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FEATURES OF HEMOGRAM INDICATORS FOR CIRROSIS OF THE LIVER

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Abstract: It is known that, against the background of the progression of chronic hepatitis, significant changes in blood elements are occurring. The number of red blood cells, the level of hemoglobin, the color index, the content of reticulocytes, platelets and leukocytes in patients with chronic diffuse diseases of the liver are significantly lower than in people without diseases of the hepatobiliary system, and blood counts decrease as the activity of inflammation in the liver and the transformation of chronic hepatitis B increase cirrhosis of the liver. The purpose of this work is to identify the features of the hemogram in patients with cirrhosis of the liver.

Keywords: cirrhosis, immature blood cells, reticulocytes, platelets, red blood cells.

Introduction

Currently, modern automated blood analysis systems provide a set of new hemogram indicators, which, in essence, are “research” and need a clinical interpretation. So, for example, flow cytofluorometry - the technology of a number of Sysmex analyzers - significantly expands the possibilities of studying cells of various hematopoietic sprouts. Using optical detection, the qualitative features of a blood cell are analyzed, depending on the size/volume, internal structure, nucleic acid content (RNA/DNA, maturity and metabolic activity). The diagnostic significance of flow cytometry is increased in conditions accompanied by hematological disorders.

Liver cirrhosis is a fairly common disease, which in the manifest stage is characterized by dysfunction of three sprouts of hematopoiesis: leukocyte, erythrocyte and platelet. A general blood test in patients with advanced cirrhosis of the liver or liver failure can reveal signs of hemolysis, thrombocytopenia, leukocytopenia [3].

Regarding blood counts in cirrhosis of the liver, information from specialized literature is fragmented and contradictory. It is known that abnormal red blood cell counts, in particular an increase in reticulocytes and a decrease in hemoglobin concentration, are associated with an increased risk of death during liver transplantation [11]. There is evidence of both a decrease in the relative number of reticulocytes to 0.79% in the presence of fibrosis in children [6] and an increase in the absolute number of reticulocytes to 0.064 × 012/L in adults with verified liver cirrhosis [9]. A number of authors report a complex violation of the hemostatic system, including thrombocytopenia [5, 8, 10].

As for the new indicators of leukocyte, reticulocyte and platelet analysis obtained by laser detection, the question of their informative value in cirrhosis remains open.

The purpose of the work was to identify the informative value of new hemogram indicators obtained by flow cytofluorometry method for liver cirrhosis.

Material and methods. We analyzed the results of complete blood count of individuals of the main and control groups.

The main group is represented by 64 patients with verified cirrhosis associated with thrombocytopenia. The structure of cirrhosis was as follows: 38 cases of viral etiology, 24 cases of nutritional toxicity, 2 cases of cryptogenic origin. The sample is represented by 30 men and 34 women aged 62.1±39.5 years.

The control group was formed of 70 healthy volunteers undergoing a routine preventive examination. The sample is represented by 35 men and 35 women 55.3±28.7 years.

Blood samples were examined on a Sysmex-XE 2100 analyzer. The following parameters were analyzed: 1) leukocyte count: white blood cell count (WBC, 109/L); relative amount of immature granulocytes (IG,%); the absolute number of immature granulocytes (IG, 109/l); 2) red blood cells and reticulocytes: the number of red blood cells (RBC, 1012/l); hematocrit (HCT,%); the average volume of the red blood cell (MCV, fl); the average hemoglobin content in the erythrocyte (MCH, PG); the average concentration of hemoglobin in red blood cells (MCHC, g/dl); coefficient of variation of red blood cells by volume (RDW,%); the relative number of fragmented red blood cells (Frg,%); relative reticulocyte count (Ret,%); the absolute number of reticulocytes (Ret, 1012/l); relative number of immature reticulocytes (IRF,%); the relative number of reticulocytes with low, medium and high fluorescence (LFR,%, MFR,% and HFR%); the average hemoglobin content in reticulocytes (Ret-He, PG); delta hemoglobin (D-He, pg); 3) platelet count: platelet count, measured in impedance mode (PLT, 109/L); platelet count measured in optical mode (PLT-O, 109/L); the relative number of immature platelets (IPF,%); platelet variation coefficient by volume (PDW,%); mean platelet volume (MPV, fl); the percentage of large platelets is greater than 12 fl (P-LCR,%); thrombocytes (PCT,%).

The analyzed parameters are divided into two groups: obtained using impedance, or conductometric technology (traditional parameters) and flow cytofluorometry (new parameters).

