fig. 38). A statistically significant difference was also found in the MELD Na values in cases with (13.80±6.94) and without (16.09±7.25) anemia (Mann-Whitney: Z -3.097; Asimp. sign. 2-tailed: p=.002) (fig. 39).

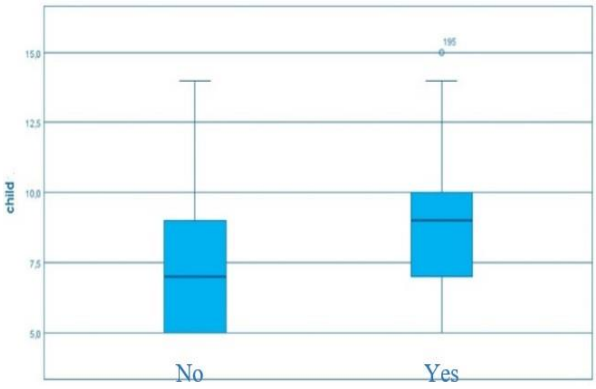


Figure. 38*. Child-Pugh in cases without and with anemia*

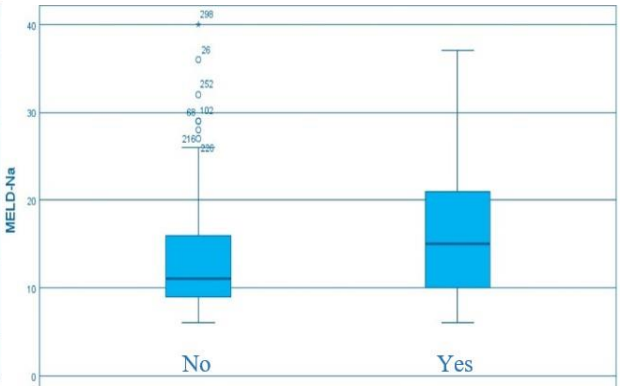


Figure. 39*. MELD Na in case without and and with anemia*

Discussion:

The most common hematological abnormality in the studied population was the presence of anemia syndrome in 71% (N=258) of all cases, with our results comparable to those of other authors (57.8%, 66%, 70.1%, 81%, 70.1%). The predominant form was mild anemia, observed in 62% (N=160), which is confirmed by other studies, despite the variation in reported frequency (41.3%, 71.2%). As the Child stage increased, both the frequency and severity of anemia also increased, with 53% in Child A, 72.22% in Child B, and 79.5% in Child C. These results align with those of another study where the rates were 57.9%, 80.9%, and 87.5% for Child A, B, and C respectively. The measured Hb values and the number of erythrocytes (Er) decrease with the progression of liver disease, with moderate and severe anemia being more common in Child B and C, consistent with findings from other studies. Although the decrease in Hb is accompanied by an increase in MELD Na, no strict correlation was found, unlike other studies that report an absolute relationship. The number of erythrocytes showed absolute significance in relation to both the Child-Pugh and MELD scores, with previous studies demonstrating a better correlation of erythrocyte count with the severity of liver damage compared to Hb values. A statistically significant difference was found in the mean MELD Na value between cases with and without anemia in the studied population, with values of 13.80±6.94 and 16.09±7.25, respectively. In studies, a mean MELD Na value of 12 is reported as a threshold for cases with anemia. Severe anemia was found in only 13% (N=33) of all anemic cases, which were proportionally distributed between Child B and C, with different frequencies reported in other studies (20.1%, 17.3%, 7.5%). These discrepancies are likely due to differences in the research groups in terms of sample size, etiology, disease stage, and definitions of severe anemia cases.

The distribution of anemia cases based on MCV showed that normocytic anemia was the most common (52.3%, N=135), followed by macrocytic anemia (34.1%, N=88), and microcytic anemia was the least common (13.56%, N=35). These findings are comparable with another study showing similar distributions: 51.4%, 30.9%, and 16%. Worldwide studies have established that normocytic anemia is the most frequent in the cirrhotic population, with varying case frequencies reported (52%, 58.97%, 46%, 39.4%). Microcytic anemia was the least common in our study, matching another study (13.3%), but significantly differing from others, which report much higher frequencies (22.6%, 33.3%, 40%, 43.8%). The most likely cause of these discrepancies is the absence of additional biochemical markers for assessing iron metabolism, which would allow for a more accurate determination of the nature of anemia, as well as differences related to the clinical-epidemiological profile of the studied patients. Of the cases with microcytic anemia, 42.4% (N=14) had severe anemia, and this was associated with a high Child class, which corresponds with data from another study. This contrasts with other studies where microcytic anemia is predominantly observed in compensated liver disease. The high frequency of macrocytosis in our patients was linked to the predominant alcoholic etiology, a finding also reported by other studies. Among all 116 cases with macrocytosis in the studied population, regardless of the presence of anemia, 89.7% (N=104) had an alcoholic etiology. It has been established that 50% to 70.3% of alcoholic cirrhosis cases exhibit macrocytosis. An MCV above 100 fl is an important predictor of alcoholic etiology in chronic liver disease, regardless of whether it is associated with anemia. The frequency of macrocytosis among alcoholics ranges from 64% to 84.5%. In our population with macrocytosis, 24.14% (N=28) of the cases had no anemia. A significant correlation was found between increasing MCV and Child-Pugh scores, which was associated with the predominant alcoholic etiology in the studied group and the severity of liver disease. The correlation with MELD Na was similar in significance, unlike other authors who confirm an absolute significance.

4.2. Platelet Count Analysis:

Thrombocytopenia was found in 47.4% (N=171) of all cases, regardless of its severity and disease stage, with mild thrombocytopenia occurring in 46% (N=79) of all those with the condition. The most common finding is the combination of thrombocytopenia with anemia, which is present in 64% (N=109) of all thrombocytopenia cases. In 26% (N=45) of these patients, or 12.46% of the entire

studied cirrhotic population, thrombocytopenia is observed without other concurrent hematological abnormalities (fig. 40).

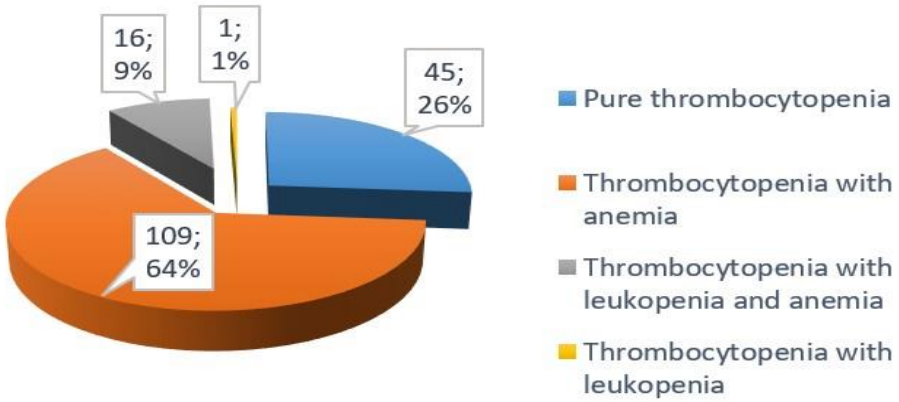
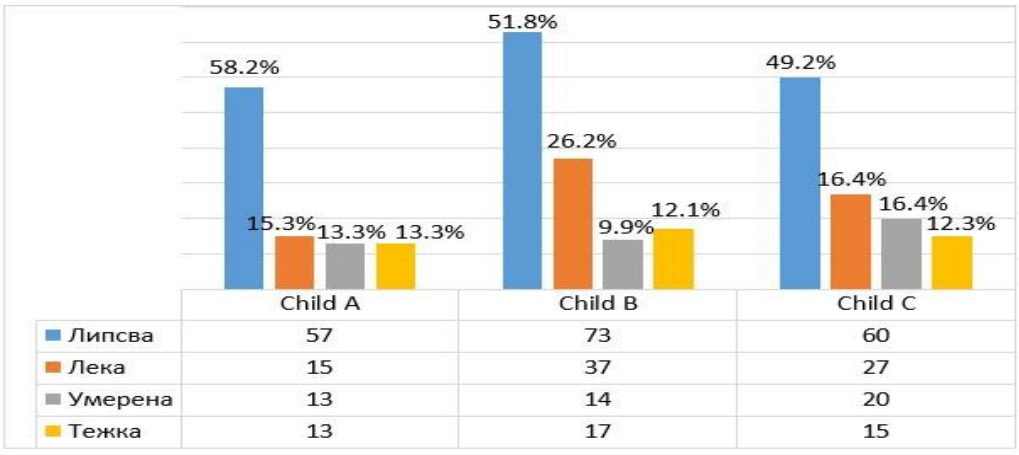


***Figure. 40**. Combination of thrombocytopenia with other hematological abnormalities*

The distribution of cases with and without thrombocytopenia, depending on its severity and the Child-Pugh stage, did not show a statistical relationship. In all three Child groups, the majority of cases were without thrombocytopenia (Pearson Chi-Square test: 6.208, df 6, p=.400) (fig. 41).



