# Complete Blood Count–Derived Indices in Chronic Lymphocytic Leukemia: Prognostic Significance, Biological Basis, and Clinical Applicability

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## *Abstract*

**Background:** Chronic lymphocytic leukemia is characterized by marked clinical heterogeneity, ranging from indolent disease that may never require treatment to rapidly progressive leukemia associated with early therapeutic intervention and shortened survival. Although established prognostic systems incorporate clinical stage, age, serum beta-2 microglobulin, immunoglobulin heavy-chain variable-region mutational status, and TP53 abnormalities, access to molecular and cytogenetic testing remains unequal across healthcare settings. Complete blood count–derived indices are inexpensive, rapidly available, reproducible, and routinely obtained during diagnosis and follow-up. Beyond conventional parameters such as hemoglobin concentration, absolute lymphocyte count, and platelet count, several derived markers—including red cell distribution width, mean platelet volume, platelet distribution width, plateletcrit, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio, and composite systemic inflammatory indices—have emerged as potential indicators of tumor burden, marrow dysfunction, immune dysregulation, systemic inflammation, and microenvironmental activity in chronic lymphocytic leukemia.

**Aim:** This review evaluates the prognostic significance, biological rationale, and clinical applicability of complete blood count–derived indices in chronic lymphocytic leukemia. It examines their reported associations with Rai and Binet stage, time to first treatment, treatment-free survival, progression-free survival, overall survival, and adverse biological features. Particular attention is given to the mechanisms linking altered erythrocyte, leukocyte, and platelet parameters with disease progression, including chronic inflammation, impaired hematopoiesis, cytokine-mediated changes, immune-cell interactions, and platelet activation. The review also considers whether these indices can complement established prognostic models, particularly in resource-limited settings.

**Conclusion:** Complete blood count–derived indices represent promising, accessible biomarkers for risk assessment in chronic lymphocytic leukemia. Their principal advantages are low cost, universal availability, and suitability for repeated longitudinal monitoring. However, their prognostic performance remains inconsistent because of retrospective study designs, heterogeneous cutoff values, limited sample sizes, treatment-era differences, and susceptibility to confounding by infection, autoimmune cytopenias, comorbidities, renal dysfunction, and medications. These markers should therefore not replace validated molecular or clinical prognostic systems. Their greatest potential lies in supporting preliminary risk stratification, identifying patients who may require closer surveillance, and enhancing multivariable prognostic models. Prospective multicenter validation, standardized analytical thresholds, and integration with molecular biomarkers are required before routine clinical implementation.

**Keywords:** chronic lymphocytic leukemia; complete blood count; prognostic biomarkers; hematologic indices.

## Introduction

Chronic lymphocytic leukemia (CLL) is a mature B-cell lymphoid malignancy characterized by the progressive accumulation of clonal, immunologically dysfunctional lymphocytes in the peripheral blood, bone marrow, lymph nodes, and spleen. It predominantly affects older adults and demonstrates remarkable clinical heterogeneity. Some patients remain asymptomatic for decades and never require leukemia-directed treatment, whereas others develop rapidly progressive lymphadenopathy, organomegaly, marrow failure, recurrent infections, or transformation into aggressive lymphoma. This variability makes prognostic assessment essential from the time of diagnosis, even though treatment initiation continues to depend on evidence of active or symptomatic disease rather than prognostic risk alone. Accurate risk evaluation can guide surveillance intensity, patient counseling, interpretation of clinical changes, and selection of appropriate therapeutic strategies once treatment becomes indicated.[1]

The Rai and Binet staging systems remain clinically valuable because they use readily available findings, including lymphocytosis, lymphadenopathy, hepatosplenomegaly, anemia, and thrombocytopenia, to classify disease burden. Nevertheless, patients within the same clinical stage may experience substantially different rates of progression and survival. Contemporary prognostication therefore incorporates biological variables such as TP53 deletion or mutation, immunoglobulin heavy-chain variable-region gene mutational status, serum beta-2 microglobulin, and recurrent cytogenetic abnormalities identified by fluorescence in situ hybridization. The CLL International Prognostic Index combines TP53 status, IGHV mutational status, beta-2 microglobulin concentration, clinical stage, and age to stratify patients into four prognostic categories with distinct survival outcomes. Although these variables improve risk discrimination, their availability, financial cost, turnaround time, and technical requirements may limit routine application in resource-constrained healthcare systems.[2]