Statistical data processing was performed using Excell. The following statistical parameters were used: M — mean value, Sd — standard deviation, Sd. er. - standard error. Intergroup differences were evaluated based on Student's test at a significance level of $p < 0.05$. Statistically significant ($p < 0.05$) Pearson correlation coefficients (g) were analyzed. To analyze the distribution of the indicator values, we calculated curves representing the probability density p (x) (the ratio of probability to the length of the interval) and representing a theoretical analogue of the histogram.

Results.

Tables 1 and 2 present the results of the analysis of hemograms (traditional and new indicators) in patients with liver cirrhosis associated with thrombocytopenia, and individuals in the control group.

Table 1

Traditional blood counts for patients with cirrhosis associated with thrombocytopenia

Indicators	Main group (cirrhosis)	Control group
	M ± Sd (St. er.)	
WBC, 109/L	5,06 ± 3,37 (0,42)	7,01 ± 1,81 (0,18)

RBC, 1012/L	4,02 ± 0,75 (0,09)	4,94 ± 0,53 (0,05)
HGB, g / dl	11,49 ± 2,10 (0,26)	13,95 ± 1,57 (0,16)
HCT, %	36,32 ± 6,02 (0,75)	44,94 ± 3,58 (0,36)
MCV, fl	91,51 ± 11,17 (1,4)*	91,84 ± 3,8 (0,38)*
PLT, 109/L	82,45 ± 30,51 (3,81)	256,03 ± 53,36 (5,31)
RDW, %	16,08 ± 3,05 (0,39)	13,15 ± 0,76 (0,08)
PDW, %	13,31 ± 1,99 (0,29)*	13,17 ± 1,66 (0,17)*
MPV, %	11,19 ± 0,91 (0,13)*	11,08 ± 0,78 (0,08)*
P-LCR, %	34,4 ± 7,27 (1,06)*	33,64 ± 6,82 (0,69)*
PCT, %	0,09 ± 0,03 (0,01)	0,28 ± 0,06 (0,01)

According to the tables, in patients with cirrhosis, compared with the control group, the number of leukocytes (WBC) was statistically significantly reduced to 5.06 ± 3.37 × 09/L, the content of immature granulocytes (S) was increased to 0.44 ± 0.77%, or 0.04 ± 0.15CH09/l. According to the results of an individual analysis, in 46.8% of the main group of people, leukocytopenia was registered (WBC <4.0 × 09/L).

Table 2

Flow cytometry in patients with cirrhosis associated with thrombocytopenia

Indicators	Main group (cirrhosis)	Control group
	M ± Sd (St. er.)	
IG, %	0,44 ± 0,77 (0,10)	0,19 ± 0,11 (0,01)
IG, 109/L	0,04 ± 0,15 (0,02)	0,01 ± 0,01 (0,00)
PLT-O, 109/L	92,08 ± 32,30 (4,04)	290,81 ± 61,53 (6,28)
IPF, %	3,23 ± 1,7 (0,22)	1,89 ± 1,16 (0,12)
Ret, %	1,99 ± 1,54 (0,19)	1,10 ± 0,33 (0,03)
Ret, 1012/L	0,07 ± 0,04 (0,00)	0,05 ± 0,02 (0,000)
IRF, %	5,03 ± 4,85 (0,61)	3,35 ± 1,78 (0,18)
LFR, %	94,97 ± 4,84 (0,61)	96,59 ± 1,82 (0,18)
MFR, %	4,56 ± 4,15 (0,52)	3,18 ± 1,67 (0,17)
HFR, %	0,47 ± 0,9 (0,11)	0,18 ± 0,20 (0,02)
Ret-He, pg	29,15 ± 5,52 (0,69)	32,54 ± 1,32 (0,13)
D-He, pg	2,71 ± 1,97 (0,25)*	2,90 ± 0,72 (0,07)*
Frg, %	0,83 ± 1,21 (0,15)	0,10 ± 0,14 (0,01)

Compared with the control group, the values of traditional erythrocyte indices (the number of red blood cells, hematocrit, hemoglobin concentration) in patients with cirrhosis are statistically significantly reduced ($p < 0.05$), and the coefficient of variation of erythrocytes in volume was significantly increased (see Table 1). There was a lack of intergroup differences regarding the average volume of red blood cells ($p > 0.05$).