	Child A	Child B	Child C
Липсва	57	73	60
Лека	15	37	27
Умерена	13	14	20
Тежка	13	17	15

***Figure 41.** Distribution of cases according to platelet count and Child stage (blue-absent, orange-mild, gray-moderate, yellow-severe)*

There was no significant difference in the Child-Pugh scores between cases with (8.20±2.43, median 8) and without thrombocytopenia (8.58±2.51, median 9) (Mann-Whitney U: 14819.000; Wilcoxon W: 32964.00; Z = -1.452; Asimp. sig. 2-tailed: p = .147) (fig. 42). The average MELD Na score was higher in cases with thrombocytopenia (16.33±6.83, median 15) compared to those without

(14.62±7.5, median 12) (Mann-Whitney: Z = -3.111; Asimp. sign. 2-tailed: p = .002) (fig. 43).

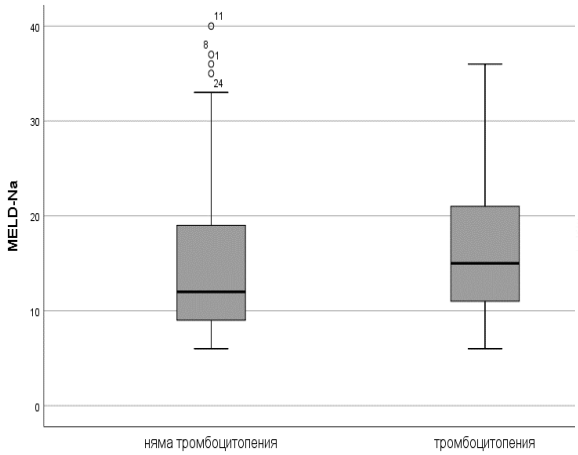


***Figure. 42**. MELD Na in cases without and with thrombocytopenia*

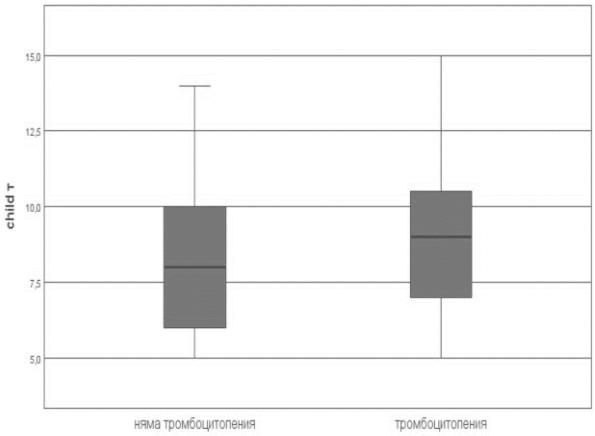


***Figure. 43**. Child-Pugh in cases without and with thrombocytopenia*

Thrombocytopenia is more frequently associated with non-alcoholic etiology of the disease (N=58; 58.6% for non-alcoholic, compared to N=113; 43.12% for alcoholic), although there was no statistically significant difference between the two groups (Pearson Chi-Square test: 9.360, df 3, p = .025). A significant difference was observed in the average platelet count between cases with and without esophageal varices (EV), with the number of platelets significantly decreasing as the size of the varices increased (ANOVA: df 3, F = 7.938, p = .000). Among all cases with thrombocytopenia (N=137), 73.7% (N=101) had varices, while 50% (N=63) of those without thrombocytopenia (N=126) had varices (Chi-Square test: F = 27.414, df 3, p = .000) (fig. 44).

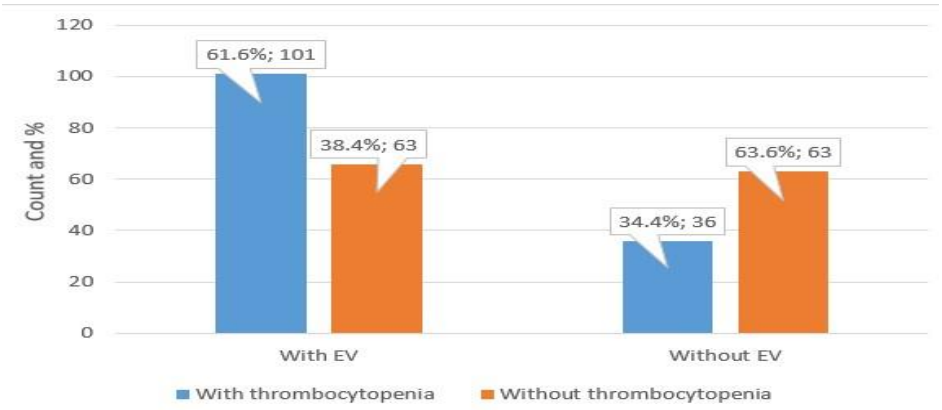


***Figure 44**. Distribution of cases with and without thrombocytopenia depending on the presence of EB*

The distribution of cases with and without thrombocytopenia did not show a statistical dependence related to the presence of hepatic encephalopathy (HE) (Pearson Chi-Square test: 2.806, df 4, p = .591) (fig. 45).

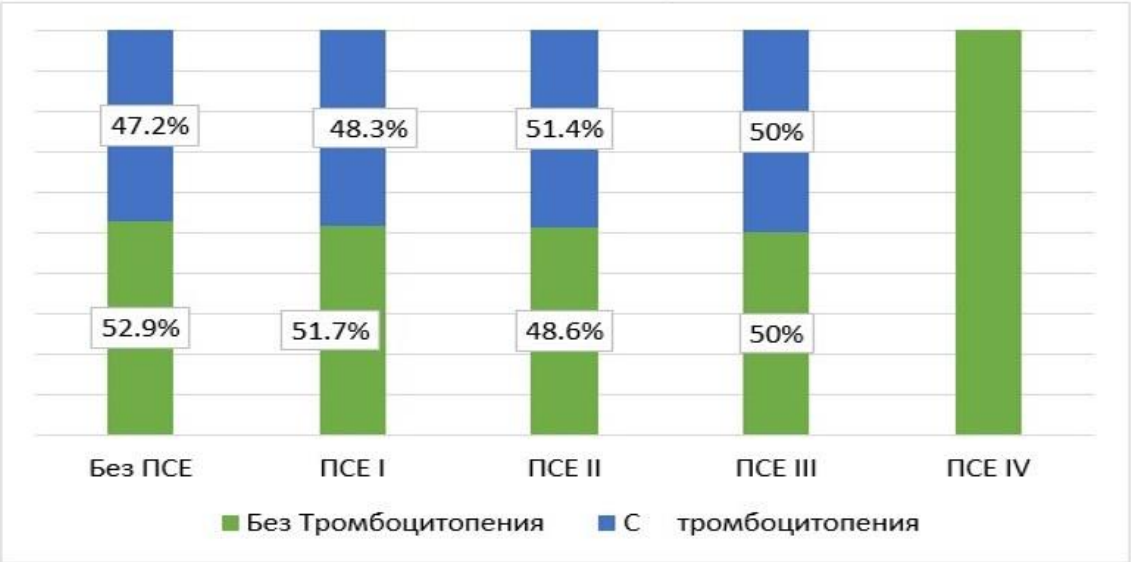


***Figure. 45**. Distribution of cases with and without thrombocytopenia depending on PSE(green-without thrombocytopenia, blue-with thrombocytopenia)*

Discussion:

In our study, thrombocytopenia was found in 47.4% (N=171) of all patients, regardless of its severity and disease stage. These results are in line with other studies (48.7%, 50%, 51%) but differ from those that report higher frequencies (56%, 58.9%, 60%, 61.4%, 64%), with the discrepancies likely attributable to the varying proportions of decompensated cases in the studied populations. In 26.3% (N=45) of all cases with thrombocytopenia, or 12.46% of the entire cirrhotic population, thrombocytopenia was isolated without other accompanying hematological abnormalities. This finding suggests that the presence of isolated thrombocytopenia could be a reason to exclude chronic liver disease in the differential diagnosis. One study demonstrated that 35% of cases with a low platelet count, who underwent bone marrow biopsy, had undiagnosed liver cirrhosis. Our results did not show a statistical dependence related to etiology, despite a higher frequency of thrombocytopenia in non-alcoholic cirrhosis, which also aligns with findings from other studies. There was no correlation between platelet count and the Child-Pugh stage, which differs from studies reporting near-significant relationships, and other research where disease progression to Child B and C was associated with a decrease in platelet count. Similarly, no correlation

with the MELD Na score was found, which is consistent with studies indicating no relationship between platelet count and spleen size. A significant difference was found in the mean MELD Na score when comparing cases with and without thrombocytopenia, which aligns with data from other studies. The average MELD Na values reported in these studies (16.89 and 19.7) for cases with thrombocytopenia are close to our result. The discrepancies likely arise from differences in the etiological profile of the groups studied; in our group, alcohol-related liver disease predominated, whereas in comparison groups, viral etiology was more common. Supporting this, a study showed that thrombocytopenia correlates well with the severity of cirrhosis in cases with viral etiology but not in alcohol-related cirrhosis. Despite the above, it has been demonstrated that in patients with the same MELD Na score, those with severe thrombocytopenia have three times the mortality rate. Among the 73.7% (N=101) of patients with thrombocytopenia who underwent endoscopic examination, varices were detected in the esophagus. Of all patients with varices (N=164), 61.6% (N=101) had laboratory-confirmed thrombocytopenia, confirming a relationship between the two. These findings are consistent with prior studies. As the size of the varices increases, the platelet count significantly decreases, which aligns with other authors' findings. Despite this, it has been proven that the severity of thrombocytopenia does not have a direct relationship with hemorrhagic risk in patients with high-grade varices in studies involving TIPS procedures. A cut-off value of 181 G/L was found with a sensitivity of 73% and specificity of 54.5%, predicting the occurrence of varices. This differs significantly from another study, which identified a cut-off value of 123 G/L with a sensitivity of 75% and specificity of 65%. Although thrombocytopenia predicts the appearance of varices, the sensitivity of this method is insufficient for reliable clinical practice application. In our study, no dependence was found between the presence of thrombocytopenia and hepatic encephalopathy (HE), in contrast to other studies that report that the combination of thrombocytopenia, hypoalbuminemia, and prolonged INR is more commonly associated with cognitive dysfunction.