The complete blood count is universally incorporated into the diagnosis, staging, follow-up, and treatment monitoring of CLL. Conventional abnormalities such as absolute lymphocytosis, anemia, and thrombocytopenia already reflect central aspects of disease biology, including leukemic clonal expansion, bone marrow infiltration, splenic sequestration, autoimmune cytopenias, and treatment-related myelosuppression. Modern automated hematology analyzers provide additional quantitative parameters without requiring extra blood sampling or substantial additional expenditure. These include red cell distribution width, mean corpuscular volume, mean platelet volume, platelet distribution width, and plateletcrit. Ratios calculated from routinely reported cell counts—including the neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio—may further represent the balance between tumor burden, systemic inflammation, immune competence, and microenvironmental support.[3]

The biological rationale for studying these indices extends beyond their statistical association with clinical outcomes. Altered erythrocyte parameters may reflect inflammation, nutritional deficiency, ineffective erythropoiesis, marrow infiltration, renal impairment, or shortened red-cell survival. Changes in platelet number and morphology may indicate impaired marrow reserve, peripheral consumption, inflammatory stimulation, or platelet activation. Leukocyte-derived ratios may capture interactions among the malignant B-cell clone, residual innate immune responses, circulating monocytes, and the tumor-supportive microenvironment. Because many of these biological processes contribute to disease progression, hemogram-derived indices could potentially provide an integrated and inexpensive representation of host–tumor interactions that is not fully captured by the absolute lymphocyte count alone.[3]

Despite increasing interest, the evidence supporting complete blood count–derived prognostic indices in CLL remains fragmented. Most available investigations are retrospective, originate from single institutions, include relatively small or clinically heterogeneous cohorts, and use different thresholds for

defining abnormal values. The indices may also be influenced by infection, autoimmune hemolysis, nutritional status, renal or hepatic dysfunction, cardiovascular disease, corticosteroid exposure, anticoagulant treatment, previous therapy, and preanalytical laboratory conditions. Furthermore, many studies were conducted during different therapeutic eras, complicating comparisons of overall survival and progression-related outcomes. Consequently, it remains uncertain whether these parameters provide independent prognostic information, act primarily as surrogates for advanced stage and marrow dysfunction, or meaningfully improve established clinical and molecular models.[4]

This review aims to critically evaluate the prognostic significance, biological basis, and potential clinical applicability of complete blood count–derived indices in CLL. It examines erythrocyte-, leukocyte-, and platelet-derived parameters in relation to disease stage, time to first treatment, treatment-free survival, progression-free survival, and overall survival. It also explores their possible integration with validated systems such as the Rai and Binet classifications, CLL-IPI, and early-stage prognostic models. The principal research gap addressed is the absence of standardized, prospectively validated approaches for incorporating these inexpensive biomarkers into contemporary CLL risk assessment. Particular emphasis is therefore placed on methodological limitations, confounding factors, clinically meaningful endpoints, and priorities for future multicenter research.

**Contemporary Prognostication in Chronic Lymphocytic Leukemia**

Clinical staging remains the foundation of initial CLL risk assessment. The Rai system classifies patients according to lymphocytosis, lymphadenopathy, organomegaly, anemia, and thrombocytopenia, whereas the Binet system considers involved lymphoid regions and cytopenias. Both systems are inexpensive and accessible but cannot adequately explain the heterogeneous outcomes observed among patients within the same stage.[5]

The CLL International Prognostic Index improves risk discrimination by integrating age, clinical stage, serum beta-2 microglobulin, IGHV mutational status, and TP53 abnormalities. Its weighted score separates patients into low-, intermediate-, high-, and very-high-risk groups. However, its survival estimates were largely developed before widespread use of modern targeted therapies, and molecular testing may not be consistently available in resource-limited settings.[6]

For asymptomatic early-stage disease, the International Prognostic Score for Early-Stage CLL estimates the probability of requiring treatment using unmutated IGHV, an absolute lymphocyte count above 15 × $10^9$/L, and palpable lymphadenopathy. It is particularly useful for counseling and surveillance planning but does not justify therapy in patients who lack established criteria for active disease.[7]