It was found that with cirrhosis of the liver associated with thrombocytopenia, the platelet count, calculated by the impedance method (PLT), was significantly reduced to 82.45 ± 30.5L109 / L (see Table 1). The platelet count, measured in the optical mode of the analyzer (PLT-O), is 10.5% higher than PLT, and is 92.08 ± 32.30 × 09 / L (see table 2). Against the background of thrombocytopenia, a statistically significant increase in immature platelets (IPF) was recorded to 3.23 ± 1.7%. According to the results of the correlation

analysis, there was an inverse relationship between the platelet count, measured in the optical mode, and the number of their immature forms (r= -0.45).

The fig. 1 shows histograms of the distribution of immature platelet values of the main and control groups.

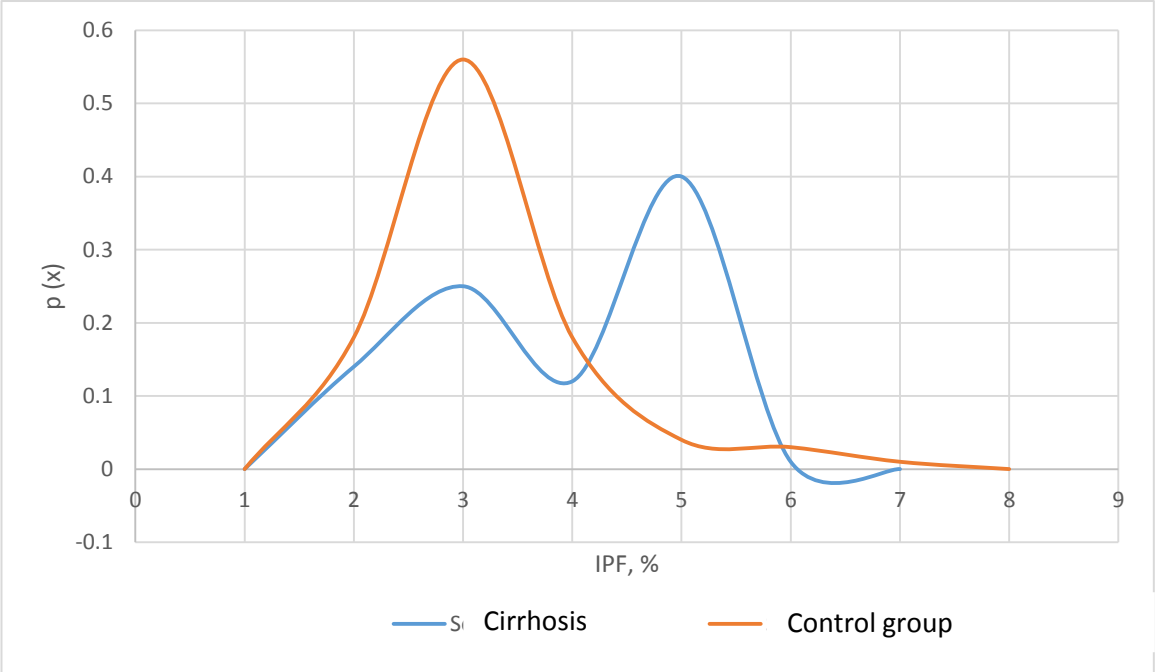

Fig.1.Histograms of the distribution of immature platelet counts.

According to fig. 1 most likely value (distribution mode) of IPF for cirrhosis associated with thrombocytopenia is 4.5%, while in individuals in the control group it is 2%. According to the results of an individual analysis, in 6 patients IPF significantly exceeds the norm and amounts to 6-10%.

The intergroup comparative analysis did not reveal significant differences regarding the traditional indicators of platelet cell series (PDW, MPV, P-LCR), p> 0.05. A statistically significant decrease in thrombocrit (PCT) in patients with cirrhosis is due to the presence of thrombocytopenia.

In patients of the main group, there was a statistically significant increase in the relative and absolute content of reticulocytes to 1.99%, or 0.07 × 012 / L (see table. 2). Significant differences were revealed regarding other indicators of reticulocyte analysis. In particular, the content of immature reticulocytes (IRF) in case of cirrhosis is increased to 5.03 ± 4.85%, which is 33.4% higher than the value of the same indicator in the control group. Since the fraction of immature reticulocytes is composed of low and high fluorescence reticulocytes, an increase in IRFis obviously associated with an increase in the fractional contribution of HFR and MFR to the total reticulocyte pool. In general, with cirrhosis of the liver associated with thrombocytopenia, a tendency toward rejuvenation of the reticulocyte formula is recorded.

