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RESEARCH ARTICLE

Ferritin as a Dual-Purpose Biomarker: Unraveling its Role in Iron Storage and as a Surrogate for Tumor Burden in CML

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Abstract

Background: Hyperferritinemia observed in patients with chronic myeloid leukemia (CML) presents an interpretive challenge, as its underlying cause may be attributable to either iron overload or an inflammatory response associated with the tumor. Accurate identification of the primary driver is essential for precise clinical assessment. **Objective:** This investigation sought to elucidate the principal cause of elevated ferritin levels in patients with newly diagnosed chronic myeloid leukemia (CML) and to assess the diagnostic effectiveness and utility of the calculated Iron/Ferritin and TIBC/Ferritin ratios. **Materials and Methods:** This retrospective, cross-sectional study involved 90 adult patients with untreated chronic-phase CML. At diagnosis, serum ferritin, lactate dehydrogenase (LDH), iron levels, and total iron-binding capacity (TIBC) were measured. The relationships between ferritin, LDH, and iron parameters were examined using Spearman's correlation and multiple linear regression, with ferritin log10-transformed. Patients were divided at the median LDH level, and the Mann-Whitney U test was used to compare the proposed ratios between groups with high and low disease burden. **Results:** The cohort demonstrated pronounced hyperferritinemia, with a median ferritin level of 339.5 µg/L, and elevated lactate dehydrogenase (LDH), with a median of 269.2 U/L. Concurrently, serum iron and total iron-binding capacity (TIBC) were markedly reduced. A moderate positive correlation was observed between ferritin and LDH (ρ=0.52, $p<0.001$), whereas the correlations with iron and TIBC were weak and not statistically significant. Regression analysis identified LDH as the only independent predictor of ferritin levels ($\beta = 0.56$, $p < 0.001$). Furthermore, the ratios of iron to ferritin and TIBC to ferritin were significantly lower in the high LDH group (median Iron/Ferritin: 0.038 vs. 0.068; median TIBC/Ferritin: 0.150 vs. 0.295; $p<0.001$ for both), indicating inflammation-driven alterations and suggesting an association with inflammation-driven iron metabolism changes. **Conclusion:** This investigation introduces a pragmatic and economical diagnostic methodology (the utilization of the Iron/Ferritin and TIBC/Ferritin ratios) that facilitates clinicians in precisely determining hyperferritinemia caused by tumor-associated inflammation in patients with newly diagnosed CML, thereby obviating the need for superfluous iron-related examinations. In this cohort of treatment-naïve CML patients, hyperferritinemia was primarily associated with tumor-related inflammation rather than iron overload. The Iron/Ferritin and TIBC/Ferritin ratios may serve as simple, cost-effective tools to suggest an inflammatory etiology, though further validation in prospective studies with ROC analysis is warranted.

Keywords: Chronic Myeloid Leukemia (CML)- Ferritin- Hyperferritinemia- Inflammation- Tumor Burden- Iron Metabolism

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1. Introduction

Ferritin plays a critical and intricate role in clinical diagnostics owing to its dual biological functions. Mainly, it serves as a vital intracellular iron storage protein, essential for maintaining iron balance and preventing the toxicity of excess iron [1]. However, it is also recognized as a sensitive acute-phase reactant, with its hepatic synthesis significantly increased by pro-inflammatory cytokines, especially interleukin-6

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(IL-6), during systemic inflammatory responses [2]. This duality in function underscores a prevalent diagnostic challenge: significantly elevated serum ferritin levels can indicate either pathological iron overload, as seen in hemochromatosis, or an active inflammatory response, as in sepsis or malignancy. Consequently, A clinician confronted with hyperferritinemia faces a vital interpretive challenge: determining whether elevated ferritin reflects iron overload necessitating phlebotomy or indicates inflammation associated with underlying pathologies such as hematologic malignancies. Accurate differentiation is essential for guiding appropriate management and improving patient outcomes [3].

In patients with hematologic malignancies, this clinical dilemma is especially relevant because evaluation frequently reveals elevated ferritin levels. While hyperferritinemia has been recognized in all of the leukemia subtypes, the pathophysiological mechanisms behind these, particularly chronic myeloid leukemia (CML) remain controversial [4]. In other myeloproliferative neoplasms, high tumor burden directly correlates to cytokine driven inflammation [5]. In contrast, alternative hypotheses surrounding iron homeostasis also propose that dysregulated iron metabolism is a secondary late-stage feature of disease or its sequelae [3].

In short, Chronic myeloid leukemia (CML) is a chronic inflammatory disease driven by the constitutive activity of BCR-ABL1 oncoprotein. Alongside fueling dysregulated expansion of myeloid cells, this kinase drives synergistic secretion of cytokines and chemokines by both leukemic and niche populations within the bone marrow microenvironment [6]. This results in chronic, low-grade systemic inflammation. The release of intracellular components resulting from the fast turnover of malignant cells also plays a role in this environment [6], and one major component that is both released into circulation and observed as a solid tumor burden marker for epidermal malignancies is lactate dehydrogenase (LDH) which is arguably one of the most defined among circulating biomarkers linked to total tumor burden; often serving against immune inflammatory response [7]. Regarding LDH release in the future, it must be emphasized that aside from a marker of symptomless to effectively dying cells and its efflux coupled with DAMPs being involved in recruiting inflammatory signaling pathways. In conclusion, high levels of LDH are an applicable and basic marker both for the process of cell turnover as well as cytokine-induced inflammatory response. The truth of cell proliferation, protein solubilization and elevated lactate dehydrogenase levels underlines why inflammation is another significant pathophysiology that haunts chronic myeloid leukemia well behind the genomic oughts [8].

This pathophysiologic triad represents a key technical issue for the interpretation of hyperferritinemia in CML patients [29]. In these patient populations, it is easy to ascribe very high ferritin the most recognized biomarker for assessing iron excess seen in disease entities such as hereditary hemochromatosis [9] to similar pathophysiology. Clinicians could therefore inadvertently be driven against studies or instituted therapies directed at iron overload which is a rather uncommon complication of untreated (but not untreated) CML and fail to notice more likely inflammatory culprit [10, 11]. Such uncertainty, however, has direct implications with respect to patient management. Therapeutic approaches for iron overload and inflammatory anemia are markedly different [3]. Therefore, the unresolved question whether hyperferritinemia in CML patients is based only on inflammatory activity of tumor versus true overlap with iron storage disorder remains a diagnostic dilemma potentially affecting initial clinical evaluation and treatment strategy.