TP53 disruption and unmutated IGHV remain major adverse biological features, while cytogenetic abnormalities and serum biomarkers provide additional information. Nevertheless, these tests require specialized facilities and are not intended for frequent repeated monitoring. CBC-derived indices may therefore offer complementary, low-cost measures of tumor burden, marrow reserve, inflammation, and host response, although their incremental value over validated models requires further confirmation.[8]

**Biological Basis of Complete Blood Count–Derived Indices**

CBC-derived indices may reflect several biological processes relevant to CLL progression. Expansion of the leukemic clone alters the proportions of circulating lymphocytes, neutrophils, monocytes, and platelets, while marrow infiltration impairs normal hematopoiesis. These changes are further influenced by cytokine signaling, immune dysfunction, splenic sequestration, autoimmune cytopenias, infection, and treatment exposure. Consequently, routine blood-cell parameters may provide an indirect measure of tumor burden, marrow reserve, and host response.[9]

Leukocyte-derived ratios are especially relevant because CLL progression depends on interactions between malignant B cells and the surrounding immune microenvironment. Monocytes and neutrophils can support leukemic-cell survival through inflammatory mediators, chemokines, and tissue trafficking, whereas a high circulating lymphocyte burden may indicate clonal expansion. Ratios such as the neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and monocyte-to-lymphocyte ratio may therefore summarize the balance between tumor burden and innate immune activity.[10]

Erythrocyte-derived parameters may reflect marrow infiltration, chronic inflammation, nutritional

deficiency, renal dysfunction, or autoimmune hemolysis. Red cell distribution width is particularly attractive because it captures variation in erythrocyte size and may rise in states of ineffective erythropoiesis, oxidative stress, and systemic inflammation. In CLL, elevated red cell distribution width may therefore indicate both disease-related marrow dysfunction and broader physiological deterioration.[11]

Platelet-derived indices may also carry prognostic information. Thrombocytopenia is already incorporated into Rai and Binet staging, but additional measures such as mean platelet volume, platelet distribution width, and plateletcrit may reflect platelet production, activation, consumption, and marrow reserve. Because platelet size and number are influenced by inflammatory cytokines and megakaryocytic activity, these parameters may provide information beyond the absolute platelet count alone.[12]

The clinical value of these indices lies in their accessibility, repeatability, and low cost. However, they are nonspecific and can be altered by infection, corticosteroids, autoimmune disease, nutritional deficiencies, renal impairment, cardiovascular conditions, and preanalytical variation. Their prognostic interpretation should therefore be integrated with clinical stage, molecular markers, and treatment history rather than used as isolated predictors.[13]

**Leukocyte-Derived Indices**

The absolute lymphocyte count reflects circulating tumor burden but has limited prognostic value when interpreted alone. A rapidly increasing count and short lymphocyte-doubling time are more informative because they indicate active clonal expansion. Nevertheless, lymphocyte values can fluctuate with infection, corticosteroid exposure, hydration, and treatment; therefore, serial measurements are more meaningful than a single baseline result.[14]

Circulating monocytes may support CLL-cell survival through cytokine production, immune suppression, and differentiation into leukemia-associated macrophages. Elevated absolute monocyte counts have been associated with shorter time to first treatment and inferior overall survival, suggesting that monocyte expansion may represent a clinically measurable feature of a supportive tumor microenvironment.[15]

The lymphocyte-to-monocyte ratio and its inverse combine leukemic burden with monocyte-mediated microenvironmental support. Abnormal ratios have been associated with advanced stage and earlier treatment requirement in retrospective cohorts. However, the optimal cutoff remains uncertain, and the direction of risk may vary according to whether the ratio is dominated by extreme lymphocytosis or increased monocyte counts.[16]

Neutrophil-derived measures are more difficult to interpret in CLL. Neutrophilia may reflect infection, inflammation, corticosteroid therapy, or aggressive disease biology, while neutropenia may indicate marrow failure or treatment toxicity. Although neutrophil-to-lymphocyte ratio is widely studied in solid tumors, its independent prognostic role in untreated CLL remains insufficiently validated and should be interpreted cautiously.[17]

