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Role of Iron Metabolism Markers in Predicting Outcomes of Anemia of Chronic Diseases

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Annotation: Chronic disease anemia (CHD) is the second most common form of anemia after iron deficiency anemia and is accompanied by a wide range of inflammatory, infectious, oncological, and autoimmune processes. The purpose of the study was to assess the prognostic significance of ferritin and the transferrin saturation coefficient (TSA) as key biomarkers that allow differentiating ASD, determining the depth of functional iron deficiency, and predicting the severity of the underlying disease. 120 patients with confirmed AH were examined, divided into three groups depending on the severity of the inflammatory process. It has been established that low CNT (<20%) and high ferritin (>200 ng/ml) significantly correlate with inflammation activity (CRP, ESR), organ damage severity, and disease duration. ROC analysis showed high diagnostic accuracy of the "ferritin + KNT" combination (AUC=0.87). The obtained data confirm that these indicators can be used as reliable prognostic markers in clinical and laboratory practice.

Keywords: chronic disease anemia, ferritin, transferrin, CNT, inflammation, functional iron deficiency.

Problem relevance. Anemia of Chronic Disease (ACD) represents a heterogeneous clinical-hematological condition arising in the setting of sustained inflammatory activity and long-standing systemic disorders, including chronic infections, malignant processes, autoimmune diseases, as well as advanced cardiac and renal insufficiency. Contemporary international epidemiological analyses published between 2018 and 2024 indicate that the prevalence of ACD among hospitalized patients ranges from 25% to 40%, while in specialized oncological, hematological, and rheumatological populations it may reach 60–85%. These figures position ACD as the second most frequent form of anemia after iron deficiency anemia. The clinical presence of ACD is strongly associated with adverse outcomes, including increased mortality, functional decline, reduced tolerance to therapeutic interventions, prolonged hospital stays, higher rates of rehospitalization, and a substantial rise in overall healthcare expenditures (5,7).

The underlying pathophysiology of ACD is primarily driven by dysregulation of iron homeostasis mediated by excessive production of hepcidin, the central hormonal regulator of systemic iron balance and erythropoietic activity. Elevated hepcidin concentrations inhibit iron export from enterocytes and macrophages by inducing ferroportin degradation, resulting in restricted iron availability for erythroid precursors despite normal or increased total body iron stores. Concurrently, pro-inflammatory cytokines, particularly interleukin-6 and tumor necrosis factor-α, exert a direct suppressive effect on bone marrow erythropoiesis, further aggravating the severity and persistence of anemia (1,6).

From a diagnostic perspective, accurate interpretation of iron metabolism parameters is critical for clinical decision-making. Serum ferritin reflects intracellular iron storage; however, as a classical acute-phase reactant, its concentration markedly increases in response to inflammatory stimuli, thereby limiting its reliability as a standalone marker of iron sufficiency for erythropoiesis. In contrast, the transferrin saturation coefficient (TSC) provides an estimate of circulating, bioavailable iron directly involved in hemoglobin synthesis. In the context of ACD, TSC values are typically reduced, rendering this parameter a more specific indicator of functional iron deficiency and impaired iron transport (2,4).

Recent research highlights the importance of integrated assessment of ferritin and TSC dynamics rather than isolated evaluation of individual markers. Their combined analysis enables more precise

differentiation between anemia of chronic inflammation and absolute iron deficiency, allows estimation of inflammatory burden, and facilitates the selection of individualized therapeutic strategies. These may include iron supplementation, erythropoiesis-stimulating agents, or targeted anti-inflammatory treatment. Consequently, investigation of the prognostic relevance of ferritin and transferrin saturation parameters holds substantial clinical value for optimizing the management of patients with anemia of chronic disease (3).

Research objective. The present study aimed to evaluate the prognostic significance of serum ferritin and the transferrin saturation coefficient (TSC) in anemia of chronic disease, as well as to determine their diagnostic performance in distinguishing functional iron deficiency and characterizing the intensity of the underlying inflammatory process.

Materials and methods of research. This investigation was carried out in a multidisciplinary clinical hospital and enrolled 120 patients with a verified diagnosis of anemia of chronic disease. Anemia was defined by hemoglobin concentrations below 120 g/L in women and below 130 g/L in men, in the presence of preserved or increased iron stores. Eligibility criteria included documented chronic inflammatory or oncological pathology, serum ferritin levels ≥100 ng/mL, reduced transferrin saturation (<20%), and normal or elevated depot iron indices, thereby excluding absolute iron deficiency.

