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## CHRONIC LIVER DISEASE AND ANEMIA – WHAT A FAMILY DOCTOR SHOULD KNOW

**Abstract.** The article is devoted to a relevant issue in clinical practice — chronic liver diseases (CLD) of various aetiologies, the progression of which is frequently accompanied by haematological abnormalities. In patients with CLD, haematological deviations are observed in 75% of cases, most commonly in the form of anaemia, which, according to WHO criteria, is diagnosed when haemoglobin concentration falls below 120 g/L in women and 130 g/L in men. The close association between anaemia and such adverse outcomes of CLD as increased disease severity, heightened risk of decompensation, and elevated mortality underscores the importance of this research direction.

**Aim:** to identify the haematological characteristics specific to patients with CLD of various aetiologies and anaemia, based on correlation analysis of routine

laboratory parameters commonly used in outpatient clinical practice. The obtained data aim to enhance understanding of these changes and to improve family physicians' awareness and management of such patients.

The study sample consisted of 73 individuals aged between 37 and 69 years (mean age  $46.7 \pm 10.4$  years;  $M \pm SD$ ). Inclusion criteria were: a confirmed diagnosis of CLD and anaemia based on WHO guidelines; referral from a family physician for consultation with a gastroenterologist; and availability of a basic set of laboratory tests typical for primary healthcare settings (complete blood count, total serum protein, serum iron, ferritin, and activated partial thromboplastin time).

Depending on the aetiology of CLD, patients were divided into four statistically comparable groups: Group 1 — 16 patients with chronic hepatitis C; Group 2 — 17 patients with chronic alcoholic hepatitis; Group 3 — 12 patients with liver cirrhosis; Group 4 — 28 patients with non-alcoholic fatty liver disease (NAFLD).

The study demonstrated that, in patients with CLD and anaemia, the severity of anaemia was determined by the presence of direct correlations with red blood cell count, erythrocyte indices (MCV, MCH), serum iron levels, and total protein, along with a bidirectional inverse association with APTT prolongation. Furthermore, prolongation of APTT, as a factor contributing to increased bleeding risk, was directly influenced by decreased haemoglobin concentration, MCH, serum iron, and total protein levels.

The analysis of laboratory parameters in patients with CLD and anaemia provides insights into the adaptive capacity of liver function. In patients with chronic hepatitis C and alcoholic hepatitis, the adaptive response resembled an acute inflammatory reaction. In cases of liver cirrhosis, findings reflected a near-complete exhaustion of hepatic reserves, whereas patients with NAFLD exhibited the highest degree of compensation according to laboratory indicators.

Thus, the findings of this study contribute to a better understanding of the specific alterations in routine haematological parameters used at the primary healthcare level in patients with chronic liver diseases and anaemia.

**Keywords:** chronic liver disease, hepatitis, liver cirrhosis, non-alcoholic fatty liver disease, anemia, hemoglobin, erythrocytes, erythrocyte indices, total protein, serum iron, ferritin, activated partial thromboplastin time, correlation analysis, outpatient practice.

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## **ХРОНІЧНА ХВОРОБА ПЕЧІНКИ ТА АНЕМІЯ - ПРО ЩО ТРЕБА ЗНАТИ СІМЕЙНОМУ ЛІКАРЮ**

**Анотація.** Стаття присвячена актуальній проблемі клінічної практики – хронічним хворобам печінки (ХХП) різної етіології, при прогресуванні яких достатньо часто реєструються гематологічні відхилення. У пацієнтів з ХХП в 75% випадків гематологічні відхилення пов'язані з формуванням анемії, яка за даними ВООЗ визначається при зниженні концентрації гемоглобіну ( $< 120$  г/л для жінок і  $< 130$  г/л для чоловіків). Тісний зв'язок між анемією та такими несприятливими наслідками ХХП, як збільшення важкості перебігу, ризику розвитку декомпенсації та ризику смертності у цих пацієнтів актуалізує вибір напрямку дійсного дослідження.

Мета роботи – на підставі проведення кореляційного аналізу між лабораторними показниками, що призначаються в рутинній клінічній амбулаторній практиці, відокремити особливості гематологічних характеристик пацієнтів з ХХП різної етіології та анемією, що буде сприяти розумінню цих змін та підвищить обізнаність сімейних лікарів.