4.3 Analysis of Leukocytes in the Studied Population:

Among all the examined patients (N=361), 69% (N=249) had a normal leukocyte count, 26% (N=94) had leukocytosis, and 5% (N=18) had leukopenia, regardless of the disease stage. In 89% (N=16) of the leukopenia cases, it was combined with thrombocytopenia and anemia; in 1 case, there was only leukopenia and anemia,

and in another, leukopenia with thrombocytopenia. There were no isolated cases of leukopenia in the studied population (Fig.46).

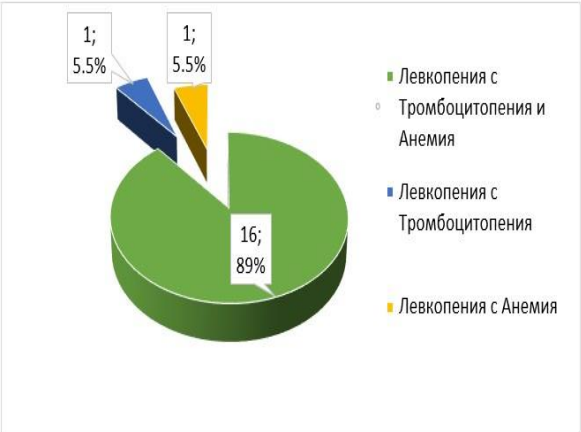


***Figure. 46**. Combination of leukopenia with other hematological abnormalities*

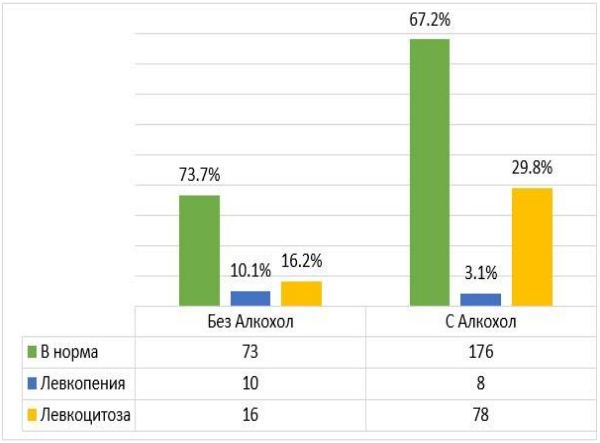


***Figure. 47**. Distribution by etiology and leukocyte count (normal-green, leukopenia-blue, leukocytosis- yellow)*

The distribution of cases showed a dependency related to etiology, with leukocytosis being primarily associated with alcohol-related etiology, while leukopenia was more frequently observed in non-alcoholic etiology (Pearson Chi-Square test: 12.716 df 2 p=.002) (Fig.47). Of all the patients with leukopenia in the non-alcoholic etiology group (N=10), 70% (N=7) had purely viral etiology. Among them, 85.7% (N=6) had hepatitis C, and 14.3% (N=1) had hepatitis B, while the remaining 30% (N=3) had another non-alcoholic cause. The cases with a normal white blood cell count are proportionally distributed across all three Child groups, while the number of cases with leukocytosis significantly increases with the stage of the Child classification (Pearson Chi-Square test 40.265 df 4 p=.000) (Fig. 48).

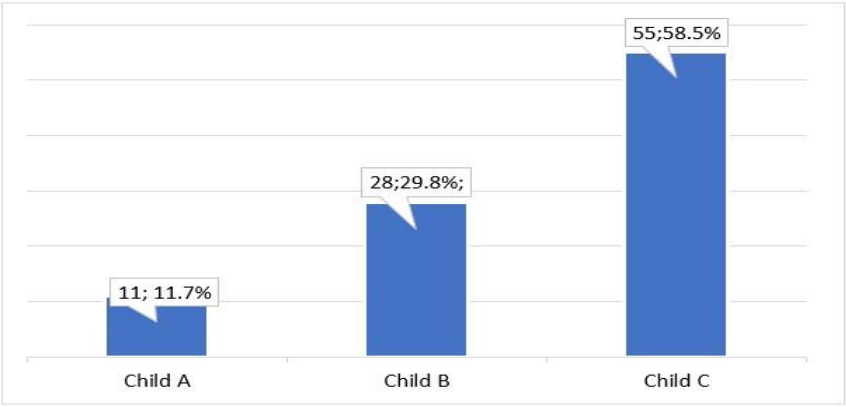


***Figure. 48**. Distribution of cases with leukocytosis by Child*

Discussion:

In our study, leukopenia was found in 5% (N=18) of all cases, with the majority occurring in Child A and B groups, making it the rarest hematological deviation in the studied population. It was found that its frequency in compensated newly diagnosed cirrhosis is about 5.5%, with a subsequent increase as the disease progresses. The result significantly differs from other studies that report a much higher frequency (12%, 15.6%). A possible reason for this discrepancy is the difference in the threshold value for leukopenia (below 4) used in their results, as well as a higher proportion of viral etiology in their populations. Our result confirmed that leukopenia is more frequently associated with viral etiology, as established by other authors as well. In our study, there was no isolated case of leukopenia; all were combined with other hematological deviations. The most common combination was with thrombocytopenia in 94.4% (N=17), and 83.33% (N=15) also had a concurrent anemic syndrome, which confirms that its appearance is most likely to occur after the manifestation of other hematological deviations. A study has shown that the decrease in leukocytes chronologically follows thrombocytopenia, and their combination is associated with advanced fibrosis and poorer prognosis for patients even in the compensated stage. Leukocytosis was found in 26% (N=94) of the entire population, with different studies reporting varying frequencies (18%, 30%, 45.6%) of the same. A dependence was established between the increased white blood cell count and higher Child-Pugh and MELD Na scores, confirming that its presence is associated with disease decompensation, which is consistent with foreign results.

V. Analysis of Cases with Acute Alcoholic Hepatitis Superimposed on Cirrhosis:

1. Demographic Characteristics:

Of all the studied cases (N=361), acute decompensation was found in 29.4% (N=106), regardless of its cause (excluding cases with acute hemorrhage) and the etiology of the disease. Among all cases without alcohol as the etiology (N=99), 12% (N=12) had acute decompensation, while among those with alcoholic etiology (N=262), it was observed in 36% (N=94) of cases. Of all the acutely decompensated cases with alcoholic etiology (N=94), 90.4% (N=85) were related to superimposed acute alcoholic hepatitis, while in the remaining 9.6% (N=9), another cause was present. The obtained result showed that the frequency of acute decompensation at the time of diagnosis was significantly higher in cases with

alcoholic etiology, primarily associated with superimposed acute alcoholic hepatitis (Pearson Chi-Square test 47.187 df 3 p=.000) (Fig. 49).

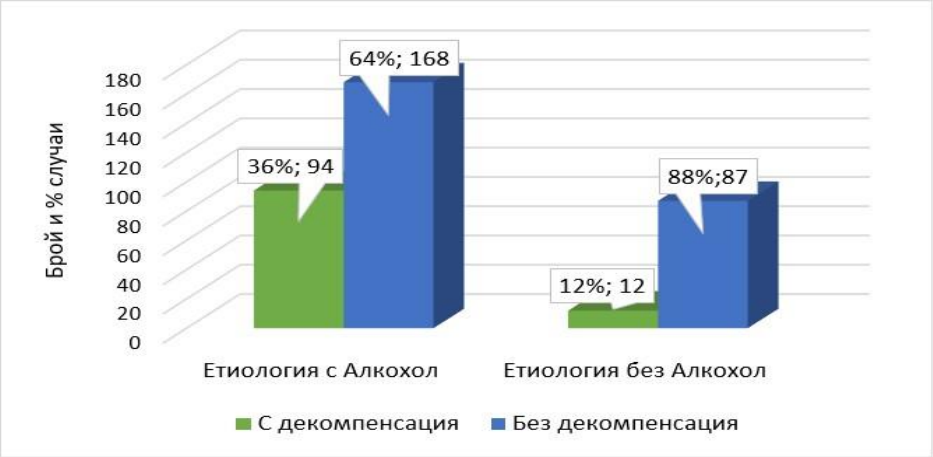


***Figure 49**. Distribution between cases with and without decompensation depending on etiology (green-with decompensation, blue-without decompensation; first column-etiology alcohol, second column-etiology without alcohol)*

Among all women with alcohol as the etiology (N=52), 42% (N=22) were diagnosed with AH, while among men (N=210), only 30% (N=63) were diagnosed (Fisher's Exact Test 2-tailed .001, 1-tailed .064). Of all the AH cases, 74% (N=63) are men and 26% (N=22) are women. The cases with AH are younger, with this difference being more pronounced in women, despite the lack of established absolute significance (df 1 F 4.388 p=.037) (Fig. 50).

