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Evaluating Body Mass Index and Platelet-to-Lymphocyte Ratio as Predictors of Survival in Diffuse Large B-Cell Lymphoma Treated with R-CHOP

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ABSTRACT

Background: Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, accounting for approximately 30–40% of adult cases worldwide. The standard first-line therapy, consisting of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), achieves high response rates; however, outcomes vary significantly among patients with similar clinical features. While the International Prognostic Index (IPI) remains a cornerstone for risk stratification, increasing attention has been given to host-related biomarkers, such as body mass index (BMI) and inflammatory markers, which may reflect tumor biology, immune competence, and treatment tolerance. The platelet-to-lymphocyte ratio (PLR), a simple and inexpensive marker derived from peripheral blood counts, has emerged as a potential prognostic factor in various malignancies, including hematologic cancers. This review critically examines the evidence on BMI and PLR as predictors of survival in patients with DLBCL treated with R-CHOP. The goal is to synthesize mechanistic insights, epidemiological data, and clinical trial findings to evaluate whether these markers provide independent prognostic information beyond established clinical models, and to explore their potential integration into personalized treatment strategies. **Conclusion:** Available evidence suggests that BMI may exert a U-shaped prognostic effect in DLBCL, with underweight patients exhibiting poorer survival due to frailty and treatment intolerance, and overweight/obese patients demonstrating variable outcomes possibly linked to altered pharmacokinetics, immune modulation, and comorbidities. The prognostic role of PLR is supported by its association with systemic inflammation, immune suppression, and tumor-promoting platelet activity; high PLR has been correlated with inferior progression-free and overall survival in multiple cohorts. However, heterogeneity in cutoff values, retrospective designs, and limited prospective validation hinder definitive conclusions. Preliminary data indicate that combining BMI and PLR could improve risk discrimination, particularly in patients with intermediate IPI scores. Nevertheless, the translation of these findings into clinical practice requires prospective, multi-center studies with standardized methodologies. Integrating BMI and PLR with molecular subtyping and genomic profiling may further refine prognostication and guide individualized therapeutic approaches in DLBCL.

Keywords*:* *Body Mass Index, Platelet-to-Lymphocyte Ratio, Diffuse Large B-Cell Lymphoma, R-CHOP*

Introduction

Diffuse Large B-Cell Lymphoma (DLBCL) represents a clinically and biologically heterogeneous group of aggressive B-cell non-Hodgkin lymphomas, accounting for approximately one-third of newly diagnosed cases globally. Despite advances in molecular profiling and targeted therapies, the backbone

10.48047/jocaaa.2024.33.06.102
of treatment for most patients remains the combination of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), which has been the standard of care for over two decades. While the majority of patients achieve complete remission with first-line therapy, relapse or refractory disease occurs in approximately 30–40% of cases, and survival outcomes remain highly variable even among patients with similar baseline characteristics [1].

Risk assessment in DLBCL traditionally relies on the International Prognostic Index (IPI), which incorporates age, stage, serum lactate dehydrogenase (LDH), performance status, and extranodal disease sites. Although the IPI provides clinically meaningful stratification, it does not account for host-related biological factors or systemic inflammation, both of which have been increasingly recognized as influential determinants of cancer outcomes [2]. Moreover, novel molecular classifications based on cell-of-origin (COO) and genetic signatures have improved biological understanding but have yet to be universally adopted into routine prognostic algorithms [3].

Body Mass Index (BMI) is a widely available anthropometric measure that has been linked to outcomes across various cancers, including hematologic malignancies. Its prognostic role in DLBCL is complex, with evidence suggesting both detrimental effects of low BMI due to frailty and conflicting data regarding overweight and obesity, which may influence pharmacokinetics, immune function, and the tumor microenvironment [4]. The Platelet-to-Lymphocyte Ratio (PLR), derived from routine complete blood counts, is an emerging inflammatory marker that reflects the interplay between platelet-mediated tumor promotion and lymphocyte-mediated anti-tumor immunity. Elevated PLR has been associated with inferior survival in multiple solid and hematologic tumors, potentially serving as a surrogate of systemic inflammation and immune suppression [5].

The aim of this review is to evaluate current evidence regarding BMI and PLR as prognostic indicators in DLBCL patients treated with R-CHOP, to assess their potential integration into existing risk models, and to explore future directions for their clinical application. By consolidating mechanistic insights, epidemiological findings, and clinical outcomes, this review seeks to clarify whether these markers can contribute to a more personalized prognostic framework for DLBCL management [6].

Overview of DLBCL and R-CHOP Outcomes

Diffuse Large B-Cell Lymphoma (DLBCL) encompasses a biologically diverse set of aggressive lymphoid malignancies characterized by rapid clinical progression in the absence of treatment. Epidemiologically, DLBCL affects both younger and older adults, but its incidence increases with age, with a median age at diagnosis of approximately 65 years [7]. Over the last two decades, the addition of rituximab to the CHOP regimen has transformed treatment outcomes, yielding significant improvements in complete remission rates and overall survival (OS) across patient populations [8]. Despite these advances, a substantial subset of patients—estimated at 30–40%—either fail to achieve

10.48047/jocaaa.2024.33.06.102

remission or relapse within the first two years of therapy, underscoring the need for better prognostic tools [9].