Генеральна вибірка - 73 особи віком від 37 до 69 років, ( $46,7 \pm 10,4$  років;  $M \pm SD$ ). Критерії включення: наявність встановленого за МКХ-10 діагнозу ХХП та анемії за критеріями ВООЗ; скерування пацієнтів сімейним лікарем на консультацію до гастроентеролога; відповідність обсягу лабораторного обстеження пацієнтів первинному рівню надання медичної допомоги (загальний аналіз крові, загальний білок, сироваткове залізо, феритин, АЧТЧ). В залежності від етіології ХХП пацієнти були розподілені на 4 групи (1 група - 16 осіб з хронічним вірусним гепатитом С; 2 група - 17 осіб з хронічним алкогольним гепатитом; 3 група - 12 осіб з цирозом печінки; 4 група - 28 осіб з неалкогольною жировою хворобою печінки), які були статистично порівня-

ними за кількістю осіб. Доведено, що у пацієнтів з ХХП та анемією, ступінь важкості анемії була обумовлена наявністю прямих кореляційних взаємовпливів з кількістю еритроцитів, еритроцитарних індексів MCV, MCH, сироваткового заліза та рівня загального білку з подовшенням АЧТЧ (двобічний обернений вплив). Безпосередньо на тривалість АЧТЧ у бік його подовження, як фактору підвищення ризиків розвинення кровотеч, впливали зниження вмісту гемоглобіну, MCH, концентрації сироваткового заліза та загального білку в сироватці крові. Проведений нами аналіз лабораторних показників у пацієнтів з анемією та ХХП різної етіології дає підстави для розсуду стосовно особливостей адаптивних можливостей стану печінки. У пацієнтів з ХВГС та ХАГ адаптивний процес відбувається по типу гострої запальної реакції. У пацієнтів з ЦП має місце майже повне виснаження печінкових резервів, в той час як лабораторні показники пацієнти з НАЖХП мають з найбільший рівень компенсації. Таким чином, результати та висновки дійсного дослідження сприяють розумінню особливостей змін рутинних гематологічних показників, які зазвичай використовуються на первинному рівні медичної допомоги.

**Ключові слова:** хронічна хвороба печінки, хронічний гепатит, цироз печінки, НАЖХП, анемія, гемоглобін, еритроцити, еритроцитарні індекси, загальний білок, сироваткове залізо, ферритин, АЧТЧ, кореляційний аналіз, амбулаторна практика.

**Introduction.** Liver diseases represent a significant proportion of the global burden of disease, affecting more than 30 million people worldwide and accounting for approximately 2 million deaths annually. In addition to mortality, liver diseases are associated with considerable loss of working capacity, reduced quality of life, and substantial healthcare-related costs, which collectively justify the sustained scientific and clinical interest in this problem [1,2].

Despite sharing certain common features, liver diseases present distinct pathophysiological, clinical, and therapeutic profiles. In developed countries, the majority of chronic liver disease (CLD) cases are attributed to alcoholic liver disease, chronic viral hepatitis, and non-alcoholic fatty liver disease (NAFLD) [3,4].

Haematological abnormalities are frequently encountered in patients with CLD, regardless of its aetiology, with anaemia being one of the most common findings. Approximately 75% of patients with CLD develop anaemia, which significantly impairs their quality of life and adversely affects clinical outcomes [5,6]. According to the World Health Organization (WHO), anaemia is defined as a haemoglobin concentration below 120 g/L in women and below 130 g/L in men [7], a condition that is most often identified at the outpatient level during routine laboratory screening [8,9].

The pathogenesis of anaemia in CLD is complex and multifactorial. The underlying causes may include iron deficiency, acute or chronic gastrointestinal



bleeding, malnutrition, hypersplenism secondary to portal hypertension, haemolysis, coagulopathy, among others [10]. The close association between anaemia and unfavourable outcomes in CLD — including increased disease severity, higher risk of decompensation, and elevated mortality — highlights the clinical significance and relevance of this research topic.

General practitioners and family physicians frequently encounter patients with CLD of varying aetiologies, and anaemia is often identified in the course of routine laboratory assessment in this patient population.

The aim of this study was to identify the specific haematological characteristics of patients with CLD of various aetiologies and concomitant anaemia through correlation analysis of laboratory parameters routinely used in outpatient clinical practice. The findings are intended to improve the understanding of these alterations and enhance the awareness of family physicians when managing such patients.

**Materials and Methods.** All patients included in this study were referred by their family physicians for specialist consultation, accompanied by appropriate medical documentation confirming an established diagnosis of CLD and anaemia.