To clarify this diagnostic ambiguity, it is necessary to consider surrogate biomarkers that directly reflect the tumor's inflammatory burden. Lactate dehydrogenase (LDH), a widely expressed cytoplasmic enzyme, is released into the bloodstream following cell death or membrane damage. In the context of hematologic malignancies, elevated serum LDH has long been recognized as a reliable, albeit non-specific, marker indicating high tumor burden and increased cellular turnover [12, 13]. The level of LDH often correlates with the stage of disease, prognosis, and overall tumor lysis. Since the inflammatory state in chronic myeloid leukemia (CML) is directly proportional to the leukemic cell burden and activity, LDH serves as a practical, indirect marker of this underlying inflammatory drive. Therefore, examining the relationship between ferritin and LDH in CML provides a logical approach to ascertain whether ferritin elevation is more closely associated with this quantifiable inflammatory burden rather than static iron status indicators [7].

This pattern of discordant biomarkers is indicative of anemia of chronic disease (ACD), a condition characterized by functional iron deficiency. During inflammatory states, cytokines such as interleukin-6 (IL-6) stimulate hepatic production of hepcidin, which serves as the primary regulator of iron homeostasis [14]. Mechanistically, Elevated hepcidin binds to ferroportin, promoting its degradation and thereby inhibiting cellular iron export. This sequestration of iron within macrophages of the reticuloendothelial system and hepatocytes reduces plasma iron levels, impairing erythropoiesis and contributing to anemia [15]. Simultaneously, the sequestration of iron within storage cells contributes to increased ferritin synthesis. Additionally, inflammatory signals independently stimulate ferritin as a positive acute-phase reactant while simultaneously suppressing transferrin production, which is measured as total iron-binding capacity (TIBC). This coordinated response results in the biochemical triad characteristic of anemia of chronic disease (ACD), commonly seen in malignancies: elevated ferritin levels, reduced serum iron, and decreased TIBC, despite adequate or increased total iron stores [16].

This inherent ambiguity highlights a significant deficiency within the diagnostic toolkit for chronic myeloid leukemia (CML). The current biomarkers are often assessed independently, leading to potentially conflicting interpretations: elevated ferritin levels may indicate iron overload, whereas low iron and total iron-binding capacity (TIBC) are suggestive of inflammation [3]. More specific

inflammatory markers, such as interleukin-6 (IL-6) or hepcidin, are not routinely accessible in many clinical laboratories, thereby limiting their practical usefulness [17, 18]. The soluble transferrin receptor-ferritin index is a valuable diagnostic tool for distinguishing anemia of chronic disease from iron deficiency anemia, but its reliance on specialized, often costly assays limits widespread use. Therefore, developing a practical alternative is necessary. Consequently, there is an urgent requirement for a straightforward, cost-effective, and universally accessible instrument capable of integrating these conflicting signals. We suggest that simple ratios from common, cost-effective tests namely Iron/Ferritin and TIBC/Ferritin may serve as reliable markers. These ratios have shown promise in distinguishing iron overload from inflammatory hyperferritinemia across various inflammatory conditions, meriting further research in chronic myeloid contexts.

To address this diagnostic gap, the present study was systematically designed to identify the primary etiology of hyperferritinemia in a treatment-naïve cohort of chronic myeloid leukemia (CML) patients, hypothesizing that elevated ferritin levels at diagnosis are primarily attributable to tumor-associated inflammation rather than genuine iron overload. To evaluate this, correlations between ferritin levels and established inflammatory markers, such as lactate dehydrogenase (LDH), as well as traditional iron parameters, were examined. Additionally, the diagnostic efficacy of the easily calculable ratios Iron/Ferritin and TIBC/Ferritin for differentiating inflammation-induced hyperferritinemia from other etiologies was assessed, aiming to provide a practical, reliable tool for clinical decision-making at the point of care.

2. Materials and Methods

2.1. Study Design and Setting

This retrospective, single-center, cross-sectional study was conducted at the Oncology Teaching Hospital and the National Center of Hematology within the Baghdad Teaching Hospital (Medical City) in Baghdad. The retrospective cross-sectional design was chosen to efficiently analyze the relationships among ferritin, inflammatory markers, and iron parameters at diagnosis, without delaying urgent treatment. This method suits hypothesis generation about biomarkers in treatment-naïve patients, where prospective data collection would be logistically difficult and might hinder prompt clinical care. The investigation aimed to elucidate the dual factors contributing to elevated ferritin levels in chronic myeloid leukemia (CML) by analyzing its relationship with an inflammatory disease burden marker (LDH) and iron metabolism indicators (serum iron, TIBC). Notably, the study introduced the assessment of calculated ratios (Iron/Ferritin, TIBC/Ferritin) to distinguish whether hyperferritinemia in individual patients was predominantly due to inflammation or iron overload.

2.2. Study Population

The study included 90 consecutive adult patients (≥18 years) with a confirmed diagnosis of CML in chronic phase, defined by the World Health Organization (WHO) criteria and the presence of the Philadelphia chromosome or a BCR-ABL1 transcript [19], who presented to our center between 18-1-2024 and 18-1-2025. Patients were included if they had a complete set of laboratory parameters, including ferritin, LDH, iron, and total iron-binding capacity (TIBC), measured at the time of initial diagnosis prior to the initiation of any tyrosine kinase inhibitor (TKI) therapy or cytoreductive treatment.

a. Inclusion Criteria

Eligible participants were adults diagnosed with chronic-phase CML, confirmed by standard WHO criteria and verified by the presence of the Philadelphia chromosome or a BCR-ABL1 transcript. Participants were required to have complete baseline laboratory data, including ferritin, LDH, serum iron, and TIBC measurements, all obtained prior to any targeted or cytoreductive therapy. All participants were evaluated at the participating center within the designated one-year recruitment period.

b. Exclusion Criteria

Patients excluded from the study comprised individuals under 18 years of age, those diagnosed with chronic myeloid leukemia (CML) in accelerated or blast phase, and individuals lacking complete pre-treatment laboratory data. To reduce potential confounding factors impacting the primary biomarkers of interest, exclusion also applied to patients with known hereditary hemochromatosis, thalassemia major, or other primary iron overload disorders; those with chronic liver disease such as viral hepatitis or cirrhosis; individuals with active acute or chronic inflammatory conditions including rheumatoid arthritis or active infections; patients with stage 4 or 5 chronic kidney disease; and those with a recent history of blood transfusion within the past three months. Additionally, individuals on medications affecting iron metabolism such as regular iron supplements or causing significant hepatic inflammation, as well as patients who had undergone prior cytoreductive or tyrosine kinase inhibitor therapy for CML, were deemed ineligible.

