

Editorial

Pretreatment hyperuricemia and hypoalbuminemia as predictors for one-year mortality in diffuse large B-cell lymphoma beyond the international prognostic index

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The International Prognostic Index (IPI), developed more than three decades ago, remains the cornerstone of risk stratification in Diffuse large B-cell lymphoma (DLBCL). By incorporating age, performance status, Ann Arbor stage, serum lactate dehydrogenase (LDH) level, and the number of extranodal sites, the IPI effectively discriminates among broad prognostic groups.¹ Nevertheless, the IPI has well-recognized limitations. Its prognostic discrimination within intermediate-risk groups is suboptimal, it does not account for biological heterogeneity, and it was largely derived from cohorts treated in the pre-rituximab era. Updated tools, such as the revised IPI (R-IPI) and the National Comprehensive Cancer Network IPI (NCCN-IPI), have improved prognostic discrimination; however, considerable prognostic uncertainty persists, underscoring the need for additional, easily accessible biomarkers.^{2,3}

Serum uric acid (SUA), the end-product of purine catabolism catalyzed by xanthine oxidase, has emerged as a potential biomarker in hematological malignancies. Elevated pretreatment SUA reflects increased cellular turnover and tumor burden, and hyperuricemia has been associated with adverse outcomes in several lymphoma subtypes.^{4,5} Beyond its role as a surrogate of proliferative activity, uric acid exerts direct pro-inflammatory and pro-oxidative effects that may promote an immunosuppressive tumor microenvironment, potentially facilitating disease progression and treatment resistance. Importantly, SUA is a universally available, inexpensive and reproducible laboratory parameter, making it an

attractive candidate for routine prognostic assessment, particularly in resource-limited settings.⁶

Serum albumin concentration, a well-established marker of nutritional status and systemic inflammation, has been incorporated into prognostic scoring systems across a wide spectrum of malignancies. In DLBCL, hypoalbuminemia at presentation may reflect the combined effects of cancer-induced cachexia, chronic inflammatory cytokine activity and impaired hepatic synthetic function.^{7,8} Low serum albumin levels have been associated with inferior treatment tolerance, increased chemotherapy-related toxicity and impaired immune reconstitution following cytotoxic therapy. Several retrospective series have demonstrated that hypoalbuminemia independently predicts overall survival in patients with aggressive lymphomas; however, it has not been formally incorporated into standard prognostic indices.⁹

In this issue of the journal, the authors present a retrospective cohort study evaluating the prognostic significance of pretreatment hyperuricemia and hypoalbuminemia for one-year mortality in patients with newly diagnosed DLBCL. The authors demonstrate that both elevated SUA levels and reduced serum albumin concentrations at diagnosis are independently associated with inferior one-year overall survival, retaining their prognostic value even after adjustment for conventional IPI components. These findings contribute meaningfully to the growing body of evidence supporting the use of readily available biochemical parameters to refine risk

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stratification in DLBCL beyond that provided by the IPI. The biological rationale underpinning these associations is compelling. Tumor cell lysis, whether spontaneous or therapy-induced, releases large quantities of intracellular purines that are subsequently converted to uric acid. In high-grade lymphomas, persistently elevated pretreatment SUA may therefore reflect a high proliferative index and substantial tumor burden, both of which independently confer a poor prognosis.^{4,5} Concurrently, hypoalbuminemia serves as a proxy for the systemic inflammatory state that frequently accompanies aggressive lymphoma. The albumin-to-globulin ratio and similar derived indices have been shown to correlate with cytokine-mediated immune dysregulation, and hypoalbuminemia has been associated with reduced expression of drug transporter proteins, potentially diminishing intracellular anthracycline concentrations and thereby attenuating chemotherapy efficacy.^{7,8}

The potential synergism between hyperuricemia and hypoalbuminemia warrants particular attention. When co-present, these abnormalities may reflect a state of high tumor burden coupled with systemic metabolic derangement that collectively undermines the host's capacity to mount an effective antitumor response. Future studies should explore whether combining these two parameters into a composite score, similar to the albumin-bilirubin (ALBI) grade used in hepatocellular carcinoma, could provide additive discriminatory power beyond that of existing prognostic indices.¹⁰ Such a tool, requiring only two inexpensive and widely available biochemical measurements, would be particularly valuable in low- and middle-income countries, where access to advanced molecular profiling remains limited.

From a clinical standpoint, incorporating SUA and serum albumin into routine pre-treatment assessment may help identify a subset of patients with intermediate-risk DLBCL who may benefit from more intensive therapeutic strategies, earlier salvage planning or

enrollment in clinical trials investigating novel agents. For instance, patients with both hyperuricemia and hypoalbuminemia might be prioritized for dose-dense regimens, polatuzumab vedotin-based combinations or consolidative autologous stem cell transplantation in first remission, provided that fitness criteria are met.^{11,12} Conversely, these biomarkers could assist in identifying frail patients for whom aggressive therapy may carry a disproportionate risk of toxicity, thereby guiding individualized treatment de-escalation.

Several methodological considerations merit discussion. The retrospective design inherently limits causal inference, and residual confounding from unmeasured variables, including cell-of-origin subtype, MYC/BCL2 double-expression status and comorbidity burden, cannot be excluded. Pre-analytical variability in SUA measurement, including the effects of dietary purine intake and concurrent medication use (e.g., diuretics and low-dose aspirin), may introduce non-differential misclassification. Similarly, hypoalbuminemia may reflect concurrent non-malignant conditions, such as liver disease or nephrotic syndrome, rather than tumor-driven catabolism. Prospective multicenter validation across diverse ethnic and socioeconomic populations is essential before these biomarkers can be recommended for routine clinical implementation.

In conclusion, the study provides encouraging evidence that pretreatment hyperuricemia and hypoalbuminemia are clinically meaningful and readily accessible prognostic biomarkers that enhance risk stratification in DLBCL beyond that provided by the IPI. As the field moves toward precision oncology, the judicious incorporation of simple biochemical parameters alongside molecular profiling may bridge the gap between biological complexity and practical clinical utility, ultimately improving risk-adapted management for patients with this potentially curable yet frequently lethal disease.

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