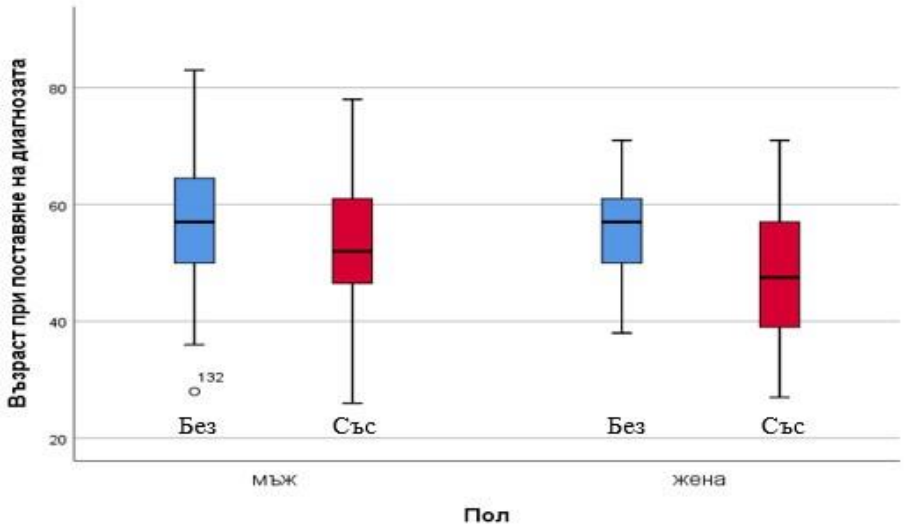


***Figure. 50**. Age distribution among men and women (blue-man, red-women)*

Discussion:

In our study, it was found that 29.4% (N=106) of all analyzed cases (N=361) presented with acute decompensation at their first hospitalization, with a significantly higher frequency of 36% (N=262) in cases with alcoholic etiology, compared to 12% (N=99) in cases with other etiologies. The results are consistent with a previous study, where 29.1% of hospitalized cirrhosis patients presented with acute decompensation, primarily associated with alcoholic etiology of the disease. It was established that the main precipitating factor for acute decompensation is persistent alcohol consumption, and less frequently, coexisting infection or reactivation of chronic viral hepatitis, as well as gastrointestinal bleeding. In 23.6% of the entire cirrhotic population (N=361), acute decompensation was attributed to superimposed acute alcoholic hepatitis, while in the remaining 5.8%, other causes for its appearance were present (without gastrointestinal bleeding), which were not further studied. According to literature data, in one-third of cases, acute liver decompensation is associated with concurrent alcoholic hepatitis. Its appearance is a result of excessive and prolonged alcohol consumption, and it is more frequently observed in the setting of underlying liver cirrhosis (37.3% to 83% of cases). Its prevalence shows significant geographic variation, with the highest rates in Western and Southern Europe and the UK, and the lowest in Muslim countries. In the United States, it shows high heterogeneity, linked to the combination of different ethnicities. The exact prevalence is not well defined due to a preceding oligosymptomatic period and underdiagnosis. According to a meta-analysis, the prevalence of acute liver failure in cirrhosis in Europe is about 30.9%, with alcohol accounting for 60.3% of the cases, and acute alcoholic hepatitis present in 24.5% of the affected cases. Data from the U.S. show a prevalence of 28.7%, India 24.6%, China 14.4-33.7%, and relatively higher prevalence in Japan (39.3%) and Korea (67.4%), despite the lower proportion of alcoholic etiology in their populations. In the cases we studied (N=85) with alcoholic hepatitis, the majority were male: 74% (N=63). These results are in line with other studies, which also indicate a predominance of male cases (55.73%, 61.2%, 69.7%, 70.1%, and 95.18%). Of all the women (N=103) in the entire study group, 49.5% (N=51) had alcoholic etiology, with 43% (N=22) presenting with AH at the time of diagnosis, compared to 30% in men. It has been demonstrated that, despite the less frequent involvement of women overall, the harmful effect of alcohol is more pronounced in women even with smaller quantities, and they are more likely to have severe forms of AH. The concerning trend of increasing alcohol use among young women in recent years is associated

with a higher frequency of mental disorders and lower social status. We found that the active working age was most affected, with an average age of 53.95±11.49 years for men, compared to 48.41±10.76 years for women, though no statistically significant difference was found between them. These results are consistent with other researchers, who also found that the active working age is most affected, with the highest frequency between 40-60 years old. The reported average age of the populations they studied is comparable to our results.

2. Frequency of observed complications and laboratory values in AH:

No statistically significant difference was found in the frequency of ascites between cases with and without acute alcoholic hepatitis (AH), although the frequency was higher in AH cases (Fisher Exact's test: 2-sided p = .316, 1-sided p = .161). The frequency of hepatic encephalopathy (HE), regardless of its degree, was significantly higher in AH cases (Fisher Exact's test: 2-sided p = .005, 1-sided p = .003). The frequency of chronic renal failure (CRF) and acute renal failure (ARF) was slightly higher in AH, with the difference between the two groups being borderline significant (Pearson Chi-Square test: 7.626 df 3 p = .054). A statistically significant increase was observed in the values of Child-Pugh score (Mann-Whitney test: Z = -8.928; p = .000), MELD Na (Mann-Whitney test: Z = -9.211; p = .000), and ALBI score (Mann-Whitney test: Z = -8.356; p = .000) in AH cases compared to the others without AH (Table 7).

Table 7*. Values of the three scores in cases without and with AH*

Indicators:	No AH N=177	Yes AH N=85	df	F	p-value
Child-Pugh (mean±sd)	7.93±2.08	10.79±1.98	1	111.735	.000
MELD Na (mean±sd)	13.57±6.19	22.55±6.56	1	116.135	.000
ALBI score (mean±sd)	-1.88±0.74	-0.91±0.49	1	118.766	.000
N=262 Number of cases;					

The study group of cases with acute alcoholic hepatitis (AH) (N=85) was divided into two subgroups—mild and severe forms—based on MELD Na values <20 and >20. Significant differences were found in the calculated Child-Pugh score, ALBI, and MELD Na, which were mainly associated with increased bilirubin and INR, as well as worsening hypoalbuminemia, which are the most significant factors determining liver function. The average white blood cell count increased

with the progression of liver dysfunction, while other hematological parameters did not show any significant correlation. An increase in urea and creatinine levels was also observed, along with a tendency toward hyponatremia in the severe cases (Table 8).

Table 8. *Laboratory values in cases with mild and severe AH*

Indicators mean±sd	MELD Na <20 N=38(44.7%)	MELD Na>21 N=47(55.3%)	ANOVA			Mann-Whitney p<0.05
			df	F	Sig	
ASAT	187.30±251.52	174.71±103.23	1	.098	.755	.150
ALAT	72.03±129.02	65.61±47.05	1	.100	.753	.086
ASAT/ALAT	3.32±1.69	3.09±1.73	1	.378	.540	.488
GGT	1095.68±1138.99	668.47±763.58	1	4.254	.042	.052
AF	209.48±128.84	197.19±102.80	1	.239	.626	.895
Albumin	29.36±6.45	25.49±3.71	1	11.983	.001	.008
Total bilirubin	113.40±77.96	223.44±119.79	1	19.825	.000	.000
Direct biliburin	90.98±76.52	176.93±97.03	1	19.825	.000	.000
Serum sodium	137.82±3.74	131.79±5.73	1	31.198	.000	.000
INR	1.36±0.313	1.77±0.45	1	22.30	.000	.000
Fibrinogen	257.73±121.67	214.80±113.89	1	2.808	.098	.065
Blood urea	4.15±2.81	9.48±9.71	1	10.709	.002	.002
Creatinin	71.22±50.96	139.57±141.73	1	7.988	.006	.009
Haemoglobin	110.53±19.51	104.06±22.82	1	1.913	.170	.233
Eritrocyte count	3.24±0.62	2.99±0.63	1	3.231	.076	.084
MCV	101.17±5.59	101.96±10.6	1	.168	.683	.234
Plt count	161.34±84.14	155.74±83.51	1	.094	.760	.234
Leucocyte count	9.57±4.35	12.86±6.37	1	7.330	.008	.004
Child-Pugh point	9.92±2.12	11.49±1.55	1	100.21	.000	.000
ALBI score	-1.20±.514	-0.68±.323	1	8.792	.004	.000
MELD Na	16.74±2.59	27.26±4.77	1	148.617	.000	.000

A cut-off value was identified for ALBI (AUC = 0.806): -0.675 (sensitivity 55.3% and specificity 94.7%), for Child-Pugh (AUC = 0.723): 11.50 points (sensitivity 57% and specificity 76%), and for total bilirubin (AUC = 0.846): 101.25 µmol/L (sensitivity 93.6% and specificity 63.2%), predicting severe AH. Upon examining the correlation between the main biochemical markers in the entire group with alcohol in the etiology (N=262), a significant positive correlation was found

between increasing AST, total bilirubin, and GGT levels, as well as a positive correlation between increasing GGT and ALP levels. A significant correlation was also observed between increasing total bilirubin and prothrombin time, and decreasing serum albumin levels (Table 9).