Based on inflammatory activity, assessed by C-reactive protein (CRP), patients were stratified into three comparable groups:

Group I (n=40): low-grade inflammatory activity (CRP <10 mg/L);

Group II (n=40): moderate inflammatory activity (CRP 10–30 mg/L);

Group III (n=40): high inflammatory activity (CRP >30 mg/L).

Laboratory assessment comprised determination of serum ferritin using immunochemiluminescent assays, measurement of serum iron and total iron-binding capacity followed by calculation of the transferrin saturation coefficient, and evaluation of inflammatory markers (CRP, erythrocyte sedimentation rate), hemoglobin concentration, and reticulocyte index. When clinically indicated, ultrasonographic examination of the liver and spleen was performed to detect inflammatory or infiltrative changes and to assess complications associated with the underlying disease.

Data processing included Student's t-test and one-way analysis of variance (ANOVA). Associations between variables were examined using Pearson's correlation coefficient. The diagnostic performance of ferritin and TSC was evaluated by receiver operating characteristic (ROC) curve analysis. Statistical significance was established at a p-value of less than 0.05.

Research results: during the study, laboratory indicators of iron metabolism and inflammatory activity were assessed in patients of three clinical groups, differing in the level of systemic inflammation. The results are presented in Tables 1-4

Table 1 reflects the pronounced dependence of ferritin concentration on the degree of activity of the inflammatory process.

Table 1.Ferritin levels (M±m) in the studied groups

Indicator	Gr. I	Gr. II	Gr. III
Ferritin (ng/ml)	148±26.	212±34*	318±41**

** p<0.01; ** p<0.001*

Ferritin increased proportionally to the increase in inflammation, reflecting both the overload of the iron depot and the activation of the acute phase response. In patients with high inflammatory process activity (group III), the level of ferritin exceeded the indicators of group I by 2.1 times (p<0.001), which confirms its role as a marker of systemic inflammation.

Iron and CNT indicators are presented in Table 2.

Table 2.Transferrin saturation coefficient and iron indicators

Indicator	Gr. I	Gr. II	Gr. III
Serum iron (μmol/l)	10.8±2.1	8.2±1.7*	6.4±1.5**
OJSS (μmol/l)	54±6.	50±7.	46±8
KNT (%)	20.1±3.5	15.9±2.8*	11.7±2.4**

** $p<0.01$; ** $p<0.001$*

CNT decreased from 20% in group I to 11.7% in group III ($p<0.001$), indicating a pronounced functional iron deficiency. CNT decrease correlated with CRP levels ($r = -0.58$; $p<0.01$), confirming the dependence of iron transport on the intensity of inflammation. At the same time, serum iron decreased with stable or moderately decreased OCS, which is typical for AHZ.

Correlation relationships between iron markers and inflammation are presented in Table 3.

Table 3. Correlation of ferritin and CNT with inflammatory markers

Indicator	Ferritin (r)	KNT (r)
CRP	+0.64*	-0.58*.
ESR	+0.52*	-0.49*

** $p<0.01$*

The obtained data indicate that ferritin is a positive acute phase marker: its concentration increases as inflammation progresses. Conversely, CNT exhibited negative correlations, reflecting a decrease in iron availability for erythropoiesis against a background of systemic inflammation.

Table 4.Diagnostic accuracy ROC analysis of markers

Indicator	AUC
Ferritin	0.79
KNT	0.83
"Ferritin + CNT" Combination	0.87

The combination of two indicators ("ferritin + CNT") showed the highest diagnostic value, increasing the AUC to 0.87, which indicates a high accuracy in the differentiation of AHZ and functional iron deficiency. CNT had a higher AUC (0.83) compared to ferritin (0.79), making it a more sensitive marker of the iron deficiency component of anemia.

Conclusions:

Ferritin and the transferrin saturation coefficient are key informative markers of iron metabolism in anemia of chronic diseases and reflect the degree of metabolic disorders caused by systemic inflammation.

An increase in ferritin and a simultaneous decrease in CNT are closely correlated with CRP and ESR levels, making these indicators prognostically significant for assessing the severity of the underlying disease and the risk of anemia progression.

A combination of ferritin values >200 ng/ml and CNT <20% demonstrates high diagnostic accuracy (AUC = 0.87) in confirming ACS and determining functional iron deficiency.

Using a combined assessment of ferritin and CNT allows for improved differential diagnosis, avoiding erroneous prescription of iron to patients without true iron deficiency, and optimizing the choice of therapeutic strategy.

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