The Electrolyte Storm as an Early Indicator of Cytokine Release and Tumor Lysis in Treatment-Naïve Chronic Myeloid Leukemia: A Retrospective Correlative Analysis

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Abstract

Background: In treatment-naïve chronic-phase chronic myeloid leukemia (CML), subclinical cytokine release and tumor lysis may precede overt metabolic complications, yet early, accessible biomarkers remain undefined. **Objective**: To determine whether concurrent hyponatremia and hyperkalemia—termed "Electrolyte Storm"—are independently associated with inflammatory (ferritin, IL-6) and lytic (LDH, blood urea) markers after adjusting for renal function. **Patients and Methods**: This retrospective correlational study included 150 treatment-naïve adults with chronic-phase CML. Hyponatremia (Na^+ <135 mmol/L), hyperkalemia (K^+ >5.2 mmol/L), and Electrolyte Storm (both) were predefined. IL-6, IL-1β, and antidiuretic hormone were measured. Multivariate regression, Spearman correlations, and sensitivity analysis (excluding creatinine >1.2 mg/dL) were applied. **Results**: Hyponatremia occurred in 32.0% (48/150), hyperkalemia in 44.7% (67/150), and Electrolyte Storm in 18.0% (27/150). Sodium correlated inversely with ferritin ($\rho = -0.52$, $p<0.001$) and IL-6 ($\rho = -0.48$, $p<0.001$). Potassium correlated positively with LDH ($\beta = 0.49$, $p<0.001$) and blood urea ($\beta = 0.31$, $p<0.001$), but not with creatinine ($p=0.38$). The Electrolyte Storm group showed markedly higher LDH (378.5 vs. 264.2 U/L), ferritin (498.5 vs. 312.3 ng/mL), and IL-1β (12.3 vs. 5.6 pg/mL) (all $p<0.01$). All associations remained significant after excluding patients with renal impairment (n=130). **Conclusion**: The Electrolyte Storm phenotype serves as an early, low-cost surrogate for underlying cytokine release and tumor lysis in untreated CML, independent of kidney dysfunction. Clinically, hyponatremia should raise suspicion of paraneoplastic inflammation rather than simple volume depletion, while disproportionate hyperkalemia signals high lytic burden. Routine electrolyte panels may aid in risk stratification before initiating tyrosine kinase inhibitors**.**

Keywords: Chronic myeloid leukemia; electrolyte storm; hyponatremia; hyperkalemia; cytokine release syndrome; tumor lysis syndrome; ferritin; lactate dehydrogenase.

1. Introduction

Chronic myeloid leukemia (CML) accounts for approximately 15% of adult leukemias, with an annual global incidence of one to two cases per 100,000 population. The disease typically follows a triphasic course, beginning with an indolent chronic phase that may last years before progressing to the accelerated phase and blast crisis **(1)**. Although the chronic phase is traditionally considered clinically benign with only modest metabolic abnormalities, emerging evidence indicates that even at this stage, low-grade cytokine release and spontaneous cellular breakdown occur without overt symptoms. These subclinical processes may predispose patients to unexpected electrolyte and metabolic complications prior to any therapeutic intervention, particularly before initiating tyrosine kinase inhibitor (TKI) therapy, the current standard of care **(2).** Recognizing these silent perturbations has meaningful implications for early risk stratification and preemptive supportive care.

Before disease-modifying treatment, untreated CML harbors two biologically significant yet clinically silent mechanisms. First, paraneoplastic inflammation arises from uncontrolled proliferation of myeloid progenitors, followed by the activation of innate and adaptive immune responses. Second, spontaneous tumor lysis results from rapid granulocyte turnover and release of intracellular contents into the extracellular space. These processes frequently evade detection on routine physical examination and standard laboratory tests, yet they subtly alter organ homeostasis—particularly renal function, fluid balance, and electrolyte equilibrium **(3, 4) .** Understanding their interaction is critical for clinicians managing newly diagnosed CML. Moreover, identifying patients with heightened inflammatory or lytic activity before TKI initiation could guide preemptive hydration, urate-lowering strategies, and intensified monitoring, thereby reducing early treatment-related complications.

Current biomarkers for detecting subclinical metabolic disturbances in CML have notable limitations. Isolated measurements of serum uric acid, lactate dehydrogenase (LDH), or routine renal function tests lack sufficient sensitivity or specificity to reliably identify patients at risk for impending cytokine release syndrome or tumor lysis syndrome **(5, 6) .** Conventional assays also fail to distinguish electrolyte shifts driven by inflammation from those driven by primary renal dysfunction, leaving a critical gap in pre-treatment risk assessment. LDH, although useful as a general marker of cell turnover, does not differentiate lytic activity from other causes of cellular injury. Similarly, ferritin—an acute-phase reactant—is often elevated in various inflammatory states but is rarely measured routinely at the time of CML diagnosis. The absence of a simple, low-cost, readily accessible biomarker panel means many patients with substantial subclinical pathology may be misclassified as low-risk, only to develop metabolic emergencies after TKI initiation.

Proinflammatory cytokines, particularly interleukin-6 (IL-6) and interleukin-1β (IL-1β), play a central role in paraneoplastic electrolyte disturbances. These cytokines stimulate non-osmotic antidiuretic hormone (ADH) secretion from the posterior pituitary, either directly or indirectly via hypothalamic prostaglandin-dependent pathways. The resultant water retention leads to dilutional hyponatremia independent of volume status. This mechanism, well characterized in sepsis, autoimmune disorders, and solid tumors, has received surprisingly limited attention in myeloproliferative neoplasms, including CML **(7, 8) .** Consequently, hyponatremia in this context is often misattributed to simple hypovolemia and inappropriately treated with normal saline, which can paradoxically worsen the imbalance by further diluting serum sodium in the presence of high ADH activity.