The study cohort consisted of 73 patients (37% female and 63% male) diagnosed with CLD and anaemia, aged between 37 and 69 years (mean age  $46.7 \pm 10.4$  years;  $M \pm SD$ ). Inclusion criteria were: a confirmed diagnosis of CLD in accordance with the International Classification of Diseases, 10th Revision (ICD-10); diagnosis of anaemia based on WHO criteria; referral by a family physician to a gastroenterologist for consultation; and availability of a laboratory test panel consistent with the standard diagnostic framework at the primary healthcare level (complete blood count, total serum protein, serum iron, ferritin, and activated partial thromboplastin time — APTT).

It should be noted that, for patients in Groups 2 and 3, the selection criterion additionally required a serum bilirubin level not exceeding 70 mmol/L, primarily attributable to the direct fraction, which was considered a prerequisite for inclusion in these observation groups.

Depending on the aetiology of CLD, patients were divided into four groups: group 1: 16 patients diagnosed CHC; group 2: 17 patients with CAH; group 3: 12 patients with LC; group 4: 28 patients with NAFLD. The groups were statistically comparable in terms of the number of participants. The duration of CLD across the entire cohort ranged from 2 to 5 years, with a median disease duration of 3 years.

The study was conducted in accordance with the principles outlined in the Council of Europe's Convention on Human Rights and Biomedicine, the Declaration of Helsinki of the World Medical Association regarding ethical principles for medical research involving human subjects, as well as the current regulatory guidelines of the Ministry of Health of Ukraine. In compliance with bioethical standards, informed consent was obtained from all patients for the use of their examination results for research and publication purposes.

Statistical analysis was performed using STATISTICA 6.1 software (StatSoft Inc., serial number AGAR909E415822FA). The normality of the distribution of quantitative variables was assessed using the Shapiro–Wilk test. For normally distributed data, descriptive statistics were reported as the arithmetic mean (M), standard error (m), and standard deviation (SD). Intergroup comparisons were performed using one-way analysis of variance (ANOVA) followed by Scheffe's post hoc test for multiple comparisons. The strength of association between variables was assessed using Pearson's linear correlation coefficient (r). A p-value of  $<0.05$  was considered statistically significant.

**Results and Discussion.** In this study, male patients in Groups 1, 3, and 4 did not differ significantly in age from female patients ( $p > 0.05$ ), while Group 2 included only male participants.

The clinical profile of the examined patients ( $n = 73$ ) was characterised by a high prevalence of complaints, including: weakness (93.2%), easy fatigability (87.7%), decreased or absent appetite (76.7%), heartburn (60.3%), bitter taste and dry mouth (78.1%), postprandial abdominal pain and bloating (83.6%), and frequent diarrhoea (74.0%).

Additionally, all patients demonstrated signs of skin trophic disturbances (dryness and loss of turgor, spontaneous bruising), trophic changes of mucous membranes with increased bleeding tendency, angular cheilitis, "beefy red tongue," altered menstrual patterns in women (more profuse and prolonged periods), nail ridging and brittleness, hair thinning and excessive hair loss, vitiligo, as well as neurological and psychosomatic disorders. These symptoms were most pronounced in the clinical presentation of patients with liver cirrhosis.

According to the obtained data, patients in Groups 1, 2, and 3 exhibited moderate disease severity, whereas patients in Group 4 generally maintained a relatively satisfactory clinical condition.

The severity of anaemia varied across the groups: patients in Groups 1 and 4 demonstrated mild anaemia, Group 2 exhibited moderate anaemia, and Group 3 — severe anaemia (Figure 1).

Pairwise comparisons of laboratory parameters across the study groups revealed significant differences in haemoglobin levels:  $94.3 \pm 5.7$  g/L,  $74.3 \pm 6.6$  g/L,  $66.5 \pm 6.3$  g/L, and  $101.5 \pm 4.3$  g/L for Groups 1, 2, 3, and 4, respectively ( $p_{1,2,3,4} < 0.001$ ). Similarly, the red blood cell count showed significant variation:  $3.16 \pm 0.22 \times 10^{12}$ /L,  $2.79 \pm 0.51 \times 10^{12}$ /L,  $2.47 \pm 0.17 \times 10^{12}$ /L, and  $3.78 \pm 0.24 \times 10^{12}$ /L for Groups 1, 2, 3, and 4, respectively ( $p_{1,2,3,4} < 0.001$ , except for  $p_{1-2} < 0.05$  and  $p_{2-3} < 0.05$ ). The highest haemoglobin and red blood cell counts were observed in Group 4, and the lowest — in Group 3.

