

The C-Reactive Protein-to-Albumin Ratio in Chronic Lymphocytic Leukemia: Links to Disease Biology, Treatment Response, and Survival

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Abstract

Background: Chronic lymphocytic leukemia (CLL) is characterized by marked clinical heterogeneity, ranging from indolent disease requiring prolonged observation to rapidly progressive leukemia associated with treatment resistance and shortened survival. Established prognostic models incorporate clinical stage, molecular abnormalities, immunoglobulin heavy-chain variable-region gene status, serum β 2-microglobulin, and selected cytogenetic lesions. Nevertheless, several of these assessments are costly or not routinely accessible, supporting continued interest in inexpensive biomarkers that reflect relevant components of CLL biology. The C-reactive protein-to-albumin ratio (CAR) combines a positive acute-phase reactant with a marker influenced by systemic inflammation, nutritional condition, hepatic synthesis, and disease burden. It may therefore provide a broader representation of the host–tumor interaction than either measurement alone. Persistent inflammatory signaling contributes to CLL-cell survival, immune dysregulation, stromal support, and resistance to apoptosis. Increased C-reactive protein may indicate cytokine-driven inflammation, infection, tissue injury, or progressive disease, whereas reduced albumin may reflect an inflammatory catabolic state, impaired nutritional reserve, comorbidity, or advanced illness. An elevated CAR has consequently been associated with unfavorable clinical and laboratory characteristics in several hematologic malignancies. Emerging evidence in CLL suggests potential relationships with leukocytosis, lymphocytosis, elevated lactate dehydrogenase, adverse cytogenetic abnormalities, reduced likelihood of complete response, and increased mortality. Its value for predicting relapse, however, remains uncertain. This review examines the biological basis of CAR in CLL, its relationship with conventional prognostic variables, and the available evidence regarding treatment response and survival. It also addresses important limitations, including inconsistent cut-off values, retrospective study designs, infection-related confounding, treatment heterogeneity, and insufficient external validation. CAR is a promising, accessible biomarker that may complement established prognostic systems, but prospective multicenter studies and standardized measurement strategies are required before it can be incorporated into routine risk stratification.

Keywords: Chronic lymphocytic leukemia; C-reactive protein-to-albumin ratio; systemic inflammation; prognostic biomarker; treatment response; survival.



Introduction

Chronic lymphocytic leukemia (CLL) is a mature B-cell neoplasm defined by a persistent circulating clone of at least $5 \times 10^9/L$ CD5-positive B lymphocytes with a characteristic immunophenotype. It predominantly affects older adults and displays exceptional clinical heterogeneity. Some patients remain asymptomatic without treatment for many years, whereas others develop progressive lymphadenopathy, marrow failure, constitutional symptoms, or treatment-resistant disease soon after diagnosis.^{1,2}

Current evaluation combines clinical assessment with hematologic, biochemical, cytogenetic, and molecular variables. The International Workshop on CLL criteria standardize diagnosis, treatment indications, and response assessment, while the Rai and Binet systems retain value for describing tumor burden and marrow compromise. These clinical stages, however, do not fully explain the different outcomes observed among patients within the same category.^{3,4,5}

The CLL International Prognostic Index (CLL-IPI) improves risk classification by integrating age, stage, serum beta-2 microglobulin, immunoglobulin heavy-chain variable-region gene (IGHV) status, and TP53 disruption. Although this framework is well validated, molecular testing may be unavailable or delayed in resource-constrained settings, and the prognostic weight of some variables has changed with targeted therapy. This has sustained interest in inexpensive routine markers that capture additional information about disease-host interactions.^{6,7}

The C-reactive protein-to-albumin ratio (CAR) is calculated from two widely available laboratory measurements. It combines the rise in C-reactive protein (CRP) accompanying systemic inflammation with the decline in albumin that may accompany inflammatory redistribution, increased catabolism, reduced synthesis, or poor physiologic reserve. This review examines how those processes intersect with CLL biology and critically evaluates whether CAR can inform treatment response and survival beyond established prognostic assessment.^{7,18}

Biological and Prognostic Heterogeneity of CLL

CLL arises from antigen-experienced B cells whose behavior reflects both intrinsic genomic lesions and continuous signals from lymphoid tissues. Recurrent copy-number changes, somatic mutations, epigenetic alterations, and stereotyped B-cell receptors shape clonal fitness. The disease is not simply an accumulation of long-lived circulating lymphocytes; active proliferation occurs mainly within lymph nodes and marrow niches, followed by recirculation into peripheral blood.^{8,9}