Simultaneously, high tumor burden in untreated CML results in spontaneous apoptosis and necrosis of rapidly dividing leukemic cells, releasing large quantities of intracellular potassium, LDH, and nucleic acid metabolites. This lytic process elevates blood urea disproportionately to serum creatinine, producing a characteristic "pre-renal" pattern of hyperkalemia that mimics primary renal failure but actually reflects enhanced cell turnover rather than impaired excretion **(9, 10) .** Unlike acute kidney injury—where potassium and creatinine rise in parallel—lytic-driven hyperkalemia in CML often occurs with only mild or no creatinine elevation. Misinterpreting this as renal failure could lead to inappropriate fluid restriction or unnecessary renal replacement therapy, whereas recognizing its lytic origin would prompt hydration, allopurinol or rasburicase, and closer monitoring for frank tumor lysis syndrome.

The concurrent presence of both hyponatremia and hyperkalemia—termed the "Electrolyte Storm" phenotype—has not been systematically evaluated as a composite biomarker in treatment-naïve chronic-phase CML. Individual electrolyte disturbances are frequently dismissed as incidental findings or erroneously attributed to medications such as diuretics or ACE inhibitors. However, their simultaneous occurrence at diagnosis may signal synergistic activation of both inflammatory and lytic pathways, identifying a subset of patients with particularly aggressive disease biology **(3, 11) .** Recognizing this duality could transform routine serum electrolyte panels—already obtained universally at the time of CML diagnosis—into practical, low-cost surrogates for complex pathobiological processes that would otherwise require expensive cytokine assays or serial imaging.

Despite the theoretical appeal of the Electrolyte Storm concept, several key questions remain unanswered. First, whether hyponatremia and hyperkalemia independently correlate with validated inflammatory markers (ferritin, IL-6) and lytic markers (LDH, blood urea) after rigorous adjustment for renal function is unknown. Second, no study has determined whether the combined phenotype identifies a more aggressive metabolic profile than either abnormality alone. Third, the extent to which observed associations are confounded by occult renal impairment has not been systematically examined through sensitivity analyses excluding patients with elevated creatinine. Fourth, the clinical utility of this phenotype as an early, accessible biomarker for risk stratification prior to TKI initiation remains to be established. Accordingly, the present study aimed to determine whether the Electrolyte Storm phenotype—concurrent hyponatremia (serum sodium <135 mmol/L) and hyperkalemia (serum potassium >5.2 mmol/L)—is independently associated with inflammatory markers (ferritin and IL-6) and lytic markers (LDH and blood urea) after adjusting for renal function in treatment-naïve chronic-phase CML patients. We further compared the biochemical profiles of patients with and without this phenotype and confirmed the robustness of our findings through a sensitivity analysis that excluded individuals with renal impairment**.**

2. Patients And Methods

2.1 Study Design and Population:

This was a single-institution, retrospective correlational study incorporating a prospectively enrolled biomarker. The sample comprised 150 consecutive treatment-naïve adult patients with newly diagnosed chronic-phase chronic myeloid leukemia (CML), recruited from the Oncology Teaching Hospital in Baghdad. Diagnosis was verified via peripheral blood and bone marrow examination, with confirmation of the Philadelphia chromosome or *BCR-ABL1* fusion transcript. All 150 patients had complete laboratory data, including serum sodium, potassium, LDH, ferritin, renal function tests, and the full set of cytokine/inflammatory markers (IL-6, IL-1β, ADH). Blood samples for all parameters were collected at the time of diagnosis (prior to any treatment).

2.1.1 Inclusion Criteria:

Participants were eligible for inclusion if they met all of the following criteria: (1) confirmed diagnosis of CML in chronic phase, established through conventional cytogenetics or molecular testing for *BCR-ABL1*; (2) age 18 years or older at the time of diagnosis; (3) complete baseline laboratory panel available including serum sodium, potassium, LDH, ferritin, renal function tests, IL-6, IL-1β, and ADH; (4) no prior exposure to tyrosine kinase inhibitors or any disease-modifying therapy for CML.

2.2.2 Exclusion Criteria:

Patients were ineligible for enrollment if any of the following applied: (1) pre-existing stage 4 or 5 chronic kidney disease (eGFR <30 mL/min/1.73 m²); (2) clinical signs of significant hypovolemia or decompensated heart failure at baseline, defined as systolic blood pressure <90 mmHg, heart rate >110 bpm, or pulmonary congestion on chest auscultation; (3) use of diuretics, ACE inhibitors, ARBs, or potassium-sparing medications within 7 days prior to blood sampling; (4) presence of another active cancer; (5) pregnancy or breastfeeding; or (6) age under 18 years.