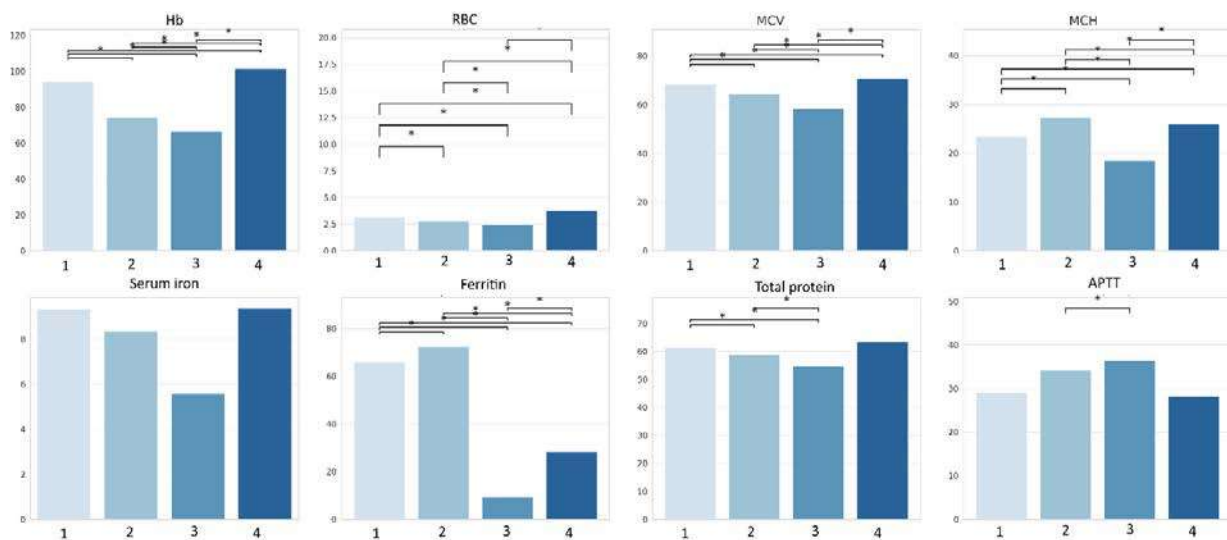
Analysis of MCV demonstrated a similar trend:  $68.3 \pm 3.9$  fL,  $64.4 \pm 4.8$  fL,  $58.4 \pm 4.5$  fL, and  $70.6 \pm 2.5$  fL, respectively ( $p_{1,2,3,4} < 0.001$ , except for  $p_{1-2} < 0.05$  and  $p_{1-4} > 0.05$ ). No significant difference in erythrocyte size was observed between patients with non-alcoholic fatty liver disease and chronic hepatitis C (Groups 4 and 1, respectively).

Pairwise comparisons of MCH showed that the lowest values were found in patients with LC, while the highest were observed in patients with CAH:  $23.5 \pm 3.1$  pg,  $27.2 \pm 2.7$  pg,  $18.5 \pm 2.1$  pg, and  $25.9 \pm 1.2$  pg, respectively ( $p_{1,2,3,4} < 0.001$ , except for  $p_{1-4} < 0.05$  and  $p_{2-4} < 0.05$ ).

Regarding serum iron levels, significant differences were also detected between groups:  $9.31 \pm 1.74$   $\mu\text{mol/L}$ ,  $8.35 \pm 1.32$   $\mu\text{mol/L}$ ,  $5.58 \pm 1.14$   $\mu\text{mol/L}$ , and  $9.36 \pm 1.16$   $\mu\text{mol/L}$  for Groups 1, 2, 3, and 4, respectively ( $p_{1,2,3,4} < 0.001$ , except for  $p_{1-2} > 0.05$ ;  $p_{1-4} > 0.05$ ;  $p_{2-4} > 0.05$ ). The most pronounced iron deficiency was observed in patients with liver cirrhosis (Group 3). The serum iron levels in Groups 1, 2, and 4 did not differ significantly.