2.3. Data Collection and Variables

Data were obtained from the institutional electronic medical record (EMR) system and a maintained hematology laboratory database by two trained research associates, M.K.A. and A.H.J., using a standardized electronic case report form. Both data abstractors received uniform training on the form and variable definitions, supported by a detailed data dictionary with explicit inclusion and exclusion criteria for each variable. Due to the retrospective design and reliance on objective laboratory data numerical values from automated analyzers blinding was unnecessary, as the data were free from subjective interpretation. An initial pilot assessment of inter-rater reliability on 10% of the sample (9 patients)

showed perfect concordance for all primary laboratory variables.

All laboratory analyses for both primary and additional parameters were conducted at the accredited central laboratories of the Oncology Teaching Hospital and the National Center of Hematology within Baghdad Teaching Hospital (Medical City), Baghdad, in accordance with standardized, quality-controlled procedures. Data collection employed a standardized questionnaire.

The specific methodologies used for each variable at the time of initial CML diagnosis are detailed below.

2.3.1. Primary Biomarkers

- Serum Ferritin (µg/L): The quantification was conducted employing a two-site sandwich chemiluminescent immunoassay (CLIA). At the Oncology Teaching Hospital, the Roche Cobas 6000 analyzer was employed for all patient analyses conducted at that facility, whereas at the National Center of Hematology, the Siemens ADVIA Centaur XP analyzer was utilized exclusively for patients from that institution. Both laboratories participate in the UK NEQAS external quality assessment scheme, thereby demonstrating their commitment to inter-instrument consistency and quality assurance. The assay measures the emitted light signal generated by an acridinium ester-labelled anti-ferritin antibody, which exhibits a direct correlation with ferritin levels [20].

- Lactate Dehydrogenase (LDH, U/L): The measurement was performed utilizing a standardized UV kinetic enzymatic assay in accordance with the guidelines set forth by the International Federation of Clinical Chemistry (IFCC) guidelines. The same analyzers specified above were used consistently for all patients at each site . LDH activity was assessed by monitoring the reduction in absorbance at 340 nm, which signifies the formation of NADH during the enzymatic conversion of pyruvate [21].

- Serum Iron (µg/dL): The iron content was determined using a colorimetric assay employing the ferrozine method. All assays were performed on the respective institutional platforms as noted above. Ferric ions (Fe^{3+}) were released from transferrin via an acidic buffer and subsequently reduced to ferrous ions (Fe^{2+}). These ferrous ions then formed a coloured complex with ferrozine, and the intensity of the complex was measured spectrophotometrically. The absorbance obtained was directly proportional to the iron concentration [22].

- Total Iron-Binding Capacity (TIBC, µg/dL): The serum transferrin concentration (mg/dL) was initially measured through an immunoturbidimetric assay employing antibodies specific to human transferrin. Subsequently, the total iron-binding capacity (TIBC) was derived using the formula: TIBC (µg/dL) = Transferrin (mg/dL) multiplied by 1.41, a constant representing the theoretical iron-binding capacity [23].

2.3.2. Derived Ratios

The Iron to Ferritin Ratio was determined retrospectively by dividing Serum Iron (µg/dL) by Serum Ferritin (µg/L). Similarly, the TIBC-to-Ferritin Ratio was calculated as TIBC (µg/dL) divided by Serum Ferritin (µg/L). To maintain consistency, all measurements were converted to µg/L prior to ratio calculation, with serum iron and TIBC values multiplied by 10. These adjustments ensured accuracy in the reported ratios, which reflect standardized unit measurements [24].

2.3.3. Additional Laboratory Parameters

Collected for descriptive and potential confounding analysis, the laboratory assessments included a Complete Blood Count (CBC) analyzed via an automated hematology analyzer (Sysmex or Abbott Cell-Dyn series), employing impedance, light scatter, and fluorescence flow cytometry principles [25]; Vitamin B12 and Folate levels measured through competitive bidding chemiluminescent immunoassays [26]; 25-Hydroxy Vitamin D3 quantified using a competitive chemiluminescent immunoassay [27]; renal function was evaluated by blood urea, analyzed with an enzymatic urease method, and serum creatinine was measured via the modified Jaffe kinetic method [28]; liver function tests included measurements of alanine transaminase (ALT/GPT) and aspartate transaminase (AST/GOT) through optimized UV kinetic methods according to IFCC standards [29], as well as alkaline phosphatase (ALP), using a kinetic colorimetric method with p-nitrophenyl phosphate as substrate [30]; electrolytes such as potassium are assessed by an indirect ion-selective electrode (ISE) [31].

2.4. Ethical Considerations

The study protocol received approval from the Institutional Review Board and Ethics Committee of the University of Kirkuk, College of Education for Pure Sciences (No. 38 C in 5/2/2026). This approval ensured adherence to the ethical standards outlined in the Declaration of Helsinki. Given the retrospective design, which used pre-existing, anonymized data, the IRB waived the requirement for individual informed consent.

2.5. Statistical Analysis

Data analysis was performed using SPSS Software (version 20). Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed variables or median and interquartile range (IQR) for non-normal data. The Shapiro-Wilk test assessed normality. Based on preliminary data indicating a moderate correlation ($\rho = 0.30$) between ferritin and LDH, a sample size of at least 84 patients was calculated to achieve 80% power at $\alpha = 0.05$ (two-tailed). The study's enrollment of 90 patients ensures sufficient power for primary and subgroup analyses.

Spearman's rank correlation coefficient (ρ) evaluated associations between non-normally distributed primary biomarkers. A multiple linear regression model, with log10-transformed ferritin as the dependent variable, examined the independent effects of LDH, serum iron, and TIBC. Multicollinearity was evaluated using the Variance Inflation Factor (VIF), with values below 2.0 deemed acceptable. Model assumptions were verified

via residual diagnostics. The median LDH level of 269.2 U/L was selected for stratification due to several reasons. First, LDH serves as a validated, continuous indicator of tumor burden in CML, although no universal clinical cutoff exists. Second, utilizing a median split is a common exploratory approach when no established thresholds are available. Third, this method maintains balanced group sizes for meaningful statistical analysis. Lastly, it is hypothesis-generating, with the proposed ratio cutoffs serving as preliminary thresholds to be validated in independent cohorts.