Genetic risk remains central to prognosis. Deletion 17p and pathogenic TP53 mutation identify impaired DNA-damage responses and historically predict poor survival and resistance to chemoimmunotherapy. Deletion 11q, trisomy 12, and deletion 13q define additional biologic groups, although their clinical effects depend on coexisting abnormalities, clonal burden, and treatment era. Consequently, CAR should be investigated as a complementary host-response marker rather than an alternative to FISH and TP53 sequencing.^{10,12}

IGHV mutation status separates biologically distinct forms of CLL. Unmutated IGHV is generally linked to stronger B-cell receptor responsiveness, shorter time to initial therapy, and less favorable long-term outcomes than mutated IGHV. CD38 and related surface markers also correlate with aggressive biology but do not perfectly substitute for IGHV analysis. An inflammatory index may partly track this biologic activity, yet direct mechanistic linkage between CAR and IGHV or CD38 remains insufficiently established.^{11,7}

The tissue microenvironment provides survival and proliferative signals through the B-cell receptor, NF-kappaB, chemokines, integrins, T cells, monocyte-derived nurse-like cells, and stromal elements. CLL cells isolated from lymph nodes demonstrate stronger B-cell receptor and NF-kappaB activation and greater proliferative activity than paired circulating cells. These observations provide a biological bridge between tumor burden, cytokine release, and systemic inflammatory measurements.^{13,14}

Inflammation, CRP, and Albumin

Cancer-related inflammation is not a passive epiphenomenon. Cytokines and transcriptional programs can support proliferation, angiogenesis, immune evasion, metabolic adaptation, and resistance to cell



death. In CLL, these pathways overlap with microenvironmental signaling that sustains the malignant clone. A systemic inflammatory marker may therefore reflect a mixture of leukemia activity, host immune response, tissue injury, infection, and comorbid disease rather than a single tumor-specific mechanism.^{15,14}

CRP is a pentraxin synthesized predominantly by hepatocytes under the influence of interleukin-6 and other inflammatory mediators. Concentrations can rise rapidly during infection, tissue injury, and active malignancy, then decline when the stimulus resolves. This dynamic behavior makes CRP clinically sensitive but biologically nonspecific. In CLL, an elevated value must never be attributed to leukemia before common infectious and inflammatory causes have been assessed.^{16,30}

Albumin behaves differently. Hypoalbuminemia during inflammation frequently reflects increased capillary permeability, expansion of the distribution volume, accelerated breakdown, and altered hepatic protein prioritization rather than inadequate dietary intake alone. Liver disease, renal or gastrointestinal protein loss, frailty, and fluid status also influence its concentration. Albumin therefore contributes information about systemic stress and physiologic reserve, but it is not a pure nutritional marker.^{17,29}

Combining CRP with albumin amplifies the contrast between a positive and a negative acute-phase variable. A high CAR can result from elevated CRP, reduced albumin, or both; these patterns are not necessarily biologically equivalent. Reporting the two component values alongside the ratio is essential because the same CAR may represent intense inflammation with preserved albumin or modest inflammation in a patient with substantial hypoalbuminemia.^{16,17}

Measurement and Interpretation of CAR

CAR is obtained by dividing the CRP concentration by the serum albumin concentration. The numeric value depends directly on the units used: CRP may be reported in mg/L or mg/dL, while albumin may be expressed in g/L or g/dL. Ratios generated from different unit combinations cannot be compared without conversion. Every study and clinical report should therefore state the assay units, sampling time, and formula explicitly.^{18,20}

A single universal threshold has not been established. Published studies have selected cut-offs using receiver operating characteristic analysis, medians, maximally selected statistics, or cohort-specific methods. Such data-derived thresholds may overestimate performance and often fail to transfer between populations. CAR should preferably be analyzed as a continuous variable, with any categorical threshold predefined and externally validated.^{18,21}

Timing is equally important. A pretreatment sample obtained during febrile infection, recent surgery, autoimmune hemolysis, corticosteroid exposure, dehydration, or intravenous fluid administration may not represent stable leukemia-associated inflammation. Repeat testing after resolution of an acute disturbance can separate transient elevation from a persistent phenotype and may be more informative than an isolated measurement.³⁰

Evidence Linking CAR to CLL Outcomes

The most direct CLL-specific evidence comes from the clinical analysis by Tang and colleagues of 322 newly diagnosed patients. Higher pretreatment CAR was associated with adverse clinical characteristics and inferior treatment-free and overall survival, and the association with outcome persisted in multivariable analysis. This study established proof of concept that a routine inflammation-based ratio may carry prognostic information in CLL.¹⁸

Earlier evidence also supports the importance of the CRP component. In 107 treatment-naïve patients, Herishanu and colleagues found that baseline CRP at or above 0.4 mg/dL was independently associated with all-cause mortality and second solid malignancies. The study did not evaluate CAR, but it showed that a systemic inflammatory signal measured before therapy was clinically relevant within CLL rather than only in aggressive lymphomas or solid tumors.¹⁹