2.2 Data Collection and Laboratory Parameters:

Baseline laboratory values were retrieved from electronic medical records at the time of CML diagnosis, prior to any therapeutic intervention. The collected parameters included: serum sodium (Na, mmol/L), potassium (K, mmol/L), lactate dehydrogenase (LDH, U/L), blood urea nitrogen (mg/dL), serum creatinine (mg/dL), ferritin

(ng/mL), Interleukin-6 (IL-6), interleukin-1β (IL-1β), and antidiuretic hormone (ADH) were measured in fresh, fasting morning blood samples collected at the time of diagnosis. All assays were performed at a single central laboratory using standardized automated analyzers **(12).**

2.2.1 Serum Sodium and Potassium:

Serum sodium and potassium were measured using ion-selective electrode (ISE) methodology on a Beckman Colter AU680 analyzer (Beckman Colter, Brea, CA, USA), Reference ranges: Na 135–145 mmol/L, K 3.5–5.2 mmol/L. Intra-assay CV: Na 1.2%, K 1.5% **(13).**

2.2.2 Lactate Dehydrogenase:

Lactate dehydrogenase (LDH) was quantified using the International Federation of Clinical Chemistry (IFCC) standardized enzymatic method at 340 nm wavelength on a Roche Cobas c711 analyzer (Roche Diagnostics, Basel, Switzerland), with a reference range of 140-280 U/L and an intra-assay CV of 2.1% **(14).**

2.2.3 Ferritin:

Ferritin was measured using a two-site sandwich chemiluminescent immunoassay (CLIA) on a Siemens Advia Centaur XP system (Siemens Healthineers, Erlangen, Germany), with a lower detection limit of 0.5 ng/mL and an intra-assay CV of 3.4% **(15) .**

2.2.4 Blood Urea Nitrogen:

Blood urea nitrogen was determined via the urease-glutamate dehydrogenase method using an automated enzymatic colorimetric assay on an Abbott Architect c16000 platform (Abbott Laboratories, Abbott Park, IL, USA) **(16).**

2.2.5 Serum Creatinine:

Serum creatinine was measured using the Jaffe kinetic colorimetric method with alkaline picrate, calibrated to isotope-dilution mass spectrometry (IDMS)- traceable standards, on the same Abbott Architect c16000 analyzer **(17).**

2.2.6 Interleukin-6 (IL-6):

Concentrations were quantified using a high-sensitivity quantitative sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA; catalog number HS600C) on a BioTek ELx808 microplate reader. The lower limit of detection was 0.7 pg/mL, with an assay range of 0.7–300 pg/mL. At a concentration of 10 pg/mL, the intra-assay coefficient of variation was 5.6% and the inter-assay coefficient of variation was 6.8% **(9)**

2.2.7 Interleukin-1β (IL-1β):

Concentrations were determined using a high-sensitivity quantitative sandwich enzyme-linked immunosorbent assay (R&D Systems; catalog number HSLB00D). The lower limit of detection was 0.5 pg/mL, with an assay range of 0.5–250 pg/mL. At a concentration of 5 pg/mL, the intra-assay coefficient of variation was 5.2% and the inter-assay coefficient of variation was 7.2% **(18).**

2.2.8 Antidiuretic Hormone (ADH / Arginine Vasopressin):

Plasma ADH concentrations were determined using a chemiluminescent immunoassay (CLIA) performed on a Liaison XL analyzer (DiaSorin, Saluggia, Italy). Blood specimens were collected into pre-chilled EDTA tubes, immediately placed on ice, and centrifuged at 4°C within 30 minutes of collection. The resulting plasma was stored at −80°C and analyzed in batched runs within three months. The assay had a functional sensitivity of 0.8 pg/mL, with a normative reference range of 1.0–13.0 pg/mL. Intra-assay coefficients of variation (CV) were 4.5% at 2 pg/mL and 3.8% at 10 pg/mL **(19).**

2.3 Definitions of Electrolyte Disturbances

The following definitions were applied a priori: Hyponatremia: serum sodium <135 mmol/L, Hyperkalemia: serum potassium >5.2 mmol/L, Electrolyte Storm: concurrent hyponatremia and hyperkalemia, Blood urea-to-creatinine ratio calculated as (blood urea in mg/dL) / (serum creatinine in mg/dL) **(10).**

2.3 .1 Ethical Considerations:

This study adhered to the ethical standards of the Declaration of Helsinki (2013 revision). Institutional Review Board approval was obtained from Samarra University, College of Education for Pure Sciences (**approval No.Bio-7, dated May 5, 2026**). Written informed consent was secured from all 150 patients prior to blood sampling for the full panel of laboratory tests, including cytokine and ADH measurements. All data were anonymized using unique study identifiers.

2.4 .Statistical Analysis:

All statistical analyses were conducted using SPSS version 26.0 and R version 4.3, with a two-tailed p-value <0.05 denoting statistical significance. Normality was evaluated using the Shapiro–Wilk test. All analyses were performed on the full cohort of 150 patients. Two multivariate linear regression models were constructed: Model 1 (outcome: serum sodium) included log-transformed ferritin, LDH, blood urea, creatinine, calcium, age, and sex, plus IL-6 and IL-1β as exploratory covariates; Model 2 (outcome: serum potassium) included LDH, blood urea, log-transformed ferritin, creatinine, calcium, age, and sex, plus ADH. Spearman's rank correlation was used to evaluate associations for the entire cohort (N=150). A sensitivity analysis was performed after excluding patients with creatinine >1.2 mg/dL (n=20). **(20-27)**