Patients were stratified by median LDH, and the Mann-Whitney U test compared the Iron/Ferritin and TIBC/Ferritin ratios between high- and low-burden groups. Subgroup analyses of ferritin-LDH correlations were conducted based on hematologic and metabolic parameters. The inclusion criteria required complete laboratory data for all primary variables, including ferritin, LDH, iron, and TIBC. As a result, the analyzed cohort exhibited no missing data for these key variables. For secondary variables, any occasional missing values were addressed through pairwise deletion. Statistical significance was assessed at a two-tailed p-value threshold of less than 0.05 [32].

3. Results

3.1. Demographic and Clinicopathological Characteristics of the Study Cohort

The study comprised ninety participants with an average age of 48.6 years (standard deviation [SD] = 12.3 years). The gender distribution was approximately balanced, including forty-six males (51.1%) and forty-four females (48.9%). The cohort exhibited significant alterations in primary biomarkers. Serum ferritin was markedly elevated, with a median of 339.5 µg/L (interquartile range [IQR]: 201.6–398.5), and 92.2% of patients exceeded the upper reference limit (URL) of 200 µg/L. Lactate dehydrogenase (LDH) levels also showed elevation, with a median of 269.2 U/L (IQR: 199.5–322.2), and 78.9% of patients had LDH values above the URL of 225 U/L. Conversely, serum iron was reduced, with a median of 15.2 µg/dL (IQR: 13.2–17.9), and 97.8% of patients fell below the lower reference limit (LRL) of 50 µg/dL. Total iron-binding capacity (TIBC) was similarly decreased, with a median of 57.9 µg/dL (IQR: 52.6–69.4), and 98.9% below the LRL of 250 µg/dL. These findings highlight significant disruptions in iron metabolism within the cohort.

Hematologic parameters were consistent with chronic-phase CML. The mean white blood cell (WBC) count was $85.4 \pm 42.3 \times 10^3/\mu L$, with 89 patients (98.9%) having WBC above the URL of $11.0 \times 10^3/\mu L$. The mean hemoglobin level was 10.8 ± 1.9 g/dL, with 68 patients (75.6%) having hemoglobin below the LRL of 12.0 g/dL (females) or 13.5 g/dL (males). The mean platelet count was $455 \pm 210 \times 10^3/\mu L$, with 62 patients (68.9%) having platelets above the URL of $400 \times 10^3/\mu L$.

Regarding metabolic and organ function parameters, vitamin B12 levels were within the normal range, with a median of 553.9 pg/mL and an interquartile range of 415.6 to 749.5. Vitamin D insufficiency or deficiency, defined as 25-Hydroxy Vitamin D_3 levels below 30 ng/mL, was identified in 75.6% of patients. Liver enzyme assessments showed predominantly normal values, although 24.4% exhibited elevated aspartate aminotransferase (AST > 40 U/L), and 20.0% had elevated alanine aminotransferase (ALT > 40 U/L). Renal function, as measured by serum creatinine, was generally preserved, with 87.8% of patients presenting with levels ≤1.2 mg/dL. Potassium levels were notably elevated, with a median of 5.7 mmol/L and 75.6% exceeding the upper reference limit of 5.0 mmol/L. Leukocytosis, with a mean white blood cell count of $85.4 \times 10^3/\mu L$, raises the possibility of pseudohyperkalemia due to in vitro cell lysis. Table 1 details the demographic and clinical characteristics (Table 1).

3.2. Ferritin Dynamics: Correlation with Inflammatory and Iron Status Biomarkers:

The four principal biomarkers serum ferritin, LDH, serum iron, and TIBC demonstrated significant departures from a normal distribution, as evidenced by the Shapiro-Wilk test ($p < 0.001$ for all). Consequently, non-parametric statistical methods were employed for subsequent analysis. Serum ferritin levels varied widely, ranging from 22.3 to 3,219.5 µg/L, with a median value of 339.5 µg/L and an interquartile range (IQR) of 201.6 to 398.5. Lactate dehydrogenase (LDH) levels also exhibited considerable variability, spanning from 120.3 to 572.5 U/L, with a median of 269.2 U/L (IQR: 199.5–322.2). Serum iron concentrations ranged from 5.2 to 35.6 µg/dL, with a median of 15.2 µg/dL (IQR: 13.2–17.9). Total iron-binding capacity (TIBC) values extended from 28.5 to 112.5 µg/dL, with a median of 57.9 µg/dL (IQR: 52.6–69.4). Spearman's rank correlation analysis identified a statistically significant positive association between serum ferritin and LDH levels ($\rho = 0.52$, $p < 0.001$). Conversely, serum ferritin demonstrated a weak, non-significant positive correlation with serum iron ($\rho = 0.18$, $p = 0.089$) and a very weak, non-significant inverse correlation with TIBC ($\rho = -0.12$, $p = 0.260$). Table 2 summarizes the distribution and correlation matrix of key biomarkers, while Figure 1 depicts the scatter plot of ferritin versus LDH, overlaid with a LOESS trend line.

3.3. Multiple Regression Analysis

A multiple linear regression analysis was conducted to evaluate the independent associations of lactate dehydrogenase (LDH), serum iron, and total iron-binding capacity (TIBC) with ferritin levels. Due to the skewed distribution of ferritin, the dependent variable was log10-transformed. Diagnostic assessments, including a normal P-P plot and a scatterplot of standardized residuals against predicted values, confirmed that the assumptions of linearity, homoscedasticity, and normality of residuals were met. Multicollinearity was examined via the Variance Inflation Factor (VIF), with all predictors demonstrating VIF values below 2.0 (LDH: 1.12, serum iron: 1.08, TIBC: 1.15), indicating minimal collinearity (Table 3).