***Table. 9**. Correlation between the studied indicators*

Indicators:	Pearson corelation	Sign (2-tailed)	Spearman's cho corelation	Sign (2-tailed)
ASAT/ALAT-ratio /Albumin	-.250**	.000	-262**	.000
ASAT/ALAT-ratio /Bilirubin	.250**	.000	.312	.000
ASAT/ALAT ratio / INR	.165	.007	.204	.001
ASAT/Albumin	-.091	.142	-.194	.002
ALAT/Albimin	-.011	.858	-.005	.933
ASAT/ Total bilirubin	.333**	.000	.578**	.000
ALAT/ Total bilirubin	.168	.006	.373**	.000
ASAT/GGT	.378**	.000	.618**	.000
ALAT/GGT	.247**	.000	.479**	.000
ASAT/ALAT ratio/GGT	.207**	.000	.253**	.000
GGT/AF	.582**	.000	.541**	.000
GGT/ Total bilirubin	.314**	.000	.232**	.000
GGT/INR	-.231**	.000	-.269**	.000
Total bilirubin/INR	.380**	.000	.542**	.000
Albumin/INR	-.477**	.000	-.521**	.000
ALAT/INR	-.056	-.149	-.048	.438
ASAT/INR	.002	.976	.106	.086
Albumin/Total bilirubin	-.338**	.000	-.453**	.000
Albumin/Total bilirubin	-.328**	.000	-.475**	.000
N=262:Number of cases; sign p<0.01**				

No correlation was found between GGT levels and ALBI (Pearson correlation: -0.029, Sign: 2-tailed .640), Child-Pugh score (Pearson correlation: -0.097, Sign: 2-tailed .116), or MELD Na (Pearson correlation: 0.030, Sign: 2-tailed .630). The AST/ALT ratio showed a weak positive correlation with these scores (Pearson correlation: 0.308**, Sign: 2-tailed .000 for ALBI; 0.185**, Sign: 2-tailed .003 for MELD Na; 0.310**, Sign: 2-tailed .000 for Child). A weak negative correlation was found between the red blood cell count and the three scores

(Pearson correlation: -0.437**, Sign: 2-tailed .000 for ALBI; -0.265**, Sign: 2-tailed .000 for MELD Na; -0.391**, Sign: 2-tailed .000 for Child). A weak negative correlation was also found between serum sodium levels and the three scores (Pearson correlation: -0.355**, Sign: 2-tailed .000 for ALBI; -0.417**, Sign: 2-tailed .000 for MELD Na; -0.327**, Sign: 2-tailed .000 for Child). The correlation coefficients found were similar when comparing the markers with the three scores, with the results for Child and ALBI being approximately the same.

Discussion:

When comparing the group with and without arterial hypertension (AH) in the population with alcoholic cirrhosis (N=262), a statistically significant difference was found in the measured values of AST, ALT, GGT, and ALP, with these values being higher in cases with AH. The increase in blood pressure, which is accompanied by significant deviations in other biochemical markers, such as elevated bilirubin, prolonged prothrombin time, lower platelet count, and higher leukocyte count, is considered a laboratory marker of acute decompensation in alcoholic cirrhosis, which is most often associated with alcoholic hepatitis and/or infection and may serve as a precursor to impending hepatic failure (HF). No statistically significant difference was found in their values between the mild and severe forms of AH, except for GGT, which was close to significance. The measured mean value of AST was higher in cases with AH compared to others, which indicates that its elevation, together with deviations in other laboratory markers, is indicative of decompensation related to AH. However, when comparing mild and severe forms of AH, no difference was noted, confirming that the severity of AH is not associated with the extent of liver damage. In the cases examined with and without AH, ALT was minimally deviated from the norm, with a mean value close to the reference range, and in severe AH it was even lower. There was no correlation with other markers reflecting the severity of liver damage, such as albumin and INR, but there was a weak correlation with total bilirubin. Our results confirmed that ALT is not a marker of liver decompensation in patients with AH. The increase in AST in alcoholic cirrhosis is associated with the release of its mitochondrial fraction from zone 3 of the hepatic acinus, while the low value of ALT is a result of vitamin B6 deficiency, which is a necessary cofactor for its synthesis. In one study, it was found that the absolute values of blood pressure in AH are significantly lower, and the AST/ALT ratio is higher when compared to viral or other types of hepatitis, where these values are significantly elevated due to hepatocellular damage, with a predominant increase

in ALT. The AST/ALT ratio showed a statistically significant difference in its mean value, being 2 in the absence of AH and 3 in the presence of AH, but without the ability to differentiate between its mild and severe forms. The result confirmed that its increase is related to worsening liver function, which is consistent with the findings of other researchers. It has been proven that it is a poor prognostic factor for mortality, regardless of the etiology of cirrhosis, the Child-Pugh score, and the age of the patients, being higher in alcoholic cirrhosis. A correlation between the AST/ALT ratio and elevated serum bilirubin in response to worsening liver dysfunction was also established. Our result also showed a weak positive correlation with it, which was significantly greater when considering only the absolute values of AST. On the other hand, a weak negative correlation was found with the lowered values of albumin. In the patients we examined, there was a significant increase in GGT, with large variations, with the maximum value reaching 5169 UI/ml. The significant increase in GGT, which does not correlate with ALP, is indicative of an alcoholic etiology, as this is observed after prolonged alcohol abuse for more than 10 years and is a result of oxidative stress triggered by ethanol. It has been established that the highest levels are measured in alcoholic hepatitis compared to other types of hepatitis. In our study, its value showed a positive correlation with blood pressure, specifically with AST, which is consistent with data from other researchers**.** A statistically significant difference was found in the values of liver enzymes between the group with and without arterial hypertension (AH). The results confirmed that higher enzyme levels are associated with more prolonged and severe liver damage. However, no significant difference was found in the values between the mild and severe forms of the disease, nor was there a correlation with the Child, ALBI, and MELD Na scores, indicating that enzyme levels are not directly related to the severity of liver dysfunction. ALP was either normal or slightly elevated, but a significant difference was still found between cases with and without AH. A positive correlation was found with the GGT level, but no difference was observed in its value when comparing mild and severe forms of AH. It has been established that a two-fold increase beyond the reference range for the GGT/ALP ratio above 2.5 is indicative of alcoholic etiology. Although this increase is rarely observed, it is associated with more severe clinical progression, which was confirmed by our results. In 30% of cases, the increase in GGT was due to a cholestatic form of AH, confirmed by histological models, and represents more severe liver damage. An increase greater than 1.5 times the reference value and a lack of response to corticosteroid treatment is considered a poor prognostic factor associated with

increased 90-day mortality in severe AH. A lower mean serum albumin level was found in cases without AH, showing a negative correlation with total bilirubin and INR. This change is associated with advanced cirrhosis in our study population, and the worsening of hypoalbuminemia in AH cases showed a significant link with its severity, as it is responsible for the progression of liver decompensation caused by AH. Hypoalbuminemia and older patient age have also been linked to lack of response to treatment in previous studies. Jaundice was present in 100% of our AH cases, with a significant correlation to the severity of liver dysfunction, while in other studies, its prevalence ranges from 75% to 100%. High bilirubin levels have been found to independently predict short-term mortality, even without other scoring systems. Worsening hypoalbuminemia, increasing hyperbilirubinemia, and rising INR, despite minimal differences in values, as well as a tendency toward hyponatremia in our AH cases, were linked to the worsening of liver decompensation and possibly a higher frequency of complications. Various studies have established that these factors are related to increased short-term mortality. Ascites were present in 74.1% (N=63) of our AH cases, compared to 67.2% in the group without AH. The lack of a statistical difference between the two groups is likely related to the fact that ascites developed in the context of previously decompensated cirrhosis. Other studies report varying frequencies of ascites (47.54%, 56%, 83%, 100%). Hepatic encephalopathy (HE) was observed in 70.6% (N=60) of AH cases, compared to 52% (N=92) in the group without AH, regardless of its severity. Despite the observed statistical difference, its frequency was relatively high in the group without AH, likely due to the same reason. Different studies report varying frequencies of HE in their populations (29.95%, 83.3%, 85.5%). A low frequency of renal complications was observed in our study group (11.5%, N=10 for renal syndrome; 7.1%, N=6 for acute renal failure), but these were still more frequent in AH cases compared to those without AH. Of all 29 cases of renal syndrome in the entire study population (N=361), 25 (86.2%) were due to alcoholic etiology. The results showed that deviations in renal function are mostly associated with alcoholic etiology of cirrhosis and have relatively high frequency in cases with concurrent AH. The onset of acute kidney injury, either preceding or during the clinical course, is associated with higher mortality, regardless of the severity of liver damage, and these cases have higher Child and MELD Na scores. Several studies have shown that elevated creatinine levels are crucial for predicting poor outcomes in AH and associated hepatic encephalopathy, with the immediate cause of death often related to worsening renal failure, sepsis, or hemorrhage. Our measured serum creatinine levels did not