Evaluation of serum ferritin concentration also revealed significant differences between groups:  $65.9 \pm 4.5$  ng/mL,  $72.5 \pm 1.8$  ng/mL,  $9.3 \pm 0.9$  ng/mL, and  $28.3 \pm 2.2$  ng/mL, respectively ( $p_{1,2,3,4} < 0.001$ ). The highest mean ferritin level was recorded in patients with chronic alcoholic hepatitis (Group 2), and the lowest — in patients with liver cirrhosis (Group 3).

Thus, the iron metabolism parameters (MCH, serum iron, and ferritin) in patients with anaemia and chronic liver disease demonstrated statistically significant differences depending on the aetiology of the liver disorder.



*Fig.1. Comparative analysis of laboratory parameters in patients with anaemia and chronic hepatopathies of different origins (Observation Groups 1, 2, 3, 4).*

The assessment of total serum protein levels in patients with anaemia and CHP demonstrated statistically significant differences across all study groups ( $61.4 \pm 3.5$  g/L;  $58.8 \pm 2.7$  g/L;  $54.8 \pm 3.1$  g/L;  $63.4 \pm 2.3$  g/L for Groups 1, 2, 3, and 4, respectively;  $p_{1,2,3,4} < 0.001$ , except for  $p_{1-2} < 0.05$ ;  $p_{1-4} > 0.05$ ). The most pronounced protein deficiency was observed in patients with liver cirrhosis (Group 3), while the highest total protein levels were recorded in patients with chronic hepatitis C (Group 4) and



non-alcoholic fatty liver disease (Group 1), with no statistically significant difference between these two groups ( $p_{1-4} > 0.05$ ).

Activated partial thromboplastin time also varied across the groups ( $29.2 \pm 4.6$  sec;  $34.1 \pm 1.8$  sec;  $36.4 \pm 3.5$  sec;  $28.2 \pm 3.4$  sec for Groups 1, 2, 3, and 4, respectively;  $p_{1,2,3,4} < 0.001$ , except for  $p_{2-3} > 0.05$  and  $p_{1-4} > 0.05$ ), reflecting the influence of CHP aetiology on coagulation status. Notably, patients in Groups 2 and 3 demonstrated significantly prolonged APTT values exceeding the reference range, which did not differ significantly between these two groups ( $p_{2-3} > 0.05$ ). These findings suggest a predisposition towards hypocoagulability in the setting of these specific liver pathologies.

In contrast, APTT values in patients from Groups 1 and 4 were comparable ( $p_{1-4} > 0.05$ ) and remained within the reference range, although significantly lower than those observed in Groups 2 and 3.

In summary, the laboratory assessment of patients with CHP and anaemia revealed that individuals with liver cirrhosis exhibited the most impaired parameters both in terms of iron metabolism and hepatic protein synthesis, in contrast to patients with non-alcoholic fatty liver disease, whose laboratory results were relatively well preserved (Figure 1).

A correlation analysis of all laboratory results in patients with CHP and anaemia revealed the presence of both identical bidirectional correlations across the groups (Figure 2) as well as group-specific patterns differing in direction (Figure 3) and structure.