Table 1. The Demographic and Clinicopathological Profile of the Study Cohort

Characteristic	Cohort Median [IQR] or Mean ± SD	Reference Value (Midpoint or Mean) [1]	p-value	Clinical Interpretation
Demographic				
Age (years)	48.6 ± 12.3	-	-	-
Primary Biomarkers				
Serum Ferritin (µg/L)	339.5 [201.6 – 398.5]	120	<0.001	Markedly elevated. Consistent with hyperferritinemia.
LDH (U/L)	269.2 [199.5 – 322.2]	172.5	<0.001	Significantly elevated. Indicates high tumor burden/inflammation.
Serum Iron (µg/dL)	15.2 [13.2 – 17.9]	120	<0.001	Markedly depleted. Suggests anemia of chronic disease/inflammation.
TIBC (µg/dL)	57.9 [52.6 – 69.4]	337.5	<0.001	Severely reduced. Characteristic of chronic inflammation.
Hematologic Parameters				
Hemoglobin (g/dL)	10.8 ± 1.9	14.5	<0.001	Significantly reduced. Indicative of anemia.
White Blood Cells (x10³/µL)	85.4 ± 42.3	7.5	<0.001	Profoundly elevated. Hallmark of CML in chronic phase.
Platelets (x10³/µL)	455 ± 210	300	<0.001	Significantly elevated. Common in CML.
Metabolic & Organ Function				
Vitamin B12 (pg/mL)	553.9 [415.6 – 749.5]	550	0.721	Within normal range.
25-Hydroxy Vitamin D3 (ng/mL)	28.6 [18.5 – 39.2]	65.02	<0.001	Significantly reduced. High prevalence of insufficiency/deficiency.
Serum Creatinine (mg/dL)	0.83 [0.66 – 0.93]	0.9	0.089	Within normal range.
ALT (GPT) (U/L)	27.8 [19.5 – 34.5]	31.5	0.052	Within normal range.
AST (GOT) (U/L)	28.5 [24.6 – 34.6]	22.5	<0.001	Mildly but significantly elevated.
Potassium (K) (mmol/L)	5.7 [5.4 – 6.1]	4.3	<0.001	Significantly elevated. May be related to cell turnover.

[1] The midpoint of the standard reference range served as the comparator for all laboratory parameters, 2 The reference midpoint for 25-Hydroxy Vitamin D3 represents the midpoint of the laboratory reference range (30–100 ng/mL), with sufficiency defined as >30 ng/mL. Statistical analyses included the one-sample Wilcoxon signed-rank test for all non-normally distributed biomarkers, which are reported as Median [Interquartile Range]. For normally distributed parameters, such as Age, Hb, WBC, and Platelets, the one-sample t-test was employed, with results expressed as Mean ± Standard Deviation. IQR: Interquartile Range, SD: Standard Deviation, TIBC: Total Iron-Binding Capacity.

The regression model demonstrated statistical significance ($F(3, 86) = 15.8$, $p < 0.001$), with an adjusted R^2 of 0.33, suggesting that the three predictors collectively accounted for 33% of the variability in log10-transformed ferritin levels. Among these, LDH was identified as a significant independent predictor ($\beta = 0.56$, 95% CI: 0.0013–0.0029, $p < 0.001$). Serum iron and TIBC were not significant predictors after controlling for LDH. Refer to Table 3 for further details.

3.4. Iron/Ferritin and TIBC/Ferritin Ratios Stratified by Disease Burden

To investigate the relationship between tumor burden and the proposed ratios, patients were divided into two groups based on the median LDH level (269.2 U/L) as an exploratory method: a high LDH group (≥269.2 U/L, n = 45) and a low LDH group (<269.2 U/L, n = 45).

The ratio of Iron to Ferritin was markedly reduced in the cohort with elevated LDH levels (median: 0.038, interquartile range: 0.030–0.052) compared to the group with lower LDH levels (median: 0.068, interquartile range: 0.048–0.105; Mann-Whitney U test, $p < 0.001$). Similarly, the TIBC to Ferritin ratio was significantly decreased in the high LDH group (median: 0.150, IQR: 0.115–0.185) relative to the low LDH group (median: 0.295, IQR: 0.201–0.422; $p < 0.001$). Table 4 summarizes the ratio analysis, and Figure 2 presents boxplots of the distributions of both ratios stratified by LDH group.

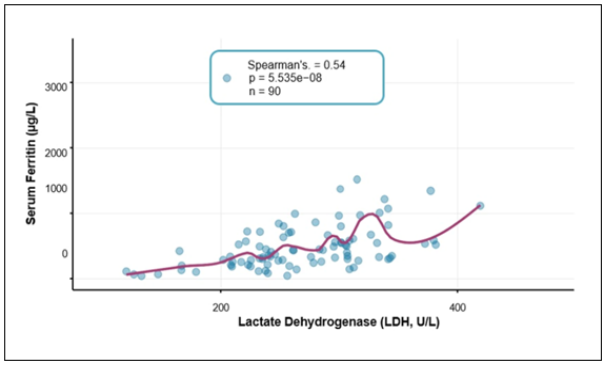

Figure 1. Scatter Plot of Serum Ferritin vs. Lactate Dehydrogenase (LDH) with Spearman's Correlation. The solid line represents the locally estimated scatterplot smoothing (LOESS) trend.)

3.5. Robustness of the Ferritin-Inflammation Association Across Hematologic Subgroups

To evaluate the consistency of the ferritin-LDH correlation across various hematologic presentations, subgroup analyses were conducted based on hemoglobin (Hb) and white blood cell (WBC) counts. These analyses are exploratory and were not adjusted for multiple

Table 2. Distribution and Correlation of Primary Biomarkers in Newly Diagnosed CML Patients (n=90)

Biomarker (Unit)	Distribution (Median [IQR] or Range)	Shapiro-Wilk Test (p-value)[1]	Correlation with Ferritin (Spearman's ρ)[2]	p-value (ρ)[3]	Interpretation of Correlation
Serum Ferritin (µg/L)	339.5 [201.6–398.5] (Range: 22.3–3219.5)	<0.001	–	–	–
LDH (U/L)	269.2 [199.5–322.2] (Range: 120.3–572.5)	<0.001	0.52	<0.001	Moderate positive correlation
Serum Iron (µg/dL)	15.2 [13.2–17.9]	<0.001	0.18	0.089	Weak, non-significant
TIBC (µg/dL)	57.9 [52.6–69.4]	<0.001	-0.12	0.26	Very weak, non-significant

IQR, interquartile range; LDH, lactate dehydrogenase; TIBC, total iron-binding capacity; CML, chronic myeloid leukemia. [1] All biomarkers demonstrated non-normal distribution according to the Shapiro–Wilk test ($p < 0.001$), thereby justifying the application of non-parametric Spearman's rank correlation. [2] Correlation strength was categorized as follows: $|\rho| = 0.00–0.19$ very weak; 0.20–0.39 weak; 0.40–0.59 moderate; 0.60–0.79 strong; 0.80–1.00 very strong. [3] A significant positive correlation was observed between ferritin and LDH ($\rho = 0.52$, $p < 0.001$), indicating that approximately 27% of the variance in ferritin levels may be attributable to tumor burden or inflammatory activity.

comparisons; thus, the results should be interpreted with caution, especially in subgroups with small sample sizes.