show a statistically significant difference between cases with and without AH, though levels were higher in severe AH. Urea levels also showed no significant difference related to the presence of AH, although in severe cases, levels were significantly higher. One study found that even an increase of 1 mg/dl (0.17 mmol/l) in AH is associated with a 2.3% increase in the risk of death. A U-shaped relationship has been established between urea levels and liver damage. Urea levels below 3.5 mg/dl (1.58 mmol/l) are seen in advanced liver fibrosis and cirrhosis due to reduced liver capacity to synthesize urea, malnutrition, and muscle mass loss, and are considered a predictor of future decompensation. Conversely, an increase in urea levels during the course of liver disease, due to reduced renal excretion, is also associated with liver decompensation. Other authors have found that in AH, urea levels are more frequently elevated than creatinine. The low frequency of renal complications in our study significantly contrasts with that reported by other authors in their results, which vary from 19% at diagnosis to 37%-65% in severe AH cases during follow-up. These discrepancies are likely due to the absence of prior laboratory data in our patients and the fact that our analysis was conducted only at their initial evaluation, without subsequent chronological follow-up. Additionally, there were no additional laboratory tests for more accurate determination of renal function, which is probably linked to its clinical under-recognition, a limitation noted in our study. Analysis of the results from the complete blood count (CBC) showed significant differences in parameters when comparing cases with and without AH, but no such differences were found when comparing mild and severe forms, except for the erythrocyte count. The analysis showed a dependency closely related to the severity of liver dysfunction, as well as a negative correlation with the increasing Child, ALBI, and to a lesser extent, MELD Na scores. This result confirmed that a decrease in erythrocyte count is directly associated with the worsening of liver function. Combined with increased MCV and decreased platelet count, it is indicative of more severe and prolonged alcohol-related liver damage, as demonstrated in previous studies. In our study, however, no statistically significant difference in platelet count was found between the examined cases, nor was there a correlation with the scoring systems used for liver function assessment, confirming that platelet count in our cases was not related to the severity of liver dysfunction. The high MCV and associated anemia syndrome were explained by the persistent effect of the etiological factor and the prolonged duration of liver damage, but were not linked to the severity of AH. It has been established that normalization of these parameters requires a period of two to four

months without alcohol consumption. A significant increase in the leukocyte count was observed in cases with AH, regardless of its severity. It has been previously confirmed that leukocytosis, as a manifestation of a systemic inflammatory response, is closely related to liver decompensation and worsening renal function in AH, regardless of the presence or absence of concurrent infection, and with increased short-term mortality.

3. Relationship between Child-Pugh, ALBI, and MELD Na in Alcoholic Cirrhosis and AH:

Among patients with AH, the majority were classified as ALBI 3 (N=71; 83.5%), while the largest proportion of those without AH were classified as ALBI 2 (N=99; 55.9%). In the AH group, the number of cases with ALBI 3 was significantly higher compared to those without AH (Pearson Chi-Square test 75.568, df 2, p=.000). The majority of AH cases were classified as Child C (N=66; 77.6%), while the largest proportion of those without AH were classified as Child B (N=90; 50.8%). In the AH group, the number of cases in Child C was significantly higher compared to the non-AH group (Pearson Chi-Square test 74.373, df 2, p=.000) (Fig. 51).

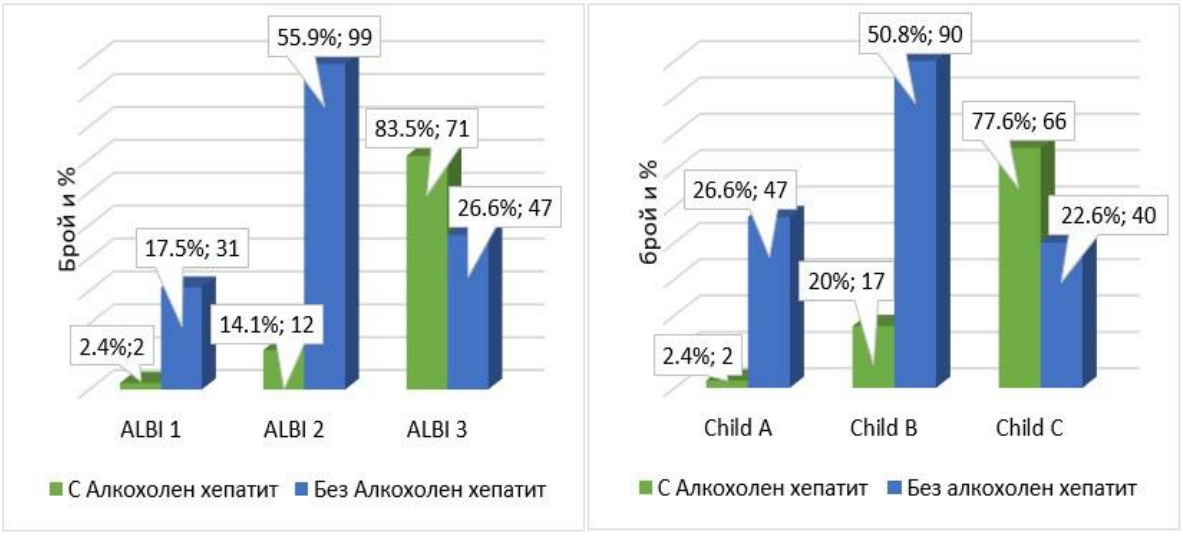


***Figure. 51**. Distribution of cases by ALBI and Child in cases without and with AH (green –with AH , blue– without AH)*

The results confirmed that the distribution of cases was approximately the same, regardless of the scoring system used, demonstrating a significant correlation between disease severity and classification according to Child-Pugh, ALBI, and MELD Na. With the progression of the Child-Pugh stage, the calculated mean

ALBI score significantly increases (Fig. 52). A significant increase in MELD Na is also observed with the rise in ALBI score (ANOVA, df 2, F = 295.676, p = .000) (Fig. 53).

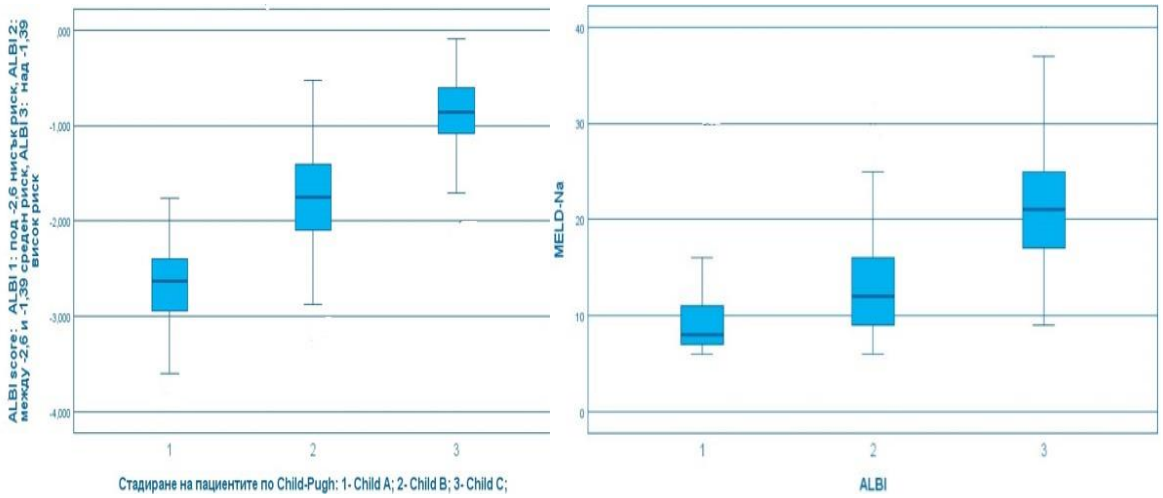


Figure 52. *ALBI persistence in the three groups the three Child groups*

Figure 53. *MELD Na persistence in ALBI groups*

A strong positive correlation was found among the three scoring systems, with the strongest correlation observed between the Child-Pugh score and both the ALBI and MELD Na scores (Table 10, Fig. 54).