**Erythrocyte-Derived Indices**

Anemia is an established adverse feature in CLL and forms part of both Rai and Binet staging. It may result from marrow infiltration, autoimmune hemolysis, hypersplenism, renal dysfunction, nutritional deficiency, bleeding, or treatment toxicity. Because these mechanisms have different clinical implications, hemoglobin should be interpreted with reticulocyte count, hemolysis markers, renal function, and marrow findings rather than viewed as a simple measure of tumor burden.[18]

Red cell distribution width reflects variability in erythrocyte size and may increase because of ineffective erythropoiesis, inflammation, nutritional deficiency, oxidative stress, or shortened red-cell survival. In CLL, elevated RDW at diagnosis has been associated with advanced stage, adverse prognostic features, shorter time to treatment, and reduced overall survival. Its low cost makes it attractive, but its limited specificity prevents independent clinical use.[19]

Mean corpuscular volume and related erythrocyte indices have received less attention as prognostic markers in CLL. Abnormal values more commonly identify coexisting iron, vitamin B12, or folate

deficiency, reticulocytosis, liver disease, or treatment effects. Their main prognostic contribution may therefore be indirect, by clarifying the cause of anemia and distinguishing reversible comorbidity from progressive marrow failure.

**Platelet-Derived Indices**

Platelet count is an established marker of disease progression because thrombocytopenia may reflect extensive marrow infiltration, hypersplenism, autoimmune destruction, or treatment-related suppression. Progressive platelet decline is clinically more informative than an isolated low value and contributes directly to advanced Rai and Binet classification. Nevertheless, platelet count alone cannot distinguish disease progression from immune thrombocytopenia, infection, medication effects, or laboratory variation.[20]

Mean platelet volume reflects platelet size and indirectly indicates marrow production and platelet turnover. In a retrospective study of 523 patients with CLL, lower mean platelet volume was associated with shorter time to first treatment and retained prognostic value in multivariable analysis. Although readily available, mean platelet volume is affected by analyzer type, anticoagulant exposure, and the interval between sample collection and testing, limiting universal cutoff selection.[21]

Platelet distribution width measures variability in platelet size and may reflect heterogeneous platelet production or activation. High platelet distribution width has been associated with advanced CLL features and inferior survival in retrospective analyses. However, the evidence remains limited, and platelet distribution width should currently be regarded as an investigational marker requiring prospective validation and standardized laboratory measurement.[22]

**Composite Inflammatory Indices**

The platelet-to-lymphocyte ratio combines platelet reserve with circulating lymphocyte burden. In CLL, a low ratio may result from marked lymphocytosis, thrombocytopenia, or both, thereby reflecting increasing tumor burden and impaired marrow function. Published studies have linked lower platelet-to-lymphocyte ratios with shorter watchful-waiting periods or more advanced disease, although the association has not consistently remained independent after adjustment for established prognostic factors.[23]

The neutrophil-to-lymphocyte ratio has a different interpretation in CLL than in solid tumors because the denominator largely consists of malignant lymphocytes. Consequently, a low ratio may indicate high leukemic burden rather than an effective antitumor lymphocyte response. Infection, corticosteroid exposure, marrow failure, and growth-factor administration also alter neutrophil counts, which may explain inconsistent prognostic findings across studies.[24]

Ratios incorporating monocytes may be biologically relevant because monocytes can differentiate into leukemia-supportive macrophages and contribute to immune suppression. The lymphocyte-to-monocyte ratio, monocyte-to-lymphocyte ratio, and neutrophil-to-monocyte ratio have demonstrated associations with treatment requirement or survival in exploratory studies. However, their incremental predictive value beyond absolute monocyte count, clinical stage, and molecular risk markers remains uncertain.[15]

The systemic immune-inflammation index is calculated from platelet, neutrophil, and lymphocyte counts and is intended to integrate inflammation, immune status, and tumor burden. Although this index has shown prognostic value in several malignancies, evidence supporting its routine use in CLL remains insufficient. Its mathematical dependence on lymphocyte count may also produce counterintuitive findings in a disease defined by clonal lymphocytosis.[24]

**Clinical Applicability**

The principal advantages of CBC-derived indices are accessibility, low cost, rapid availability, and suitability for repeated measurement. They may be particularly useful where fluorescence in situ hybridization, TP53 sequencing, IGHV analysis, or advanced imaging is unavailable. These indices may also help identify patients who require closer surveillance during watchful waiting, provided that changes are persistent and interpreted in the appropriate clinical context.[8]