Patients were classified according to anemia severity: mild/moderate (hemoglobin ≥ 10 g/dL, n = 58) and severe (hemoglobin < 10 g/dL, n = 32). A significant correlation was observed between ferritin and lactate dehydrogenase in both groups, with a stronger association in the severe anemia subgroup (rho = 0.63, $p < 0.001$) compared to the mild/moderate group (rho = 0.48, $p < 0.001$).

Patients were further classified by leukocytosis severity: moderate (WBC < 100 × 10^3/µL, n = 62) and extreme (WBC> 100 × 10^3/µL, n = 28). A significant correlation between ferritin and LDH levels was observed in both groups, with a Spearman's rho of 0.51 ($p < 0.001$) in the moderate group and 0.58 ($p < 0.001$) in the extreme group. Table 5 summarizes the subgroup analyses by hematologic parameters.

3.6. Correlation of Serum Ferritin with LDH Across Patient Subgroups Stratified by Metabolic and Hepato-Renal Function

To evaluate potential modifications in the ferritin-LDH relationship due to metabolic or organ function, subgroup analyses were conducted based on vitamin D levels, liver enzymes, and renal function. These unadjusted findings from small samples should be approached with caution.

Patients were classified by vitamin D level: deficient/insufficient (<30 ng/mL, n=68) or sufficient (≥30 ng/mL, n=22). A significant positive correlation between ferritin and LDH was observed in both groups: ρ=0.58 (p<0.001) in the deficient/insufficient group and ρ=0.49 (p=0.008) in the sufficient group.

Patients were classified based on liver enzyme levels: elevated (AST > 40 U/L or ALT > 40 U/L, n=18) and normal (AST ≤ 40 U/L and ALT ≤ 40 U/L, n=72). A significant correlation between ferritin and LDH was observed in both groups, with a Spearman's rho of 0.61 ($p < 0.001$) in the elevated group and 0.50 ($p < 0.001$) in the normal group.

Patients were classified by renal function: impaired (serum creatinine > 1.2 mg/dL, n = 11) or normal (serum creatinine ≤ 1.2 mg/dL, n = 79). The correlation between ferritin and LDH was statistically significant in both groups, with a correlation coefficient of 0.46 ($p = 0.011$) in the impaired renal function group and 0.54 ($p < 0.001$) in the normal renal function group. Table 6 summarizes these subgroup analyses.

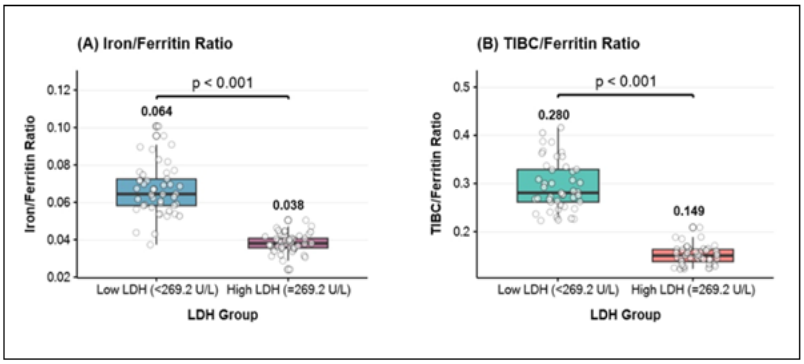

Figure 2. Diagnostic Ratios Stratified by LDH Group in Treatment-Naïve Chronic Myeloid Leukemia (CML) Patients. (Iron/Ferritin and (B) TIBC/Ferritin ratios were assessed in a cohort of 90 newly diagnosed, treatment-naïve chronic myeloid leukemia (CML) patients. These patients were stratified based on the median lactate dehydrogenase (LDH) level of 269.2 U/L. Patients with elevated LDH levels (≥269.2 U/L; n=45) demonstrated significantly lower median ratios for both Iron/Ferritin (0.038 versus 0.068) and TIBC/Ferritin (0.150 versus 0.295) compared to those with lower LDH levels (<269.2 U/L; n=45). Mann-Whitney U tests yielded p-values < 0.001 for both comparisons. Boxplots illustrate the median (central line), interquartile range (box), range (whiskers), and individual patient data points (dots). The diminished ratios observed in high-LDH patients suggest inflammation-driven alterations in iron metabolism, implying that hyperferritinemia in untreated CML predominantly stems from tumor-associated inflammation rather than iron overload. These straightforward, calculable ratios offer a pragmatic diagnostic approach for differentiating inflammatory hyperferritinemia from iron overload in CML.

Table 3. Multiple Linear Regression Model for Log10 (Serum Ferritin)

Predictor Variable	Unstandardized Beta (B)	Standard Error	Standardized Beta (β)	t-value	p-value
(Intercept)	1.452	0.205	-	7.08	<0.001
LDH (U/L)	0.0021	0.0004	0.56	5.25	<0.001
Serum Iron (μg/dL)	0.008	0.006	0.115	1.33	0.187
TIBC (μg/dL)	-0.003	0.003	-0.085	-1.01	0.315

A multiple linear regression analysis was conducted, with $\log_{10}$-transformed serum ferritin as the dependent variable to account for skewness. Diagnostic tests confirmed that the assumptions of linearity, homoscedasticity, and normality of residuals were met. The overall model was statistically significant ($F(3, 86) = 15.8$, $p < 0.001$), with an adjusted R^2 of 0.33, suggesting that approximately 33% of the variance in ferritin levels could be explained by the predictors included. Among these, lactate dehydrogenase (LDH) emerged as the sole significant independent predictor. The standardized beta (β) coefficients illustrate the relative predictive strength of each variable. LDH, lactate dehydrogenase; TIBC, total iron-binding capacity.