In patients of the main group, the average hemoglobin content in reticulocytes (Ret-He) was statistically significantly reduced to 29.15 ± 5.52 pg (p <0.05). Decrease in Ret-He associated with anemic syndrome, which, according to WHO criteria, was registered in 72% of patients in the main group. However, in 67% of cases, Ret-He did not fit into the reference norms, which, according to the literature, were 28–35 pg [4].

It was found that the number of fragmented red blood cells (Frg) in patients with cirrhosis is 88% higher than that of the control group and is 0.83 ± 1.21%. Fig. 2 shows the variation series of Frgin the analyzed samples.

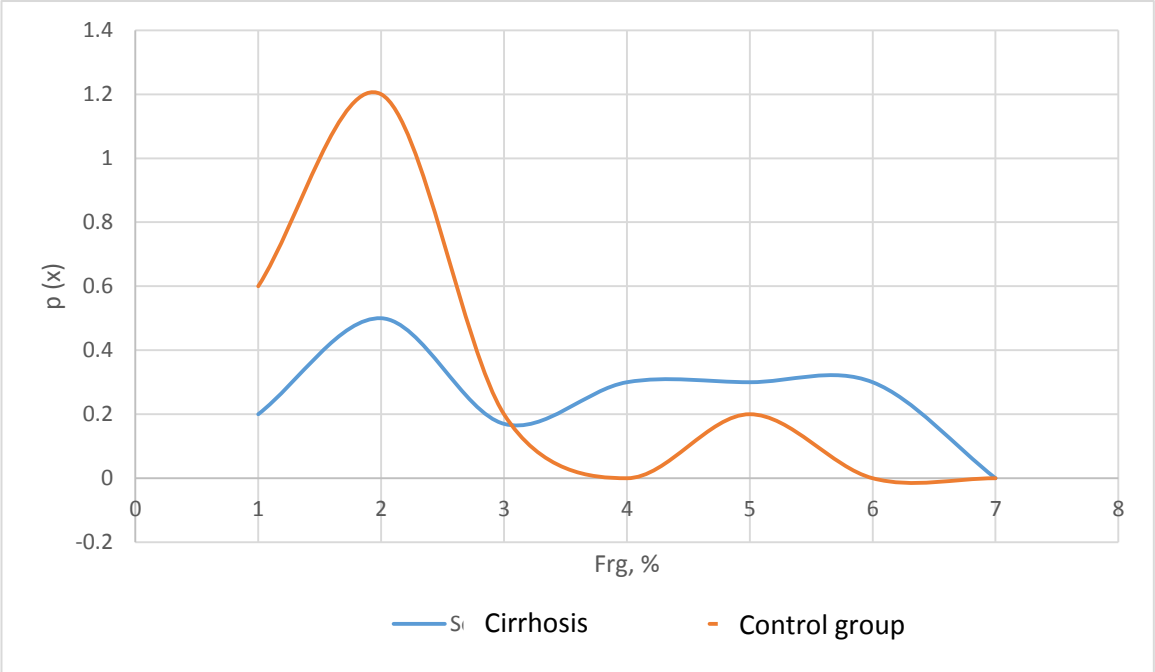

Fig.2. Histograms of the distribution of the number of fragmented red blood cells.

According to fig. 2 in case of cirrhosis of the liver, the distribution of Frgvalues is described by a gentle curve with pronounced right-side asymmetry; the maximum value of the indicator is 6%. According to individual analysis, in 40% of patients, the content of schistocytes is increased by more than 10 times. So, in 28.1% of patients, Frg≥ 1%, and in 9.4% of Frg ≥ 3%. In individuals of the control group, the histogram Frgis sharply vertex, the most probable value of the indicator (mode) is 0.5%, and the maximum value of the indicator is 1.2%.

According to the data obtained (see Table 2), the value of delta hemoglobin (D-He) did not statistically significantly differ between the individuals of the main and control groups, amounting to 2.71 ± 1.97 and 2.9 ± 0.72 pg, respectively.

According to data analysis in the control group, the number series of D-He accepts a region of positive values, the distribution is close to “normal” Gaussian. The most likely indicator value is 2.5 pg. In case of cirrhosis associated with thrombocytopenia, the range of variation of D-He includes both the region of negative and the region of positive values, varying in the interval -3.5-7.5 pg. Individual analysis showed that negative values of D-He <0 pg were registered in 6.3% of individuals in the main group. High positive values of the indicator (D-He> 4 pg), not found in the norm, were recorded in 22% of cases of cirrhosis. Correlation analysis showed the presence of close direct relationships between the level of delta hemoglobin and the hemoglobin content in reticulocytes (r = 0.57), as well as the number of immature granulocytes (r = 0.45) in conditions of impaired synthetic liver function.