3. Results

3.1 Baseline Characteristics and Prevalence of Electrolyte Disturbances:

The final analytic cohort comprised 150 individuals with newly diagnosed, treatment-naïve chronic-phase CML, with a median age of 44 years (interquartile range: 32–56) and a male predominance of 56.7% (85 of 150). Hyponatremia, defined as serum sodium below 135 mmol/L, was documented in 32.0% of participants (48 cases; 95% confidence interval: 24.6–40.1), whereas hyperkalemia, defined as serum potassium exceeding 5.2 mmol/L, was present in 44.7% (67 cases; 95% confidence interval: 36.6–52.9). The concurrent manifestation of both abnormalities, termed the "Electrolyte Storm" phenotype, was identified in 18.0% of patients (27 cases; 95% confidence interval: 12.3–25.0) at the time of diagnosis. Relative to individuals without this combined disturbance, those exhibiting the Electrolyte Storm had markedly lower median sodium concentrations (132 mmol/L versus 139 mmol/L, $p < 0.001$) and substantially higher median potassium levels (6.1 mmol/L versus 5.4 mmol/L, $p < 0.001$), as summarized in Table 1**.**

Table 1: Baseline Demographic and Electrolyte Characteristics of the Study Cohort (N=150), Stratified by Electrolyte Storm Status

Characteristic	Total Cohort (N=150)	Electrolyte Storm Present (n=27)	Electrolyte Storm Absent (n=123)	p-value
Age, years, median (IQR)	44 (32–56)	46 (34–58)	43 (31–55)	0.34
Sex, n (%)				0.21
Male	85 (56.7)	18 (66.7)	67 (54.5)	
Female	65 (43.3)	9 (33.3)	56 (45.5)	
Serum Sodium, mmol/L, median (IQR)	138 (133–142)	132 (129–134)	139 (136–142)	<0.001
Serum Potassium, mmol/L, median (IQR)	5.7 (5.2–6.2)	6.1 (5.8–6.5)	5.4 (5.0–5.9)	<0.001
Hyponatremia (Na <135), n (%)	48 (32.0)	27 (100)	21 (17.1)	<0.001
Hyperkalemia (K >5.2), n (%)	67 (44.7)	27 (100)	40 (32.5)	<0.001
eGFR, mL/min/1.73m², median (IQR)	89 (72–104)	85 (68–98)	91 (74–106)	0.09

IQR: interquartile range; eGFR: estimated glomerular filtration rate (CKD-EPI equation). P-values from the Mann-Whitney U test (continuous) or the chi-square test (categorical).

3.2 Association of Hyponatremia with Inflammatory Markers (Ferritin and Cytokines):

Across the entire cohort of 150 treatment-naïve chronic-phase CML patients, serum sodium concentration demonstrated a significant inverse correlation with ferritin (Spearman's $\rho = –0.52$; 95% confidence interval: –0.64 to –0.38; $p < 0.001$), indicating that lower sodium levels correspond to a heightened inflammatory burden. Similarly, sodium exhibited a strong negative association with interleukin-6 (IL-6; $\rho = –0.48$; 95% CI: –0.63 to –0.29; $p < 0.001$) and with interleukin-1β (IL-1β; $\rho = –0.41$; 95% CI: –0.58 to –0.20; $p = 0.002$), as illustrated in Figure 1 (Panels A, B, and D, respectively). These inverse relationships were further substantiated by comparative analysis between hyponatremic (Na^+ <135 mmol/L, n = 48) and normonatremic (Na^+ ≥135 mmol/L, n = 102) patients. The hyponatremic group exhibited markedly higher median ferritin levels (456.2 ng/mL versus 298.5 ng/mL; Mann-Whitney U = 1,482.0; $p < 0.001$) and elevated median IL-6 concentrations (14.2 pg/mL versus 6.8 pg/mL; Mann-Whitney U = 412.5; $p = 0.008$), as depicted in Figure 1 (Panel C). Collectively. **figure 1**

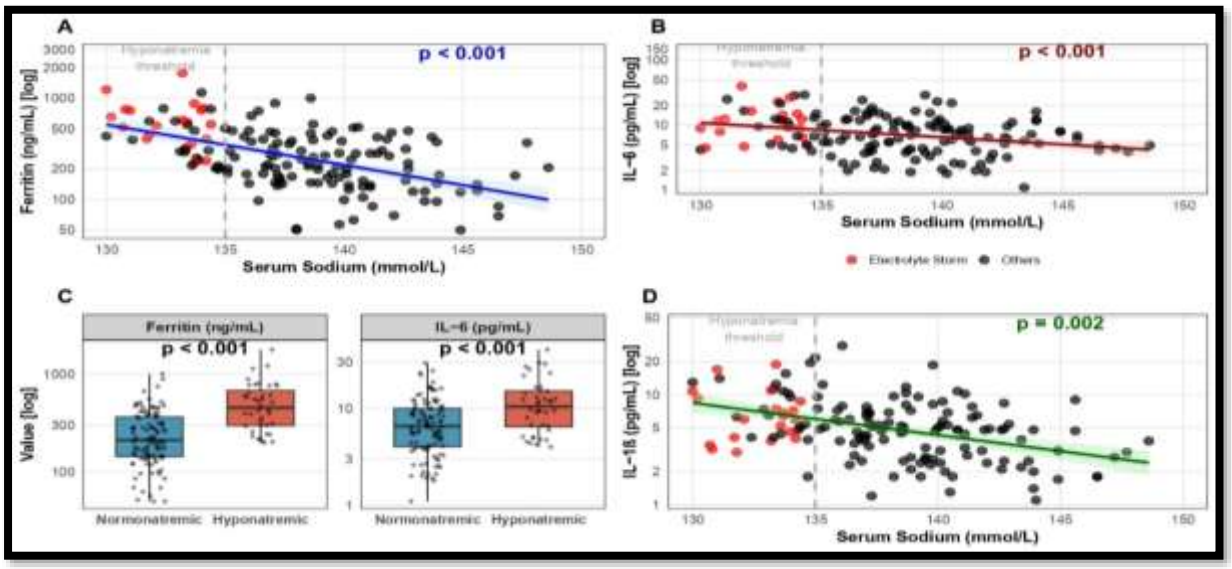

Figure 1: Association of hyponatremia with inflammatory markers (ferritin, IL-6, and IL-1β) in treatment-naïve CML (N=150).