Table 4. Proposed Diagnostic Ratios Categorized by LDH Group

Ratio	LDH Group	n	Median Ratio [IQR]	Mann–Whitney U Test (p-value)	Interpretation
Iron/Ferritin	High LDH (≥ 269.2 U/L)	45	0.038 [0.030 – 0.052]	< 0.001	The ratio is significantly lower in the high-LDH group, indicating inflammation-driven hyperferritinemia.
	Low LDH (< 269.2 U/L)	45	0.068 [0.048 – 0.105]		
TIBC/Ferritin	High LDH (≥ 269.2 U/L)	45	0.150 [0.115 – 0.185]	< 0.001	Ratio is significantly lower in the high LDH group, consistent with biochemical features of chronic inflammation.
	Low LDH (< 269.2 U/L)	45	0.295 [0.201 – 0.422]		

Stratification was conducted based on the median lactate dehydrogenase (LDH) level of 269.2 U/L within the cohort. The statistical analysis used the Mann–Whitney U test, a nonparametric test. A significance threshold was set at a two-tailed p-value of less than 0.001. Clinically, lower ratios in the high LDH group indicate that inflammation predominantly influences ferritin elevation rather than iron status in patients with newly diagnosed chronic myeloid leukemia (CML).

4. Discussion

This study systematically investigates the dual factors influencing ferritin elevation in a well-defined cohort of 90 treatment-naïve patients with chronic-phase CML. The findings reveal a moderate positive correlation between serum ferritin and LDH ($\rho = 0.52$, $p < 0.001$), while no significant associations were observed with traditional iron parameters such as serum iron and TIBC. Multiple regression analysis identified LDH as the sole independent predictor of ferritin levels ($\beta = 0.56$, $p < 0.001$). Additionally, patients with higher LDH levels exhibited significantly lower Iron/Ferritin and TIBC/Ferritin ratios ($p < 0.001$). These results suggest that hyperferritinemia in untreated CML may reflect tumor-related inflammation rather than iron overload, though causality cannot be confirmed given the observational study design.

The biochemical profile demonstrates elevated ferritin levels, reduced serum iron, and decreased TIBC, consistent with the characteristic pattern of anemia of chronic disease [33, 34]. However, this study indicates an association but does not confirm the underlying mechanism, as it lacks direct measurements of inflammatory markers [4]. The correlation analyses revealed a moderate positive association between ferritin and LDH ($\rho = 0.52$), indicating Approximately 27% of ferritin variability covaries with this cellular turnover marker [7]. Although the correlation coefficient was statistically significant, its moderate strength indicates that additional unmeasured factors likely influence ferritin levels. The weak, non-significant correlations with serum iron ($\rho = 0.18$, $p = 0.089$) and TIBC ($\rho = -0.12$, $p = 0.260$) further suggest that ferritin elevation may be more related to inflammatory processes than iron status, though residual confounding cannot be excluded [35].

The multiple regression analysis revealed that LDH was the sole significant independent predictor of log10-transformed ferritin levels ($\beta = 0.56$, $p < 0.001$), with serum iron and TIBC offering no additional explanatory benefit. The model accounted for 33% of the variance in ferritin (adjusted $R^2 = 0.33$). This suggests LDH's relevance but also highlights the complexity of ferritin regulation, indicating that other factors contribute to its variability beyond those included in the model [36, 37]. These findings warrant careful interpretation given the observational design and potential unmeasured confounders.

The study revealed that the ratios of Iron to Ferritin and TIBC to Ferritin significantly differed between patient groups distinguished by median LDH levels. Patients with LDH levels of 269.2 U/L or higher exhibited a median Iron/Ferritin ratio of 0.038, compared to 0.068 in those with lower LDH levels ($p < 0.001$). Similarly, the median TIBC/Ferritin ratio was 0.150, compared with 0.295 ($p < 0.001$). However, these findings are exploratory; no definitive clinical LDH cutoff exists. Further validation with receiver operating characteristic analysis is necessary to establish reliable cutoff values and assess the diagnostic

Table 5. Subgroup Analysis of Ferritin–LDH Correlation Stratified by Hematologic Parameters

Subgroup	n	Median Ferritin (µg/L) [IQR]	Median LDH (U/L) [IQR]	Spearman's ρ (Ferritin vs. LDH)	p-value	Interpretation
All Patients	90	339.5 [201.6–398.5]	269.2 [199.5–322.2]	0.52	<0.001	Moderate correlation
By Hemoglobin (Hb):						
Hb ≥ 10 g/dL	58	315.2 [195.4–385.6]	245.8 [185.4–305.7]	0.48	<0.001	Moderate correlation
Hb < 10 g/dL	32	398.8 [255.6–455.2]	312.5 [245.6–378.9]	0.63	<0.001	Strong correlation
By WBC Count:						
WBC < 100 x10³/µL	62	305.6 [189.5–376.8]	238.5 [185.2–298.4]	0.51	<0.001	Moderate correlation
WBC ≥ 100 x10³/µL	28	422.3 [265.8–488.5]	345.6 [278.9–412.3]	0.58	<0.001	Moderate–strong correlation

IQR, interquartile range; LDH, lactate dehydrogenase; WBC, white blood cells. Subgroup correlations remained significant ($p < 0.01$), reinforcing the robustness of the ferritin–inflammation association in CML.

Table 6. Subgroup Analysis of Ferritin–LDH Correlation Stratified by Metabolic & Organ Function Parameters

Subgroup	n	Median Ferritin (µg/L) [IQR]	Median LDH (U/L) [IQR]	Spearman's ρ (Ferritin vs. LDH)	p-value	Interpretation
All Patients	90	339.5 [201.6–398.5]	269.2 [199.5–322.2]	0.52	<0.001	Moderate correlation
By Vitamin D Status:						
Deficient/Insufficient (< 30 ng/mL)	68	355.2 [215.4–412.3]	285.6 [215.8–345.2]	0.58	<0.001	Moderate–strong correlation
Sufficient (≥ 30 ng/mL)	22	298.4 [185.2–365.8]	235.4 [178.9–295.6]	0.49	0.008	Moderate correlation
By Liver Enzymes:						
Elevated (AST > 40 or ALT > 40 U/L)	18	412.8 [268.5–488.9]	335.4 [265.8–398.7]	0.61	<0.001	Strong correlation
Normal (AST ≤ 40 and ALT ≤ 40 U/L)	72	325.6 [198.5–385.4]	255.8 [195.6–305.9]	0.5	<0.001	Moderate correlation
By Renal Function:						
Impaired (Creatinine > 1.2 mg/dL)	11	385.6 [245.8–456.3]	305.2 [245.6–365.8]	0.46	0.011	Moderate correlation
Normal (Creatinine ≤ 1.2 mg/dL)	79	332.4 [198.7–392.1]	265.4 [198.5–315.6]	0.54	<0.001	Moderate correlation