Discussion

Laboratory parameters for liver cirrhosis in most cases do not depend on the etiology of the disease and are mainly due to the level of hepatocellular insufficiency. When evaluating liver function, it is generally accepted to focus on biochemical tests, while the diagnostic significance of flow cytometry indicators, as a rule, remains beyond the scope of clinical interpretation.

Previously, the absence of a significant mathematical relationship between new hemogram parameters (relative and absolute number of reticulocytes, the number of immature platelets, delta hemoglobin level, average hemoglobin content in reticulocytes, and the number of fragmented red blood cells) with gender and age has been established [1]. Relative stability is normal, low biological variability, obviously, increases the clinical significance of these parameters in the conditions of pathology.

It is known that with cirrhosis of the liver, as a rule, all hematopoietic sprouts are affected. The tendency to leukocytopenia and rejuvenation of the leuko-formula revealed as a result of the study corresponds to generally accepted ideas about the mechanisms of granulocytopoiesisdisturbance in case of impaired liver function. Against the background of splenomegaly, which is a frequent companion of cirrhosis, accelerated destruction of neutrophils and the shortened period of their circulation in the vascular bed [4] cause a decrease in the total content of blood leukocytes. In this case, there is a delay in the maturation of some granulocytes at the stage of promyelocyte ,myelocytes or metamyelocytes. Probably, here, on the basis of the "feedback" principle, the decrease in the content of mature blood cells at the periphery is compensated by the accelerated exit of granulocytes from the bone marrow depot, including a low degree of maturity.

The red blood picture reflects the features of the kinetics and functional activity of the corresponding hematopoietic cells in cirrhosis. The proliferation rate and the level of hemoglobinization, the residence time of cells in the bone marrow, and the duration of circulation in the peripheral blood of mature cellular elements are changing. According to the data obtained, in the patients of the main sample, anemia was moderate, the values of erythrocyte indices (RBC, HGB, Hct) were reduced by 17–20% compared with the norm.

The pathogenesis of hematological disorders in cirrhosis is multifactorial. Particular importance is attached to hemolytic processes, sequestrating role of the spleen, autoimmune and toxic mechanisms. Interestingly, according to the results of the study, the absence of a statistically significant increase in the average volume of red blood cells (MCV) was recorded in the main sample, which would be natural for liver disease. Along with other possible factors, the genesis of anemia in this case is probably due mainly to a violation of the hemoglobinization and maturation of erythroid elements of the bone marrow.

Thrombocytopenia in cirrhosis of the liver is a manifestation of hypersplenism and is due to increased consumption due to increased sequestration, inhibition of megakaryocyte activity and a decrease in thrombopoietin production [10]. According to the data obtained, the platelet content measured in the optical unit of the analyzer (PLO-O) reliably reflected the true number of cells due to the correct identification of giant platelets (in the impedance method, large platelets are erroneously counted as red blood cells).

Regardless of the genesis, the number of platelets in the peripheral blood is regulated in accordance with general biological laws: excess inhibits thrombocytopoiesis, and thrombocytopenia stimulates. Indeed, compared with the control group with cirrhosis, an increase of 41% in the share contribution of immature platelets to the total platelet pool was

recorded. An increase in IPF indicated that the proliferation processes at the bone marrow level were not impaired, and even accelerated thrombocytopenia of large platelets may occur, and the genesis of thrombocytopenia is mainly due to accelerated cell consumption at the periphery.

It was found that the values of the routine indices of platelet analysis (PDW, MPV and P-LCR) did not significantly differ in the main and control groups ($p > 0.05$). The absence of statistically significant correlations with hemogram indices additionally offset the diagnostic significance of the tests. According to early research results [2], data are provided on the low informative value of P-LCR and MPV in the differential diagnosis system for pregnant thrombocytopenia.

The results of the study showed that from the entire spectrum of platelet parameters, the optical detection indices (IPF, PLT-O) most adequately reflected the characteristics of thrombocytopoiesisin cirrhosis of the liver. The relevance of measuring indicators increases in cases of severe thrombocytopenia associated with the need for a clinical decision.

Indirect markers of the functional activity of bone marrow cells are indicators of the reticulocytesseries sensitive to erythropoietin. Normally, erythropoietin is not only the main stimulator of proliferation of red blood cells, but also an inducer of the formation of megakaryocytes, an increase in the number and reactivity of platelets [8]. In this regard, it would be logical to assume the presence of a direct relationship between immature cells of erythrocyte and platelet hematopoietic cells. However, the results of the correlation analysis indicated the absence of the expected dependence ($r \approx 0$).