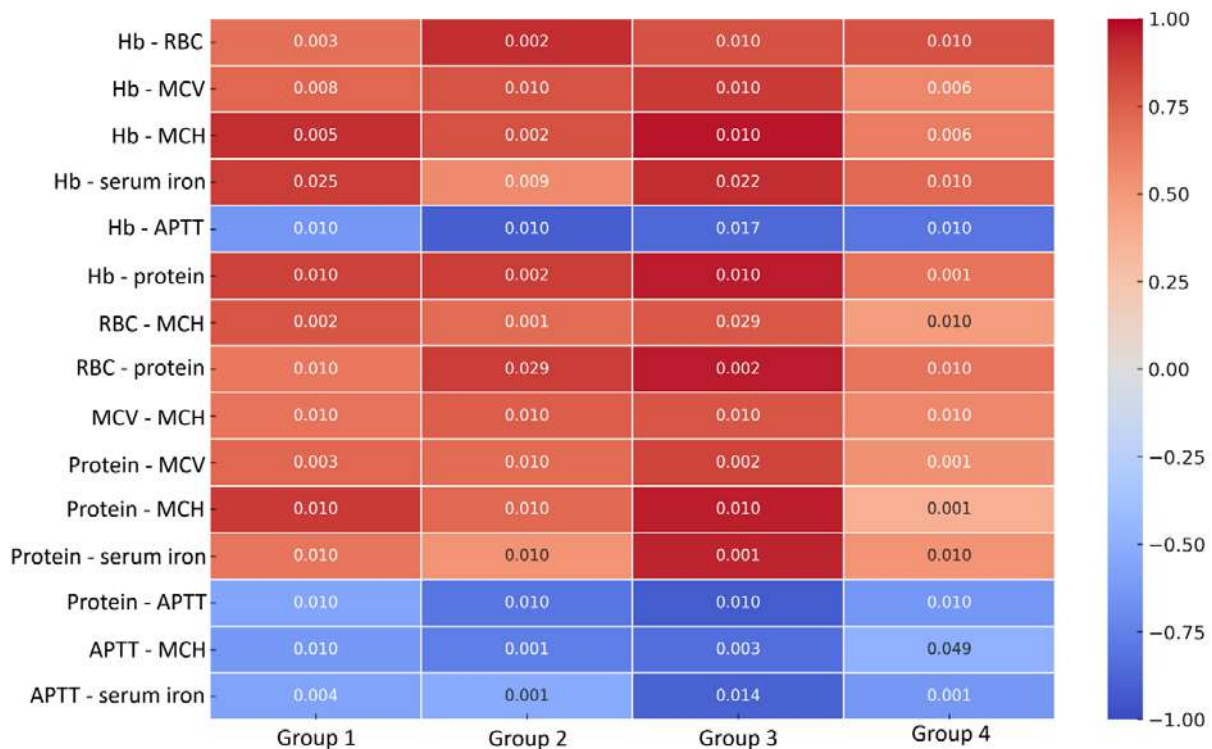
At the initial stage of correlation analysis, we identified bidirectional correlations that were consistent across all groups of patients with CHP and anaemia, presented as a heatmap (Figure 2). Across all groups, lower haemoglobin concentrations were associated with lower red blood cell counts, MCV, MCH, serum iron, and total protein levels, along with prolonged APTT (bidirectional inverse correlation).

In turn, a reduction in red blood cell count was directly linked to a decrease in total serum protein concentration and MCH, which itself was directly correlated with MCV (Figure 2).

The decline in the protein-producing function of the liver in all patients with CHP and anaemia was influenced by reduced haemoglobin, red blood cell count, serum iron, and decreased MCV and MCH values, which were consistently associated with prolonged APTT (bidirectional inverse correlation).

Specifically, the prolongation of APTT, a factor indicating increased risk of coagulopathies, was inversely influenced by decreased haemoglobin, MCH, serum iron, and total protein levels in all patients with CHP and anaemia (bidirectional inverse correlation).





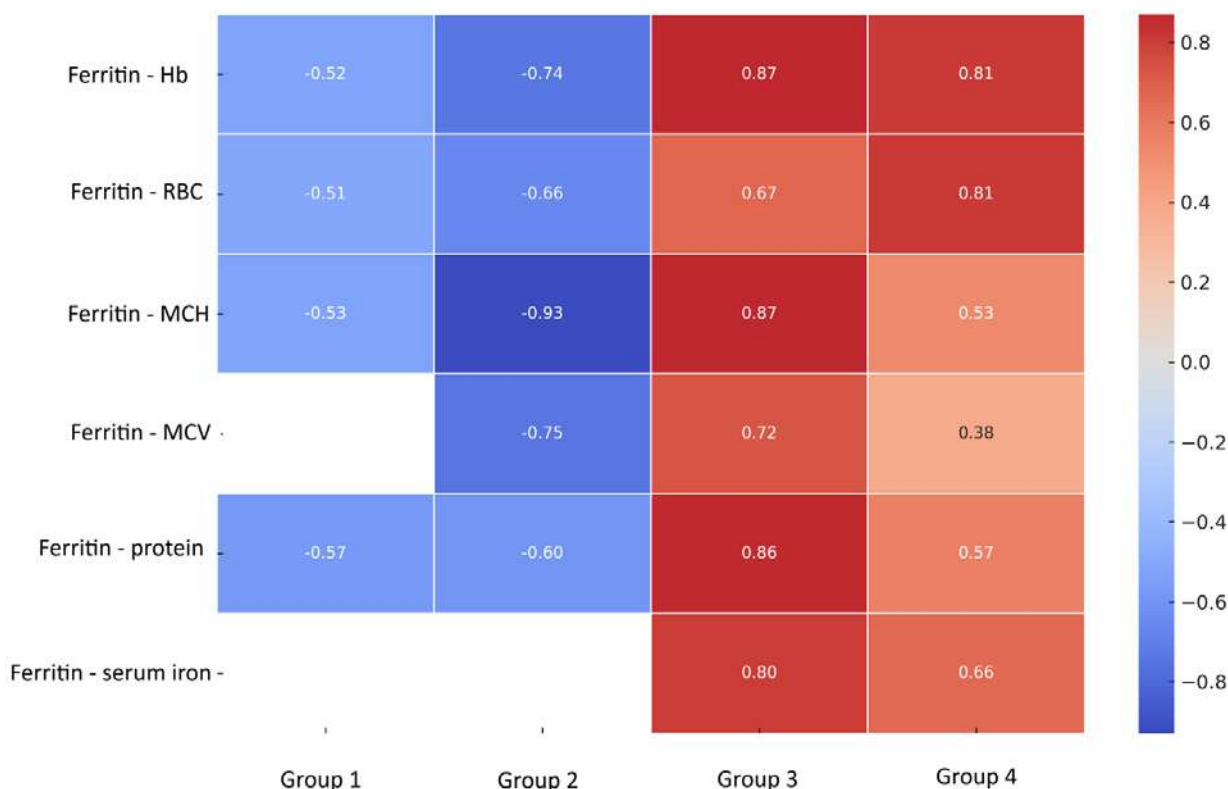
*Fig. 2. Heatmap of correlations between laboratory parameters in patients with anaemia and chronic hepatopathies, irrespective of liver disease aetiology. The colour scale reflects the strength ( $r$ ) and direction of the correlation.*