The CAR literature in CLL remains narrow, and the commentary accompanying the pivotal report correctly emphasized the need for validation. The available studies are vulnerable to retrospective design, center-specific practice, nonuniform supportive care, and incomplete adjustment for infection or comorbidity. Evidence is therefore promising but not sufficient to classify CAR as an independent

standard prognostic factor.^{20,23} Findings from other hematologic malignancies provide biological consistency but cannot be transferred directly. In diffuse large B-cell lymphoma, high pretreatment CAR was associated with a lower complete response rate and inferior survival. In newly diagnosed acute myeloid leukemia, elevated CAR also identified patients with adverse features and poorer outcomes. These observations support investigation of CAR across blood cancers, while the different disease kinetics and treatment goals require CLL-specific confirmation.^{21,22}

Table 1. Representative CLL evidence supporting inflammation-based prognostication

Evidence	Principal finding	Key limitation
Tang et al.: CLL, n=322; CAR	Higher CAR accompanied adverse features and inferior treatment-free and overall survival.	Retrospective, single-country cohort; cut-off needs external validation.
Herishanu et al.: CLL, n=107; CRP	CRP ≥0.4 mg/dL independently predicted mortality and second solid cancers.	Assessed CRP rather than CAR; modest cohort and event count.

Abbreviations: CAR, C-reactive protein-to-albumin ratio; CLL, chronic lymphocytic leukemia; CRP, C-reactive protein. Sources: ^{18,19}

Treatment Response, Remission, and Disease Control

Response assessment in CLL includes clinical examination, blood counts, marrow evaluation when indicated, and radiologic assessment according to the treatment context. Complete remission remains a meaningful outcome, but its interpretation differs among therapeutic classes. Continuous Bruton tyrosine kinase inhibition may produce durable disease control without rapid deep remission, whereas fixed-duration venetoclax-based combinations are designed to achieve deep responses and frequently undetectable measurable residual disease (uMRD).^{3,26,27} Evidence that CAR predicts complete remission in CLL is currently limited. Studies in aggressive hematologic malignancies suggest that a high ratio may identify patients less likely to achieve complete response, and small institutional CLL observations point in the same direction. However, this association could reflect stage, infection, performance status, treatment selection, or TP53 disruption rather than resistance mediated by inflammation itself. CAR should not be used to select a regimen or to withhold potentially effective treatment.^{18,21} Modern response endpoints also complicate biomarker evaluation. With ibrutinib, complete remission occurs in a minority of patients and may deepen over time, so early response category is not an adequate universal surrogate. Across trials of targeted or obinutuzumab-based therapy, uMRD is associated with longer progression-free survival, particularly after time-limited regimens. Future CAR studies should therefore evaluate response using therapy-specific endpoints, including uMRD and progression-free survival, rather than relying only on conventional complete remission.^{24,25} Dynamic CAR may prove more informative than baseline CAR. A persistent or rising ratio during therapy could indicate ongoing inflammation, infection, treatment toxicity, or uncontrolled leukemia, while normalization might accompany clinical improvement. These interpretations remain hypothetical because longitudinal CLL datasets are scarce. Sampling should be protocolized at baseline, after acute complications resolve, at response assessment, and during surveillance.^{18,23}

CAR and Survival

Overall survival in CLL reflects more than leukemic progression. Infections, second cancers,



cardiovascular disease, treatment toxicity, autoimmune complications, and age-related comorbidity contribute substantially. A high CAR may integrate several of these competing hazards, which helps explain its association with mortality but also limits its specificity for leukemia-related death.^{28,29}

The survival signal reported for CAR is consistent with evidence for CRP alone. Elevated baseline CRP independently predicted mortality in treatment-naïve CLL and was linked to subsequent second solid cancers. Tang and colleagues then demonstrated inferior overall survival among patients with higher CAR. Together, these findings support prognostic relevance, but they do not prove that lowering CRP or increasing albumin will improve leukemia outcomes.^{18,19}

Cause-specific analysis is necessary. The CLL-IPI stratifies not only survival but also the distribution of causes of death, with progressive CLL becoming more prominent at higher risk. CAR may be particularly sensitive to infection-related and comorbidity-related mortality. Future studies should report CLL-specific survival, nonrelapse mortality, infection-related death, second malignancies, and overall survival separately, using competing-risk methods where appropriate.^{28,30}

Relationship With Established Prognostic Factors

CAR and CLL-IPI describe different domains. The CLL-IPI emphasizes tumor biology and burden through TP53, IGHV, beta-2 microglobulin, stage, and age; CAR emphasizes systemic inflammation and physiologic reserve. A meaningful role for CAR would therefore be incremental: it should improve discrimination, calibration, or clinical decision-making after these validated variables are included, rather than merely remain significant in an incompletely adjusted model.^{6,7}