In patients with cirrhosis of the liver on the background of rejuvenation of the reticulocyte formula, a significantly higher number of reticulocytes compared with the norm was observed (see Table 2). Individual analysis showed that in 36% of cases, the relative content of reticulocytes exceeds 2%, and in 8% of patients, the Ret% is higher than 5%. The content of immature reticulocytes in 12% of patients exceeds 14%, while in the control group IFR $3.35 \pm 1.78\%$. With cirrhosis of the liver, an increase in the total number of reticulocytes, as well as the fractional contribution of fractions of a low degree of maturity (IFR, HFR, MFR), is due to several factors. The leading mechanism here is probably hemolysis, which stimulates erythropoiesis according to the feedback principle. The presence of a hemolytic component in liver cirrhosis was also additionally evidenced by a statistically significant increase in fragmented red blood cells: the value of Frg in individuals of the main and control groups differed by more than 8 times.

Special attention should be paid to a new research indicator, delta hemoglobin (D-He), which is the mathematical difference between the average hemoglobin content in reticulocytes and the average hemoglobin content in red blood cells. In healthy people, the value of D-He is always positive and ranges from 2-4 pg. Negative values of D-He are not common, for example, with anemia of chronic diseases. In case of inflammation, hepcidine, synthesized by the liver, blocks transfer of iron by transferrin, which leads to a deficiency of iron available for erythropoiesis [12].

According to the data obtained, pathologically high or low values ($2pg > D\text{-}He > 4$ pg) were recorded in 46% of cases of cirrhosis. In a small part of patients (6.3%), $D\text{-}He < 0$. Negative values of D-He are obviously due to concomitant inflammation. In conditions of impaired synthetic function of the liver, a statistically significant decrease in the hemoglobin content in reticulocytes (Ret-He) indicated the limited availability of iron for hematopoiesis and generally confirmed the above trend.

Changes in the functional characteristics of red blood cells in liver pathology are not limited to reticulocytes. At the same time, disturbances occur at the level of mature red blood cells. At high delta hemoglobin (D-He> 4 pg), the reticulocytes are saturated with iron. And in the genesis of the disorder, hemolysis mechanisms in the peripheral bloodstream and destruction of functionally defective red blood cells in the spleen come first. The latter is due to the fact that with cirrhosis, the synthesis of metabolites necessary for erythropoiesis, including vitamin B12, is impaired. Therefore, individual lines of red blood cells are represented by hemoglobinization ofmegalocytes: functionally inferior, short-lived and osmotically unstable.

Conclusions

In patients with cirrhosis associated with thrombocytopenia, the platelet count, measured in the optical mode (PbT-O), is 10.5% higher than that calculated by the impedance method. In the case of critically low platelet concentrations, it seems appropriate to focus on PbT-O as the most adequately reflecting the true number of platelets.

The number of immature platelets in patients with cirrhosis associated with thrombocytopenia is statistically significantly increased to 3.23 ± 1.7%, which indicates the activation of bone marrow thrombocytopenia. The degree of "request" for immature cells is regulated by the feedback principle.

Estimated platelet counts (PDW, MPV and P-LCR) do not provide additional information characterizing the characteristics of thrombocytopoiesis in cirrhosis associated with thrombocytopenia.

It was established that with cirrhosis of the liver there is a dissociation between the content of leukocytes and the number of immature granulocytes: the tendency of leukocytopenia is accompanied by a "left shift" of the cellular composition of blood.

Compared with the control group, for cirrhosis associated with thrombocytopenia, the relative and absolute number of reticulocytes were statistically significantly increased, the average hemoglobin content in reticulocytes was reduced, and the reticulocyte formula was rejuvenated ($p < 0.5$).

Delta hemoglobin (D-He) in case of cirrhosis associated with thrombocytopenia takes both positive and negative values. Negative D-He values are associated with a concomitant inflammatory component. A direct relationship between D-He and the hemoglobin content in reticulocytes ($r = 0.57$), D-He and the number of immature granulocytes ($r = 0.45$) was revealed.

With cirrhosis of the liver, a statistically significant increase compared with the norm of the average content of fragmentocytes (0.83 ± 1.21%) and / or the level of delta hemoglobin (D-He> 4 pg) is probably due to the concomitant hemolytic component, characteristic of liver pathology.

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