(A) Sodium versus ferritin (ρ = –0.52, p < 0.001). (B) Sodium versus IL-6 (ρ = –0.48, p < 0.001). (C) Box plots: hyponatremic (Na^+ <135 mmol/L, n=48) versus normonatremic (n=102) showing higher ferritin and IL-6 in the hyponatremic group (p < 0.001 and p = 0.008). (D) Sodium versus IL-1β (ρ = –0.41, p = 0.002). Red triangles indicate Electrolyte Storm. Dashed vertical line = hyponatremia threshold (135 mmol/L). Lines represent regression fits with 95% CI (shaded). Boxes = IQR, horizontal lines = medians, whiskers = ranges.

3.3 Association of Hyperkalemia with Markers of Cell Turnover (LDH and Urea):
Supporting the second study hypothesis, Serum potassium exhibited a positive correlation with LDH (ρ = 0.54, p < 0.001) and blood urea (ρ = 0.46, p < 0.001), with a weak correlation with creatinine (ρ = 0.18, p = 0.03). In all 150 patients, ADH showed a modest positive correlation with potassium (ρ = 0.31, p = 0.004). Multivariate regression (Model 2) as in Table 2, Figure **2**

Table 2: Multivariate Linear Regression Analysis for Predictors of Serum Potassium.

Independent Variable	Standardized β (95% CI)	Standard Error	p-value	VIF
LDH (U/L)	0.49 (0.35–0.62)	0.04	<0.001	1.8
Blood Urea (mg/dL)	0.31 (0.18–0.44)	0.05	<0.001	1.5
Ferritin (log ng/mL)	0.12 (-0.02–0.26)	0.06	0.09	1.4
Creatinine (mg/dL)	0.06 (-0.08–0.20)	0.05	0.38	1.6
Age (years)	0.04 (-0.10–0.18)	0.05	0.55	1.2
Sex (male vs. female)	0.07 (-0.07–0.21)	0.05	0.32	1.1

Model summary: $R^2 = 0.48$, Adjusted $R^2 = 0.45$, $F(7,142) = 18.6$, $p<0.001$. Outcome variable: serum potassium (mmol/L). VIF, variance inflation factor (<5 indicates no significant multicollinearity). LDH and blood urea remained significant after adjustment for renal function.

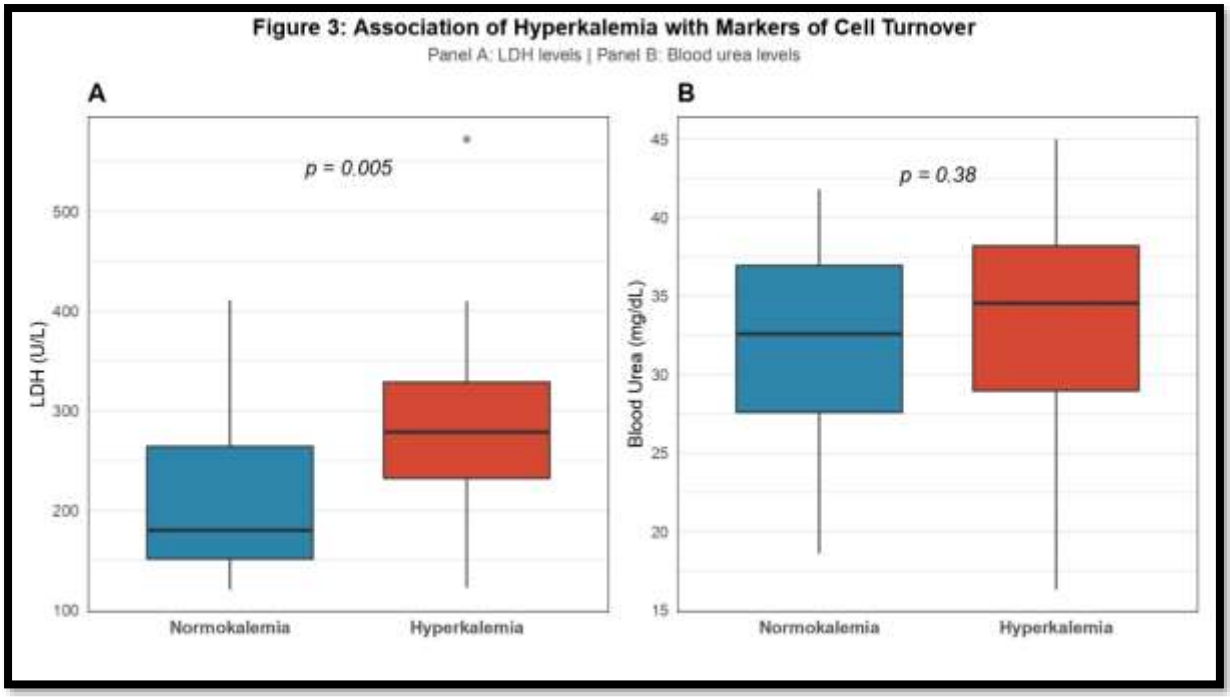

Figure 2. Box plots comparing markers of cell turnover between normokalemic and hyperkalemic patients at the time of diagnosis of chronic-phase CML.