The R-CHOP regimen, administered every 21 days for six to eight cycles, remains the gold standard for most patients, regardless of cell-of-origin (COO) classification. This chemoimmunotherapy combination targets malignant B cells via both cytotoxic mechanisms and immune-mediated antibody-dependent cellular cytotoxicity. While its efficacy is well established, survival outcomes vary widely, with five-year OS rates ranging from over 80% in low-risk patients to less than 50% in high-risk groups, as determined by the International Prognostic Index (IPI) [10]. Such heterogeneity suggests that factors beyond the IPI, including biological host characteristics, contribute to treatment outcomes. In recent years, studies have explored the prognostic influence of tumor biology, host immune status, nutritional condition, and systemic inflammation. These host-related variables may affect not only the patient's resilience to intensive chemotherapy but also the tumor microenvironment and immunologic control of lymphoma growth [11]. In particular, anthropometric measurements like BMI and inflammatory biomarkers such as the platelet-to-lymphocyte ratio (PLR) have gained attention as easily obtainable, cost-effective indicators with potential prognostic value in DLBCL [12]. By integrating such parameters with established clinical and molecular markers, clinicians may improve individualized risk stratification and guide therapeutic decision-making, potentially enhancing long-term survival outcomes.

Overview of DLBCL and R-CHOP Outcomes

Diffuse Large B-Cell Lymphoma (DLBCL) is the most frequent subtype of non-Hodgkin lymphoma (NHL) in adults, with an incidence of approximately 5–7 cases per 100,000 individuals annually. It presents with diverse clinical manifestations ranging from localized nodal disease to widespread extranodal involvement. The heterogeneity in presentation and outcome is underpinned by substantial molecular diversity, including cell-of-origin (COO) subtypes—germinal center B-cell-like (GCB) and activated B-cell-like (ABC)—as well as distinct genetic alterations that drive pathogenesis [7].

The introduction of rituximab to the CHOP chemotherapy backbone at the beginning of the 21st century represented a major breakthrough in the treatment of DLBCL. The R-CHOP regimen improved overall survival (OS) and progression-free survival (PFS) across age groups and disease stages, leading to its adoption as the global standard of care. Typical administration involves 6–8 cycles every 21 days, with supportive care tailored to minimize treatment-related toxicities [8].

Despite these advances, approximately one-third of patients relapse or develop refractory disease, with poor salvage outcomes, particularly for those not eligible for autologous stem cell transplantation. Long-term follow-up from pivotal trials demonstrates that while R-CHOP achieves cure rates approaching 60–70%, a significant subset of patients remains at high risk for treatment failure. This

10.48047/jocaaa.2024.33.06.102

underscores the ongoing need to identify additional prognostic markers beyond the International Prognostic Index (IPI) [9].

The IPI remains the most widely used clinical prognostic tool, but it primarily reflects tumor burden and general patient fitness rather than individual host biology or tumor-immune interactions. Biomarkers such as Body Mass Index (BMI) and Platelet-to-Lymphocyte Ratio (PLR) represent accessible, cost-effective parameters that could complement existing models. These markers may help refine risk prediction, particularly in intermediate-risk patients where treatment strategies are less clearly defined [10].

In this context, evaluating BMI and PLR alongside traditional clinical and molecular markers offers a potential pathway toward a more nuanced and individualized approach to prognostication in DLBCL. Their integration could ultimately inform therapeutic decision-making, optimize resource allocation, and improve patient outcomes [11].

Prognostic Factors in DLBCL

Risk stratification in DLBCL is crucial for guiding therapeutic decisions and estimating patient outcomes. Historically, the International Prognostic Index (IPI) has been the most widely adopted tool, incorporating five clinical parameters: age greater than 60 years, Ann Arbor stage III/IV disease, elevated serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status ≥2, and involvement of more than one extranodal site [12]. While the IPI effectively distinguishes between low- and high-risk patients, it does not account for the underlying biological diversity of the disease or host-related factors that may influence treatment tolerance and survival [13]. Molecular profiling has revealed that cell-of-origin (COO) classification—differentiating germinal center B-cell-like (GCB) from activated B-cell-like (ABC) subtypes—has independent prognostic value, with the ABC subtype generally associated with inferior outcomes following R-CHOP therapy [14]. More recently, genomic classifications incorporating recurrent mutations and structural alterations have identified additional prognostic subsets; however, such testing is not yet universally available in routine clinical practice [15].