Thus, the patients with CHP and anaemia included in our study demonstrated certain common patterns of haematological alterations, which suggests the existence of shared pathogenetic features in this patient population.

At the second stage of the correlation analysis, we identified distinct differences in the correlation relationships between the haematological parameters under investigation, which were visualised as two opposite correlation clusters: a bidirectional inverse relationship in patients from Groups 1 and 2, and a bidirectional direct relationship in patients from Groups 3 and 4. This observation allowed us to further explore the specific features of ferritin kinetics across the study groups (Figure 3).

In patients with chronic viral hepatitis C (Group 4) and chronic autoimmune hepatitis (Group 2) (Figure 3), lower levels of haemoglobin, erythrocytes, MCH, and total serum protein — as well as MCV (in the case of autoimmune hepatitis) — were associated with higher ferritin concentrations. This correlation pattern may indicate the presence of an inflammatory response in these groups of patients.

Conversely, in patients with liver cirrhosis (Group 3) and non-alcoholic fatty liver disease (Group 1), a decline in haemoglobin, erythrocyte count, serum iron, total protein, MCH, and MCV was associated with lower ferritin concentrations, which is indicative of depleted iron stores in these patients.



*Fig. 3. Specific features of ferritin kinetics in patients with anaemia and chronic hepatopathies depending on liver disease aetiology.*

Summarising the obtained results, it can be concluded that the performed analysis of laboratory parameters in patients with anaemia and CHP of varying aetiologies provides valuable insights into the adaptive capacity of the liver. In patients with chronic viral hepatitis C and chronic autoimmune hepatitis, the adaptive response appears to follow the pattern of an acute inflammatory reaction. In contrast, patients with LC exhibited signs of near-complete exhaustion of hepatic reserves, whereas patients with NAFLD demonstrated the highest level of compensation according to laboratory findings.

Thus, patients with anaemia and CHP exhibit both common and distinct correlation matrices between the results of routine laboratory assessments. These findings reflect differing mechanisms of ferritin kinetics, variable risks of developing hypocoagulable states, the presence or absence of systemic inflammation, and variations in protein metabolism, depending on the underlying liver disease.

**Conclusions.** In patients with CHP (CVHC, CAH, LC, NAFLD) and anaemia, the severity of anaemia was primarily determined by direct correlations with erythrocyte count, erythrocyte indices (MCV, MCH), serum iron levels, and total protein concentration, along with an inverse correlation with APTT, the latter prolonging as these parameters declined. Across all patients with CHP and anaemia,

prolongation of APTT — as a factor increasing the risk of bleeding complications — was significantly influenced by reductions in haemoglobin, MCH, serum iron concentration, and total serum protein levels. Patients with CHP require mandatory clarification of the anaemia type, and the results of this study contribute to a better understanding of the specific changes in routine haematological parameters typically used in primary healthcare settings.

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