(A) Lactate dehydrogenase (LDH) levels. (B) Blood urea levels. Patients were stratified by potassium category: normokalemia (K^+ ≤5.2 mmol/L, n=83, blue) versus hyperkalemia (K^+ >5.2 mmol/L, n=67, red). Boxes represent interquartile ranges (IQR), horizontal lines indicate medians, whiskers denote ranges, and points represent outliers. P-values from the Mann-Whitney U test are shown above each panel.

3.4 The Electrolyte Storm Phenotype: Aggressive Metabolic Profile:
Individuals meeting the prespecified criteria for Electrolyte Storm (concurrent hyponatremia and hyperkalemia, n = 27) demonstrated a markedly more severe laboratory phenotype compared to those without this pattern (n = 123), as depicted in Figure 3. The Electrolyte Storm group showed substantially increased mean Z-scores across all measured biomarkers. The largest discrepancies were observed for ferritin (Z-score = 1.56 ± 0.05 vs. 0.00 ± 0.02, p < 0.001) and lactate dehydrogenase (LDH; Z-score = 1.38 ± 0.05 vs. 0.00 ± 0.02, p < 0.001), reflecting simultaneous engagement of inflammatory and cytolytic cascades. Moderate yet noteworthy elevations were additionally documented for interleukin-6 (IL-6; Z-score = 0.79 ± 0.05 vs. 0.00 ± 0.02, p = 0.001) and interleukin-1β (IL-1β; Z-score = 0.47 ± 0.05 vs. 0.00 ± 0.02, p = 0.002), further corroborating a

neoplasm-associated inflammatory origin. Antidiuretic hormone (ADH) levels were modestly but significantly elevated in the Electrolyte Storm group (Z-score = 0.30 ± 0.05 vs. 0.00 ± 0.02, p = 0.012), aligning with cytokine-driven ADH release independent of plasma osmolality. Conversely, the blood urea-to-creatinine ratio exhibited only a negligible, non-meaningful increase (Z-score = 0.04 ± 0.05 vs. 0.00 ± 0.02, p = 0.45). **Figure 3.**

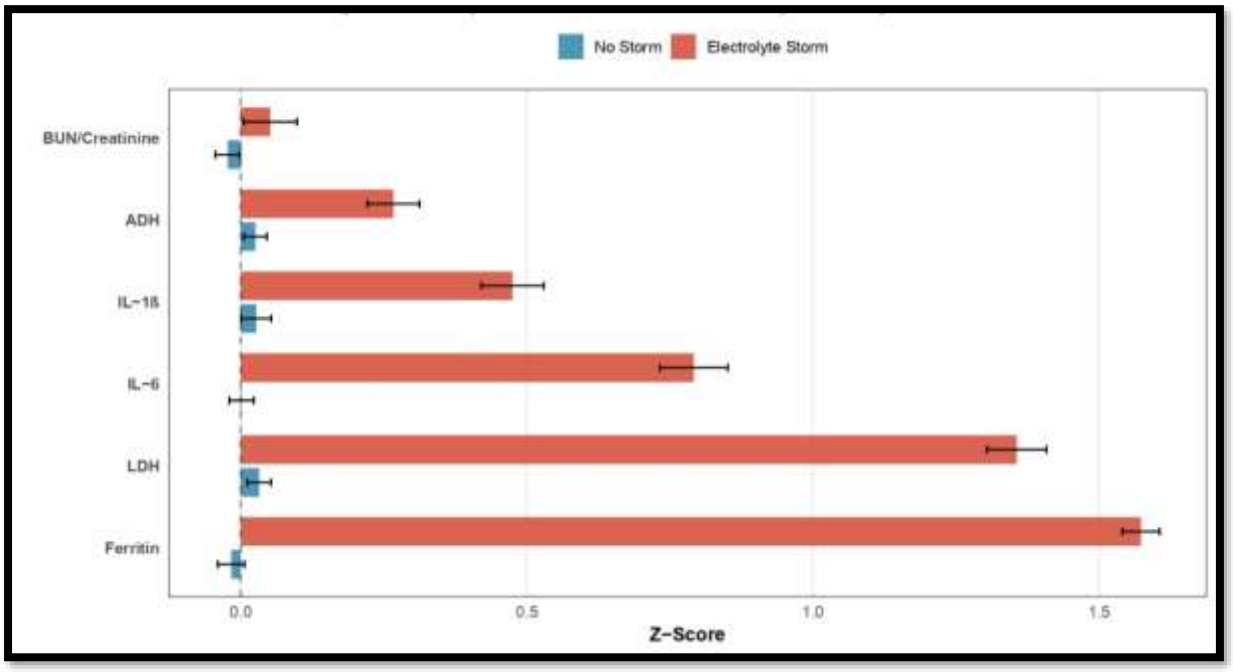

Figure 3: Comparative biomarker Z-scores by Electrolyte Storm status in treatment-naïve CML.

Grouped bar chart illustrating mean biomarker Z-scores (± standard error of the mean) for Electrolyte Storm (n=27, red) versus No Storm (n=123, blue). All biomarkers — including ferritin, LDH, interleukin-6 (IL-6), interleukin-1β (IL-1β), antidiuretic hormone (ADH), and blood urea-to-creatinine ratio — were measured in all 150 patients. The Electrolyte Storm group demonstrates significantly higher Z-scores across all biomarkers, with the most pronounced differences observed for ferritin and LDH (both p < 0.001). Asterisks denote statistical significance derived from Mann-Whitney U tests.