Associations between high CAR and leukocytosis, lymphocytosis, lactate dehydrogenase, advanced stage, or adverse cytogenetics are clinically plausible because all may accompany greater disease activity. They also raise the possibility that CAR is a surrogate for variables already available in routine evaluation. Comparative models must quantify collinearity and determine whether CAR provides information beyond beta-2 microglobulin, stage, TP53 status, IGHV status, and performance status.^{18,23}

The prognostic hierarchy is treatment dependent. TP53 disruption and unmutated IGHV remain important, but their effects are modified by targeted agents. Similarly, a CAR threshold developed in a chemoimmunotherapy cohort may not retain the same meaning among patients receiving BTK or BCL2 inhibitors. Validation must therefore be stratified by treatment class, line of therapy, and whether treatment is continuous or fixed-duration.^{12,34}

Confounding and Methodological Limitations

Infection is the most important immediate confounder. CLL causes immune dysfunction before treatment, and hypogammaglobulinemia, neutropenia, previous therapy, and advanced disease increase infectious risk. Bloodstream infections contribute appreciably to morbidity and mortality and can cause abrupt CRP elevation with concurrent albumin decline. Baseline CAR should be interpreted only after documenting whether infection was present at sampling.^{30,31}

Autoimmune cytopenias, liver disease, renal protein loss, inflammatory disorders, recent procedures, and corticosteroid treatment can alter one or both components of CAR. Autoimmune hemolytic anemia is a recognized CLL complication and may generate inflammation independent of tumor progression. Studies should prespecify exclusions or adjustment strategies and report the individual CRP and albumin values so readers can identify the dominant component.^{17,32}

Because infectious susceptibility varies across the CLL course, one exclusion at diagnosis is not enough. Studies of serial CAR should record antimicrobial treatment, immunoglobulin replacement, neutrophil counts, and microbiologically documented infection at every sampling point. This approach can reduce misclassification of infection-driven CAR elevation as leukemia progression or treatment resistance.³³

Existing evidence also faces statistical limitations. Small event counts increase model instability, while selecting a cut-off and testing it in the same cohort produces optimism. Missing molecular data can leave residual confounding, and short follow-up may be inadequate for an indolent disease. External validation, internal resampling, transparent missing-data methods, and time-dependent analyses are required before a ratio can be considered clinically reliable.^{20,23}

Clinical Implications and Future Directions



At present, CAR may be used as a contextual risk signal rather than a treatment-determining biomarker. An unexpectedly high value should prompt confirmation of units and repeat measurement, assessment for infection or inflammatory disease, review of hepatic and renal function, and examination of the separate CRP and albumin results. It should not replace iwCLL treatment indications, molecular testing, clinical staging, or direct response assessment.^{3,34}

Prospective multicenter studies should enroll patients at diagnosis and before therapy, use standardized assays and units, record acute inflammatory conditions, and obtain serial samples. Models should include the CLL-IPI components and treatment class, then test whether CAR improves C statistics, calibration, reclassification, and decision curves. Predefined thresholds should be validated in independent geographic and socioeconomic populations.^{6,18}

The most useful research question may not be whether CAR is statistically associated with survival, but whether it changes a clinical decision. Potential applications include identifying patients who need closer evaluation for infection or frailty, enriching clinical trials for high-risk host biology, and monitoring systemic recovery during fixed-duration therapy. Each application requires a distinct sampling schedule, outcome definition, and validation standard.^{17,24}

Mechanistic studies are also needed. Correlating CAR with cytokine profiles, lymph-node activity, clonal genomics, immune-cell phenotypes, and body-composition measures could determine whether the ratio primarily reflects leukemia-driven inflammation, infection susceptibility, or host reserve. Such work would clarify whether CAR is simply a prognostic reporter or a marker of modifiable biological pathways.^{13,15}

Conclusion

CAR is an inexpensive and readily available marker that links systemic inflammation with albumin-based measures of physiologic stress. The available CLL evidence associates higher pretreatment CAR with unfavorable disease features, earlier treatment requirement, and inferior survival. Its biological plausibility is strengthened by the inflammatory and microenvironmental mechanisms that support CLL-cell survival, but the ratio remains nonspecific and strongly influenced by infection, comorbidity, and organ function.

CAR should therefore be viewed as a candidate complementary biomarker, not a replacement for clinical stage, TP53 assessment, IGHV status, beta-2 microglobulin, or validated response measures. Standardized prospective validation in patients receiving contemporary targeted therapy is essential before CAR can be incorporated into routine prognostic models or treatment algorithms.

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