The interquartile range (IQR), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were analyzed. All subgroup correlations remained statistically significant ($p < 0.05$), thereby affirming the robustness of the association between ferritin and inflammation across variations in metabolic or organ function status.

utility of these ratios [24]. Third, the thresholds for Iron/Ferritin < 0.04 and TIBC/Ferritin < 0.17 are based on this cohort's interquartile ranges and may not be applicable to other populations. External validation in independent cohorts is thus imperative prior to clinical implementation.

The utility of these ratios is grounded in their derivation from standard laboratory tests ferritin, iron, TIBC that are routinely accessible. This offers a practical advantage over specialized assays such as soluble transferrin receptor or hepcidin, which are less widely available [17, 18, 38]. However, this pragmatic benefit does not replace the need for thorough diagnostic validation [39]. Currently, these ratios serve as preliminary research tools and need further study before being used as clinical diagnostics.

During inflammatory states, as evidenced by elevated LDH levels, ferritin production is enhanced as an acute-phase reactant, leading to elevated serum ferritin concentrations [2, 40]. Concurrently, functional iron deficiency arises from cytokine-induced increases in hepcidin levels, which lead to iron sequestration and suppression of transferrin (TIBC) synthesis [40, 41]. Consequently, both iron and TIBC levels may be reduced while ferritin levels remain elevated. However, it should be noted that this mechanistic pathway was not directly evaluated in the current study, as hepcidin and cytokine measurements were not conducted.

The subgroup analyses confirmed that the ferritin-LDH correlation remained statistically significant across diverse hematologic, metabolic, and organ function subgroups, with correlation coefficients ranging from 0.46 to 0.63. However, certain limitations of these subgroup analyses should be considered [42]. These analyses were exploratory and unplanned, without adjustments for multiple comparisons, which increases the likelihood of Type I errors. Additionally, subgroup sample sizes were limited, notably in categories such as impaired renal

function (n=11) and elevated liver enzymes (n=18), resulting in less reliable estimates. The cross-sectional design restricts the ability to determine if the observed relationships change over time or with treatment. Furthermore, the elevated potassium levels (median 5.7 mmol/L) might be due to pseudohyperkalemia caused by in vitro leukocyte lysis rather than a true metabolic abnormality, though this cannot be confirmed with the current data [37].

This study has notable limitations. Its cross-sectional, observational design precludes causal inference, and the small, single-center sample of 90 Iraqi patients limits its broader applicability. The absence of inflammatory markers such as IL-6, hepcidin, and CRP weakens the evidence for the inflammatory hypothesis. Lack of diagnostic validation restricts clinical use of proposed ratios. Unmeasured confounders, dual laboratory platforms, and exclusion of comorbidities further constrain generalizability and accuracy, emphasizing the need for future prospective validation. Despite certain limitations, this study offers preliminary evidence indicating that in treatment-naïve CML patients, hyperferritinemia is more likely associated with tumor-related inflammation than iron overload. Future research should validate the potential of simple ratios for clinical differentiation. Future research should validate these findings in larger, diverse populations; include prospective studies with inflammatory markers; establish cutoff values via ROC analysis; examine changes during therapy; assess predictive value for outcomes; and compare with iron overload cases, pending further validation.

In conclusion, interpreting hyperferritinemia in chronic myeloid leukemia patients remains complex, given ferritin's dual indication of inflammatory activity or true iron overload. This study systematically investigates these roles within a well-defined, treatment-naïve CML cohort.

Our findings suggest that in newly diagnosed, untreated CML patients, elevated ferritin levels predominantly reflect tumor-associated inflammation rather than iron overload. The independent correlation between ferritin and lactate dehydrogenase (LDH), an indicator of cellular activity, alongside patterns of functional iron deficiency characterized by low serum iron and TIBC supports this interpretation. The utilization of ratios such as Iron/Ferritin and TIBC/Ferritin provided a practical means to distinguish patients with varying inflammatory burdens, indicating their potential usefulness as simple tools for identifying inflammation-driven hyperferritinemia. The consistent relationship between ferritin and LDH across patient subgroups further underscores the pivotal role of inflammation.

This study highlights an association rather than causation, with a cross-sectional design and absent ROC validation for the proposed ratios representing notable limitations. The findings should generate hypotheses for future investigation. Subsequent research must validate ferritin-based ratios in larger, prospective, multi-center cohorts with diverse populations, including direct inflammatory markers like IL-6 and hepcidin. Employing ROC analysis will help establish reliable cutoff values, ultimately elucidating the diagnostic and prognostic potential of these ratios in chronic myeloid leukemia management.

Author Contributions

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Conflicts of interest

The authors state that they have no conflicts of interest.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors specify that they did not use any generative AI or AI-assisted tools in this work.

Abbreviations

ACD: Anemia of Chronic Disease. ALP: Alkaline Phosphatase. ALT: Alanine Aminotransferase. AST: Aspartate Aminotransferase. BMP: Bone Morphogenetic Protein. CBC: Complete Blood Count. CKD: Chronic Kidney Disease. CLIA: Chemiluminescent Immunoassay. CML: Chronic Myeloid Leukemia. EMR: Electronic Medical Record. GPT: Glutamate-Pyruvate Transaminase (synonym for ALT). GOT: Glutamate-Oxaloacetate Transaminase (synonym for AST). Hb: Hemoglobin. IFCC: International Federation of Clinical Chemistry. IL-6: Interleukin-6. IQR: Interquartile Range. IRB: Institutional Review Board. ISE: Ion-Selective Electrode. LDH: Lactate Dehydrogenase. MPO: Myeloperoxidase. SD: Standard Deviation. TIBC: Total Iron-Binding Capacity. TKI: Tyrosine Kinase Inhibitor. WBC: White Blood Cell (Count). WHO: World Health Organization.

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