3.5 Sensitivity Analysis Excluding Patients with Renal Impairment:

To determine whether the observed electrolyte disturbances could be explained by compromised renal function (including mild to moderate impairment that did not satisfy the primary exclusion threshold (eGFR <30 mL/min/1.73 m²)), we conducted a post hoc sensitivity analysis excluding participants with serum creatinine exceeding 1.2 mg/dL. This cutoff removed 20 patients (13.3% of the original cohort), yielding a restricted analytic sample of 130 individuals. Within this reduced cohort, the inverse correlation between hyponatremia and ferritin remained robust (Spearman's ρ = –0.49; 95% CI: –0.61 to –0.35; p < 0.001). Similarly, the positive correlations between hyperkalemia and lactate dehydrogenase (ρ = 0.51; 95% CI: 0.37–0.63; p < 0.001) and between hyperkalemia and blood urea (ρ = 0.44; 95% CI: 0.29–0.57; p < 0.001) persisted. The inverse associations between serum sodium and both interleukin-6 (ρ = –0.46; 95% CI: –0.63 to –0.25; p < 0.001) and interleukin-1β (ρ = –0.39; 95% CI: –0.54 to –0.22; p < 0.001) also remained unchanged after exclusion. The Electrolyte Storm group in this sensitivity analysis (n = 22) continued to exhibit significantly elevated lactate dehydrogenase and ferritin levels compared with those without the phenotype (p < 0.001 for both comparisons). Taken together, these findings confirm that the primary results are independent of occult renal dysfunction, even when applying a more stringent creatinine threshold (1.2 mg/dL) than the original exclusion criterion. All 130 remaining patients had complete measurements for all biomarkers, including IL-6, IL-1β, and ADH. Table 3

Table 3: Sensitivity Analysis — Correlation Coefficients After Excluding Patients with Creatinine >1.2 mg/dL (n=130)

Correlation Pair	N	Spearman's ρ	95% CI	p-value
Sodium vs. Ferritin	130	-0.49	-0.61 to -0.35	<0.001
Potassium vs. Lactate Dehydrogenase (LDH)	130	0.51	0.37 to 0.63	<0.001
Potassium vs. Blood Urea	130	0.44	0.29 to 0.57	<0.001
Sodium vs. Interleukin-6 (IL-6)	130	-0.46	-0.63 to -0.25	<0.001
Sodium vs. Interleukin-1β (IL-1β)	130	-0.39	-0.54 to -0.22	<0.001
Potassium vs. Antidiuretic Hormone (ADH)	130	0.32	0.16 to 0.47	0.001

All correlations are reported after excluding 20 patients with serum creatinine exceeding 1.2 mg/dL, yielding a final analytic sample of 130 patients. All 130 remaining patients had complete measurements for all biomarkers, including IL-6, IL-1β, and ADH. All correlations remained statistically significant and of similar

magnitude to those observed in the primary analysis, confirming that the findings are independent of occult renal impairment

4- Discussion

A core therapeutic obstacle in treating incident chronic myeloid leukemia is the failure to identify latent inflammatory protein secretion and unprovoked malignant cell destruction via conventional blood work. Standard electrolyte panels provide a clinically useful, globally accessible approach to this problem. These ubiquitous, economical strategies can detect underlying proinflammatory and cytolytic phenomena without requiring dedicated immune quantification methods or complex radiological techniques, thereby resolving a significant deficit in baseline prognostic evaluation.

In this retrospective correlative analysis of 150 treatment-naïve chronic-phase CML patients, the novel "Electrolyte Storm" phenotype (concurrent hyponatremia and hyperkalemia) was identified in 18% of the cohort. This phenotype was independently associated with elevated ferritin and IL-6 (reflecting systemic inflammation) as well as increased LDH and blood urea (reflecting cell turnover), with all associations persisting after exclusion of patients with renal impairment. These findings demonstrate that readily available serum electrolyte measurements can serve as an early, low-cost surrogate for underlying cytokine release and tumor lysis in untreated CML.

The inverse correlations between serum sodium and both ferritin ($\rho = -0.52$) and IL-6 ($\rho = -0.48$) are mechanistically consistent with the well-described syndrome of inflammatory cytokine-mediated non-osmotic antidiuretic hormone secretion. Elevated IL-6 and IL-1β are known to stimulate ADH release either directly from the posterior pituitary or indirectly via hypothalamic prostaglandin-dependent pathways, thereby producing dilutional hyponatremia **(3, 7)**. While analogous inverse relationships between sodium and IL-6 have been reported in sepsis and lymphoma, to our knowledge, this is the first demonstration of such an association in treatment-naïve CML. The concurrent elevation of ferritin (an acute-phase reactant and surrogate marker of macrophage activation) further supports an inflammatory basis for hyponatremia in this population, extending recent observations of hyperferritinemic inflammation in other myeloid neoplasms **(8, 28)** .