Serial assessment may offer greater clinical value than a single baseline measurement. Increasing

lymphocyte count, declining hemoglobin or platelets, rising red cell distribution width, and changing monocyte-related ratios may collectively suggest disease evolution. Nevertheless, treatment initiation must remain based on accepted criteria such as symptomatic progression, worsening marrow failure, bulky disease, constitutional symptoms, or rapid lymphocyte expansion.[20]

CBC-derived measures may complement established prognostic models but should not replace molecular testing. TP53 abnormalities and IGHV mutational status provide biologically specific information that directly influences treatment selection, whereas blood-count indices are nonspecific. Their most realistic role is therefore as accessible adjuncts for preliminary risk assessment, longitudinal monitoring, and refinement of established prediction models.[13]

**Limitations of Current Evidence**

Most studies evaluating CBC-derived indices in CLL are retrospective, single-center, and based on relatively small or heterogeneous populations. Differences in disease stage, previous treatment, follow-up duration, supportive care, and therapeutic era reduce comparability. Many proposed cutoff values are derived from receiver operating characteristic analyses within the original cohort and lack external validation.[10]

CBC parameters are strongly influenced by conditions unrelated to CLL. Acute infection, autoimmune cytopenias, nutritional deficiencies, renal disease, inflammatory disorders, corticosteroids, anticoagulants, and recent transfusion may substantially alter calculated indices. Failure to exclude or adjust for these factors can create misleading associations between an index and clinical outcome.[11]

Laboratory variability is another important limitation. Mean platelet volume and platelet distribution width are affected by analyzer technology, anticoagulant type, storage conditions, and processing delay. Even routine differential counts may vary between automated systems. Standardized collection, processing, reporting, and cutoff definitions are therefore required before these markers can be reliably compared across institutions.[21]

Several indices contain overlapping components and may provide redundant prognostic information. For example, the platelet-to-lymphocyte ratio is strongly influenced by lymphocyte count and thrombocytopenia, both of which are already assessed clinically. Statistical significance does not necessarily demonstrate added clinical value; future studies should test whether an index improves discrimination, calibration, and decision-making beyond validated prognostic models.[23]

**Future Directions**

Prospective multicenter studies should evaluate CBC-derived indices in clearly defined treatment-naive and treated populations. Analyses should use standardized laboratory procedures, prespecified cutoff values, and clinically relevant outcomes such as time to first treatment, progression-free survival, overall survival, infection risk, and treatment toxicity. External validation is essential before any index can be recommended for routine practice.[10]

Future prognostic models may combine longitudinal CBC changes with clinical stage, comorbidity, molecular markers, and treatment exposure. Machine-learning approaches could identify nonlinear interactions and dynamic patterns that are not captured by static ratios. However, complex algorithms should demonstrate transparent interpretation, external reproducibility, and meaningful improvement over simpler clinical assessment.[8]

The prognostic relevance of CBC-derived indices should also be reassessed in patients receiving Bruton tyrosine kinase inhibitors, BCL2 inhibitors, and targeted combination therapy. Treatment-related lymphocytosis, cytopenias, bleeding, and infection can substantially alter blood-count parameters. Separate models may therefore be necessary for untreated patients, patients receiving continuous therapy, and those managed with fixed-duration regimens.[13]

**Conclusion**

Complete blood count–derived indices represent inexpensive, readily available, and reproducible biomarkers that may provide additional prognostic information in chronic lymphocytic leukemia. Parameters derived from leukocytes, erythrocytes, and platelets can reflect tumor burden, bone marrow reserve, systemic inflammation, and interactions within the leukemic microenvironment, making them

attractive adjuncts to routine clinical assessment. Although several indices have shown associations with disease stage, time to first treatment, and survival, current evidence is largely retrospective and lacks standardized cutoff values and prospective validation. Consequently, these biomarkers should be considered complementary rather than replacements for established clinical, cytogenetic, and molecular prognostic models. Future well-designed multicenter studies are needed to validate their clinical utility and determine how they can be integrated into personalized risk stratification and management of patients with chronic lymphocytic leukemia.

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