Table. 10. *Correlation between the three scores*

Indicators:	Pearson corelation	Sign (2-tailed)	Spearman's rho corelation	Sign (2-tailed)
Child / ALBI	.780**	.000	.796**	.000
Child p. / ALBI	.883**	.000	.880**	.000
Child / MELD Na	.683**	.000	.724**	.000
Child p. / MELD Na	.728**	.000	.736**	.000
ALBI/ MELD Na	.687**	.000	.619**	.000
N=262; significans p<0.01**				

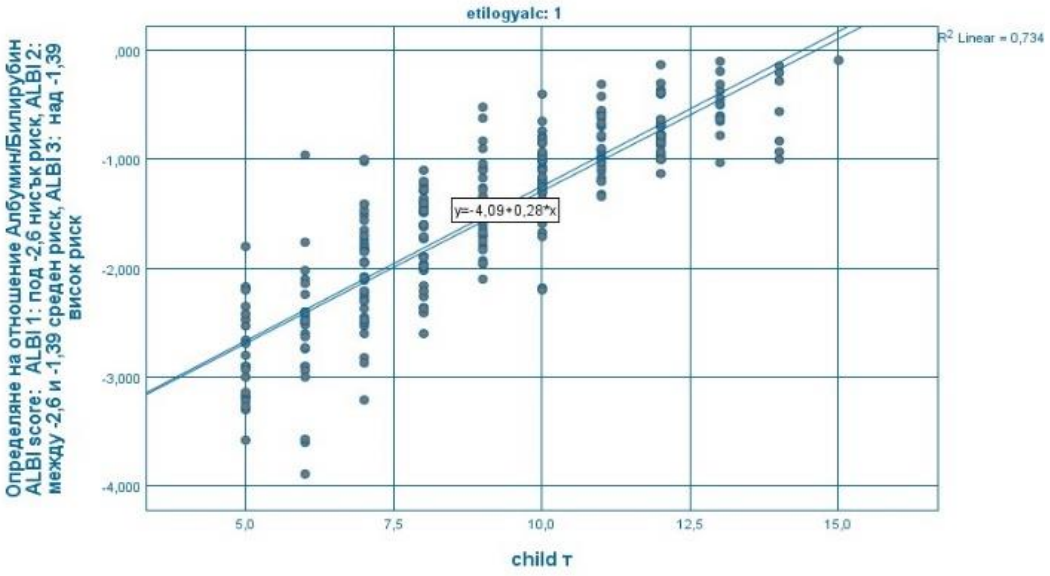


Figure 51. *Correlation between ALBI and Child*

Discussion:

We used the Child-Pugh, MELD Na, and ALBI scores to assess liver function. These scoring systems are based on various laboratory and clinical parameters, with bilirubin values included in all three and albumin in two. A systematic review of 118 studies identified serum levels of bilirubin and albumin as the most important laboratory predictors of survival in liver cirrhosis. Among our studied patients with AH, 77.6% were classified as Child C at diagnosis, a result consistent with another study where 60.24% were initially Child C. Only two cases (2.4%) were staged as Child A in the AH group, while the majority without AH were classified as Child B and, to a lesser extent, Child A. The high proportion of Child B cases among those without AH reflects the advanced cirrhotic process at baseline in our cohort. A statistically significant difference was found in Child-Pugh scores depending on the presence and severity of AH: 7.93±2.08 without AH, 10.79±1.98 with AH, and 11.49±1.55 in severe AH. This confirms that higher Child-Pugh scores are directly associated with liver decompensation and AH severity. Studies have shown that a baseline Child score above 10 points predicts ACLF, renal complications, and increased mortality. In another study, a high Child-Pugh score, alkaline phosphatase (ALP) >1.5 times the reference range, and corticosteroid non-response were associated with increased 90-day mortality in severe AH. A baseline Child score of >10.3–10.5 predicted reduced one-year survival in alcoholic cirrhosis, while a score >12 indicated a higher risk of in-hospital and three-month mortality in previous studies. Our study identified a

threshold of 11.50 points (sensitivity 57% and specificity 76%) predicting severe AH cases. Persistent elevation of the Child-Pugh score over time also suggests continued alcohol consumption after an acute decompensation episode. Among our studied cases, the mean MELD Na score was higher in AH patients (22.55±6.56) compared to those without AH (13.57±6.19), consistent with another study reporting a mean MELD Na of 20.9±8.7, regardless of AH severity. A significant increase was also observed in severe AH (27.26±4.77). These findings suggest that MELD Na more accurately reflects liver damage severity compared to the Child-Pugh score. Increasing MELD Na, renal dysfunction, ascites, worsening encephalopathy, persistent bilirubin and INR elevation, and deepening hyponatremia are important predictors of ACLF and are associated with increased short-term mortality. Our study identified a bilirubin threshold of 101.25 µmol/L (sensitivity 93.6% and specificity 63.2%) for MELD Na >21, confirming that rising bilirubin levels are the most significant factor associated with AH severity. Prior studies have shown that MELD Na scores of 19–20.9 correlate with reduced one-year survival, while a score >21 independently predicts 90-day survival. Decreasing albumin and increasing bilirubin levels are key indicators of progressing liver failure, a concept central to the development of the ALBI score, which has shown positive correlations with both the Child-Pugh and MELD Na scores. In our cohort, the mean ALBI score was -0.91±0.49 in AH patients compared to -1.88±0.74 in non-AH cases, similar to another study reporting a mean ALBI of -1.05. A further significant decrease was observed in severe AH (-0.68±0.32), confirming that ALBI effectively reflects liver dysfunction severity in alcoholic cirrhosis. An ALBI score below -1.36 (ALBI 3) identifies high-risk cases with reduced survival. In our study, 83.5% (N=71) of AH patients were classified as ALBI 3, further categorizing them as high-risk.Among non-AH patients, ALBI 2 was predominant, while ALBI 3 (N=47; 26.6%) and ALBI 1 (N=31; 17.5%) were less frequent. Despite the significant difference between groups, the small number of ALBI 1 cases among non-AH patients was associated with baseline cirrhosis decompensation. Our study identified an ALBI threshold of -0.675 (sensitivity 55.3% and specificity 94.7%) for severe AH. Another study reported an ALBI of -1.01 (sensitivity 94.92% and specificity 32.5%) as a marker of increased mortality risk in chronic alcoholic liver disease, while values below -0.6 strongly predicted ACLF and increased in-hospital mortality, and scores above -1.17 indicated better survival outcomes. Among all cirrhotic patients (N=262), 92.5% of those classified as Child C (N=106) were ALBI 3, while none of the ALBI 3 cases were Child A. Of all Child

A patients, 53.1% (N=26) were ALBI 1, and 78.8% of ALBI 1 cases were Child A. This finding confirmed a significant correlation between Child-Pugh and ALBI distribution, with the highest concordance observed between Child C and ALBI 3. The mean ALBI score significantly decreased with increasing Child-Pugh scores, consistent with previous studies. A significant correlation was also found between ALBI and Child-Pugh points (r=0.880), consistent with other findings (r=0.853). Similarly, significant correlations were observed between ALBI and MELD Na, as well as between Child-Pugh and MELD Na, consistent with previous studies in patients with variceal bleeding. Our results suggest that the ALBI score can be effectively used as an alternative to other scoring systems for evaluating liver decompensation in alcoholic cirrhosis and AH due to its simplicity, ease of calculation, and objectivity.

CONCLUSIONS:

1.The incidence of liver cirrhosis is significantly higher among men, which is associated with the predominant alcoholic etiology in the studied population. The high proportion of alcohol-related cases (72.57%) aligns with global trends reflecting the increasing prevalence of alcohol abuse and its associated diseases. The small proportion of cases with established viral etiology in the studied population corresponds to global trends of declining prevalence of chronic viral hepatitis. This decrease is due to more effective screening measures, the availability of the hepatitis B vaccination program, and wider access to antiviral treatment programs. A relatively high frequency of cases with unclear etiology of cirrhosis (9%) was observed. This may be explained by the lack of comprehensive additional investigations and the possibility that some cases are associated with NAFLD, which were insufficiently studied (likely due to the entirely retrospective study design), representing a potential limitation. The majority of affected individuals are of working age, 40–60 years (50%) and over 60 years (45%), posing a significant economic burden on society. In the smallest age group under 40 years, women predominate, which is also attributed to alcoholic etiology.

2. The high Child-Pugh score observed in most patients is due to late diagnosis, primarily linked to the alcoholic etiology of the disease. The high frequency of complications observed in the studied group is associated with the large proportion of cases with disease decompensation, mainly related to alcoholic etiology.The most common decompensating event and reason for diagnosis is the development

of ascites (64.5%), with its frequency and volume increasing as liver disease progresses.

3. The most frequent laboratory abnormality found during routine testing is the presence of anemia syndrome (71%) of varying severity, with mild normocytic anemia being predominant. Its occurrence and worsening are associated with disease progression, with red blood cell count correlating better with disease severity than measured hemoglobin levels. The high frequency of macrocytosis in the studied population is attributed to alcoholic etiology, present in 89.7% of cases with detected macrocytosis (N=116). In 24.14% (N=28) of these cases, macrocytosis was observed without accompanying anemia syndrome.

4. In 46% of all cases with thrombocytopenia (12.46% of the total studied population), it was present without other concomitant hematological abnormalities. Its detection can serve as an important criterion for identifying chronic liver disease, even in the absence of other laboratory abnormalities. Therefore, additional upper GI endoscopic screening is recommended for unclear cases of thrombocytopenia to identify esophageal varices as a sign of portal hypertension.

5. The high frequency of leukocytosis in the studied population is associated with disease decompensation and alcoholic etiology, regardless of the presence or absence of concomitant infection. Leukopenia was the rarest hematological abnormality among the studied cases and was often associated with other CBC abnormalities, being more common in non-alcoholic cirrhosis.