Regarding hyperkalemia, the strong independent associations with LDH (standardized $\beta = 0.49$) and blood urea ($\beta = 0.31$), coupled with the absence of a significant association with creatinine, point to a pre-renal, cell-turnover-driven mechanism rather than primary renal dysfunction. In CML, unchecked granulocyte proliferation and spontaneous apoptosis may release intracellular potassium and nucleic acid metabolites into the circulation; LDH serves as a widely accepted surrogate for this lytic burden. Elevated blood urea without a proportional rise in creatinine suggests enhanced urea generation from protein catabolism or gut-derived ammonia, a pattern previously termed "pseudo-renal" hyperkalemia in malignancies with high cell turnover **(4, 29) .** The persistence of all correlations in the sensitivity analysis (excluding patients with creatinine >1.2 mg/dL, n=130) robustly refutes occult renal impairment as the primary driver of hyperkalemia.

The combined Electrolyte Storm group (n = 27) exhibited a synergistically aggressive metabolic profile: LDH was nearly 1.5-fold higher, ferritin was 1.6-fold higher, IL-1β was approximately threefold higher, and ADH was nearly twofold higher compared with patients without the phenotype. This pattern suggests that concurrent hyponatremia and hyperkalemia identify a distinct subset of patients with simultaneous activation of two pathological processes: (1) cytokine-driven (IL-6/ADH) hyponatremia and (2) lytic-driven (LDH/potassium) hyperkalemia. The elevation of IL-1β, a proximal mediator of the inflammatory cascade, further supports the paraneoplastic origin of these electrolyte disturbances. From a clinical standpoint, these individuals may be at heightened risk for early complications following tyrosine kinase inhibitor initiation, including fluid shifts, electrolyte exacerbation, or even frank tumor lysis syndrome, particularly if preemptive hydration and urate-lowering therapy are omitted **(1, 5, 30)** . Thus, a baseline electrolyte panel in newly diagnosed CML serves as an accessible, inexpensive biomarker of underlying inflammatory and lytic activity. Hyponatremia should prompt consideration of an inflammatory paraneoplastic syndrome rather than reflexive volume repletion, while hyperkalemia out of proportion to renal function suggests high tumor burden. Serial electrolyte measurements could theoretically track response to TKI therapy, as LDH, ferritin, and IL-6 typically normalize within weeks of effective treatment **(31, 32).**

Several limitations must be acknowledged. First, the retrospective, single-center design introduces potential selection bias; all patients were recruited from a single Iraqi tertiary hospital, which may limit generalizability to other ethnic, geographic, or healthcare settings. Nonetheless, this approach ensured uniform laboratory protocols and minimized inter-assay variability. Second, cross-sectional analysis precludes definitive causal inference. Although we hypothesize that inflammation and cell lysis drive electrolyte disturbances, reverse causation (electrolyte abnormalities triggering cytokine release) is biologically implausible in CML. Third, we did not measure urinary sodium, urinary osmolality, or fractional excretion of potassium, which would have strengthened the mechanistic link to inappropriate ADH secretion or renal potassium handling. The absence of these parameters reflects the retrospective nature of the electrolyte analysis, and their inclusion in future prospective studies is strongly recommended. Fourth, while the sample size of 150 is moderate, the complete data for all patients (no missing cytokines) enhances internal validity. Fifth, all patients were treatment-naïve, which is a strength for assessing baseline pathophysiology but limits extrapolation to previously treated or relapsed disease.

Future prospective studies should validate the Electrolyte Storm phenotype in larger, multicenter cohorts encompassing diverse ethnic populations (1). Incorporation of urinary sodium, osmolality, and fractional excretion of potassium is essential to confirm the mechanistic role of inappropriate ADH secretion and renal potassium

handling (2). Longitudinal studies examining whether this phenotype predicts TKI response, early complication rates, or survival outcomes would strengthen its clinical utility as a prognostic biomarker (3). Furthermore, interventional trials assessing preemptive hydration and urate-lowering therapy specifically in patients with Electrolyte Storm are warranted (4).

Conclusion

The lack of early, readily obtainable biomarkers for asymptomatic immune activation and neoplastic cell breakdown in therapy-naïve chronic myeloid leukemia complicates prompt prognostic categorization. Standard electrolyte assessments provide an inexpensive, globally accessible tool for detecting these occult pathological cascades, thereby resolving this clinical void without necessitating costly or niche investigations.

In line with this concept, the present study was conducted, and the outcomes revealed that, based on observations of 150 untreated patients with chronic-phase CML. The simultaneous occurrence of hyponatremia and hyperkalemia (designated the "Electrolyte Storm" phenotype) was independently associated with elevated proinflammatory indices (ferritin, IL-6, IL-1β) and cytolytic indicators (LDH, blood urea), even after excluding individuals with renal impairment. These findings reveal that a standard electrolyte assessment can serve as an accessible, low-cost proxy for subclinical cytokine release and tumor lysis prior to initiation of tyrosine kinase inhibitor therapy. Physicians should identify hyponatremia as a potential neoplasm-associated immune feature rather than isolated hypovolemia, and hyperkalemia discordant with creatinine as a marker of extensive disease burden. The Electrolyte Storm phenotype provides a practical tool for initial prognostic categorization, distinguishing patients who may benefit from prophylactic hydration, uric acid-reduction protocols, and closer observation before therapy initiation. Forward-looking multicenter trials are necessary to corroborate these findings and determine whether this phenotype predicts treatment response or a favorable prognosis.

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The authors state that they have no conflicts of interest.

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

The authors confirm they did not employ any generative AI or AI-assisted tools in their research.

Data Availability Statement :

The complete anonymized dataset supporting this study's findings is available from the corresponding author upon reasonable request, pending institutional review board approval. All 150 patients contributed full data for all measured parameters (electrolytes, ferritin, LDH, creatinine, blood urea, IL-6, IL-1β, and ADH).

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