6. The absolute values of aminotransferases are not indicative of the severity of underlying liver disease. ALT levels were normal in 61.77% of cases and showed no significant correlation with Child stage. AST values were normal in 25.77%, with the lowest proportion in Child C (9.8%). It was found that AST deviation from normal, rather than its absolute value, is more likely associated with chronic liver disease. An elevated AST/ALT ratio, regardless of absolute enzyme values, better reflects the severity of underlying liver disease, even when transaminase levels are normal. This ratio significantly correlates with the established Child stage and rising MELD Na score.

7. An increase in direct bilirubin with normal total bilirubin can be used as a reliable marker for advanced chronic liver disease, regardless of other laboratory findings. A key laboratory marker associated with chronic liver disease

progression and observed complications (ascites, HE, and renal function impairment) is the development of hypoalbuminemia, which significantly correlates with rising Child-Pugh and MELD Na scores.

8. The frequency of acute decompensation is significantly higher in alcohol-related cirrhosis (36%) compared to non-alcoholic cirrhosis (12%). The most common cause in the studied population is superimposed acute alcoholic hepatitis (90.4% of all acutely decompensated cases with alcoholic etiology). Among all women with alcohol-related cirrhosis, 42.3% presented with acute alcoholic hepatitis (compared to 30% in men), indicating their higher susceptibility to alcohol-induced liver damage.

9. The primary laboratory marker associated with acute decompensation from AH is jaundice, observed in 100% of the studied cases. Significant elevation of total bilirubin is the most important marker for identifying the risk of ACLF. A cut-off value of 101.25 μmol/L (sensitivity 93.6% and specificity 63.2%) was identified for severe AH cases.

10. The highest GGT levels were found in AH cases, but these levels did not correlate with the severity of liver dysfunction as determined by Child-Pugh, MELD Na, and ALBI scores. AST elevation significantly correlated with GGT and total bilirubin in AH cases. An AST/ALT ratio > 2 is an important laboratory marker associated with alcoholic etiology and liver function decompensation, while a ratio > 3 is linked to AH, though not its severity.

11. A correlation was established between Child-Pugh, MELD Na, and ALBI scores for assessing liver dysfunction severity in alcohol-related liver cirrhosis and AH. The ALBI score can reliably be used as an alternative to the Child-Pugh score due to its simplicity and objectivity in assessing liver dysfunction severity in alcohol-related cirrhosis and acute alcoholic hepatitis.

CONTRIBUTIONS OF THE DISSERTATION WORK:

Original Contributions:

1. For the first time in Bulgaria, a detailed epidemiological study of newly diagnosed liver cirrhosis cases has been conducted over a five-year period in a single center.

2. A comprehensive analysis of laboratory abnormalities and their correlation with the severity of liver disease and associated complications has been performed for the first time.
3. For the first time in Bulgaria, a significant comprehensive epidemiological and laboratory analysis of acute alcoholic hepatitis cases in patients with alcohol-related cirrhosis has been conducted.
4. The role of the ALBI score has been evaluated for the first time as a potential alternative to the Child-Pugh score for assessing liver dysfunction in alcohol-related cirrhosis and acute alcoholic hepatitis.

Confirmatory Contributions:

1. It has been confirmed that the incidence of liver cirrhosis is significantly higher among men, attributed to the high prevalence of alcohol abuse in this population.
2. It has been confirmed that the high frequency of complications among cirrhotic patients is directly associated with late diagnosis.
3. It has been confirmed that biochemical abnormalities are directly related to the severity of liver dysfunction, with serum albumin and total bilirubin being the primary prognostic factors.
4. It has been confirmed that the absolute values of aminotransferases are not associated with the severity of underlying liver disease, unlike the AST/ALT ratio.
5. It has been confirmed that thrombocytopenia is directly associated with the presence of esophageal varices as a manifestation of portal hypertension.
6. It has been confirmed that the primary laboratory marker directly associated with acute decompensation from acute alcoholic hepatitis in cirrhotic patients is elevated total bilirubin, observed in 100% of the studied cases.

RECOMMENDATIONS:

Given the high social significance of chronic liver diseases (mainly due to the high prevalence of alcohol abuse in society and the increasing incidence of NAFLD), it is recommended that the existing Regulation No. 8 on preventive medical check-ups for individuals over 18 years old be amended to include:

“ **In cases of identified risk for chronic liver disease**.”

According to the current amendments and supplements to Regulation No. 8 on preventive examinations and dispensary monitoring, it is currently stipulated that:

- For all individuals aged 20–65 years: A complete blood count (CBC), AST, ALT, creatinine, uric acid, and standard urine tests should be conducted once every five years.
- For individuals over 40 years old: Screening for HBsAg and anti-HCV should be performed every five years.
- For men over 40 years old and women over 50 years old: Total cholesterol, triglycerides, and HDL should be tested every five years.

Proposed Additional Recommendations:

Annual testing of AST, ALT, GGT, CBC, creatinine, blood glucose, and standard urine analysis for all individuals, regardless of risk factors. For individuals with an identified risk of chronic liver disease, direct bilirubin should be tested. If abnormal values or liver steatosis are detected via ultrasound, these patients should be referred for non-invasive ultrasound elastography to assess liver fibrosis. This recommendation could serve as a foundation for future research. Screening for HBV and HCV should be conducted every five years for individuals over 30 years old, given the long asymptomatic course of these infections. Lipid profile testing should be conducted every five years for men over 30 years old and women over 40 years old, considering the increasing prevalence of NAFLD and its associated cardiovascular risk. Individuals with abnormal liver enzyme values and/or a history of increased risk for chronic liver disease should undergo additional consultation with a gastroenterologist and a conventional ultrasound examination. If abnormalities are detected, further investigations and follow-up should be performed according to established medical standards.

SCIENTIFIC ACTIVITIES RELATED TO THE DISSERTATION WORK:

Full-Text Publications:

1. **Mihaylova M.,** Strashilov S., Tonchev P. Value of Aminotransferases in Liver Cirrhosis. Journal of IMAB. 2024 Oct-Dec;30(4):5824-5828. [Crossref - 10.5272/jimab.2024304.5824] ISSN 1312-773X; (Web of Science (ESCI)).

2. **Mihaylova M**., Tonchev P.Relationship between Child-Pugh Score and Late Complications in Liver Cirrhosis. Journal of Biomedical and Clinical Research. 2024;17(2):187-196. DOI:10.3897/jbcr.e121855. ISSN: 1313-9053; (Web of Science CABI).

3. Mihaylova M., Lalev I., Tonchev P.Epidemiological Structure of Hospitalized Patients with Liver Cirrhosis. 21st National Scientific Session for Students and Lecturers: "With Vision Towards the Future". Medical College at MU-Pleven, October 27-28, 2023. Conference Proceedings: Publishing Center of MU-Pleven. ISBN: 978-954-756-325-4 (PDF); ISBN: 978-954-756-324-7 (CD); pp. 39-49.

Participation in Scientific Forums:

1. **Mihaylova M**., Lyubomirova D., Strashilov S., Marinova I., Ivanov C. Liver Cirrhosis – Retrospective Analysis. 11th International Medical Scientific Conference for Students and Young Doctors. Medical University Pleven, October 16-19, 2013. Abstract Book: p. 48.

2. **Mihaylova M**., Lyubomirova D., Strashilov S., Marinova I., Ivanov C. Liver Cirrhosis and Pregnancy. 11th International Medical Scientific Conference for Students and Young Doctors. Medical University Pleven, October 16-19, 2013. Abstract Book: p. 49.

3. **Mihaylova M.,** Lalev I., Tonchev P. Relationship between Child-Pugh Score and ALBI Score in Liver Cirrhosis at Different Stages. 20th Jubilee National Scientific Session for Students and Lecturers. Medical College at MU-Pleven, October 27-28, 2022 – Oral Presentation.

4. **Mihaylova M**., Lalev I., Tonchev P. Epidemiological Structure of Hospitalized Patients with Liver Cirrhosis. 21st National Scientific Session for Students and Lecturers: "With Vision Towards the Future". Medical College at MU-Pleven, October 27-28, 2023 – Oral Presentation.

5. **Mihaylova M**., Lalev I., Tonchev P. Demographic Characteristics of Hospitalized Patients with Alcoholic Liver Cirrhosis. 21st National Scientific Session for Students and Lecturers: "With Vision Towards the Future". Medical College at MU-Pleven, October 27-28, 2023 – Oral Presentation.

6. Mihaylova M., Tonchev P., Strashilov S. Relationship between Serum Albumin Levels in Liver Cirrhosis and Late Complications. 21st International Medical Scientific Conference for Students and Young Doctors. October 14-19, 2024; Medical University Pleven – Oral Presentation.

7. **Mihaylova M**., Tonchev P. Thrombocytopenia in Newly Diagnosed Patients with Liver Cirrhosis. Jubilee Scientific Conference with International Participation: "50 Years of Medical Education and Science in Pleven". Medical University Pleven, November 1-3, 2024 – Oral Presentation. Abstract Book: Publishing Center MU-Pleven. ISBN: 978-954-756-347-6.

Declaration of Originality:

As the author of this dissertation, I declare that all data presented are the result of my direct clinical and research work at the Department of Gastroenterology and Gastroenterology at the Clinic of Gastroenterology of the University Hospital “Georgi Stranski” Pleven EAD. The results obtained, the discussions and the conclusions are not correlations from other sources without correct citation.