Beyond tumor-intrinsic characteristics, host-related factors have emerged as important determinants of prognosis in DLBCL. Measures such as nutritional status, comorbidity burden, and systemic inflammation can significantly affect both treatment efficacy and tolerability. In this regard, Body Mass Index (BMI) and Platelet-to-Lymphocyte Ratio (PLR) are particularly attractive because they are simple, inexpensive, and routinely available from standard clinical evaluations [16].

BMI reflects body composition and nutritional reserves, which may impact chemotherapy pharmacokinetics, immune function, and resilience against treatment-related toxicity. PLR, on the other hand, serves as an inflammatory marker integrating both pro-tumor platelet activity and anti-tumor lymphocyte-mediated immunity. Elevated PLR has been linked to adverse survival outcomes

10.48047/jocaaa.2024.33.06.102
across various malignancies, suggesting a generalized prognostic significance that warrants exploration in DLBCL [17].

The integration of such biomarkers into existing prognostic frameworks has the potential to refine risk classification, particularly among patients who fall into intermediate IPI categories. This could facilitate more individualized treatment approaches, such as therapy intensification in high-risk individuals or de-escalation in those predicted to have favorable outcomes [18].

Body Mass Index and Cancer Outcomes

Body Mass Index (BMI) is a widely used anthropometric measure that classifies individuals into underweight, normal weight, overweight, and obese categories based on the ratio of weight to height squared (kg/m^2). While it is an imperfect surrogate for body composition, BMI remains a valuable epidemiologic tool due to its simplicity, reproducibility, and universal accessibility. In oncology, BMI has been investigated both as a risk factor for cancer development and as a prognostic indicator in patients with established malignancies [19].

In solid tumors, numerous studies have demonstrated a U-shaped or J-shaped relationship between BMI and survival, where both underweight and morbid obesity are associated with poorer outcomes. Mechanisms for these associations may include differences in pharmacokinetics of cytotoxic agents, systemic inflammation, metabolic dysregulation, and comorbidities [20]. In the context of hematologic malignancies, undernutrition has been linked to increased treatment-related toxicity and reduced treatment adherence, while excessive adiposity may influence immune surveillance, cytokine profiles, and stromal support for tumor growth [21].

The “obesity paradox” has been described in several cancer types, including certain lymphomas, where overweight or mildly obese patients appear to have improved survival compared to their normal-weight counterparts. Proposed explanations include greater metabolic reserve during intensive treatment, higher relative doses of chemotherapy when dosing is based on actual body weight, and possible immunomodulatory effects of adipose tissue [22]. However, the paradox remains controversial, with many studies confounded by differences in comorbidity burden, physical activity, and unmeasured nutritional factors [23].

For DLBCL specifically, BMI has been variably associated with treatment outcomes. Some studies have reported that overweight and obese patients treated with R-CHOP experience similar or even superior survival compared to normal-weight patients, while underweight patients consistently demonstrate inferior progression-free and overall survival. Nonetheless, conflicting findings exist, reflecting differences in study populations, BMI cutoff definitions, and adjustments for comorbidities [24].

Given its ease of measurement, BMI could serve as a useful adjunctive prognostic tool in DLBCL. However, reliance on BMI alone ignores important aspects of body composition, such as sarcopenia

10.48047/jocaaa.2024.33.06.102

and visceral fat distribution, which may better predict outcomes. Integrating BMI with other nutritional and inflammatory markers may provide a more comprehensive assessment of patient risk [25].

Mechanistic Links between BMI and DLBCL

Excess adiposity reshapes systemic metabolism and immunity in ways that may influence lymphoma biology and outcomes. Adipose tissue functions as an active endocrine organ, secreting adipokines (leptin, adiponectin, resistin) and pro-inflammatory cytokines (IL-6, TNF-α) that sustain low-grade inflammation, promote STAT3/NF-κB signaling, and can support malignant B-cell survival. Obesity-associated insulin resistance elevates insulin and IGF-1, activating PI3K–AKT–mTOR pathways implicated in lymphomagenesis and chemoresistance. These intersecting axes—chronic inflammation and growth-factor signaling—provide biologic plausibility for BMI's association with DLBCL prognosis. [26–29]

Adipokines may exert direct effects on B cells and the tumor microenvironment. Leptin can enhance lymphocyte proliferation and skew T-cell polarization toward a pro-inflammatory phenotype, potentially suppressing effective anti-tumor immunity, whereas adiponectin generally has anti-inflammatory, pro-apoptotic properties that are often reduced in obesity. Macrophage infiltration of hypertrophic adipose tissue further amplifies IL-6 and TNF-α release, fostering a milieu that can facilitate tumor growth and impair cytotoxic responses. Variability in these adipokine profiles across BMI categories could partly explain heterogeneity in outcomes, including reports of an "obesity paradox" with better survival in overweight but not severely obese patients. [26–28,30]

Body composition—not just BMI—modulates chemotherapy pharmacology. Sarcopenia and sarcopenic obesity (high fat mass with low skeletal muscle) are associated with altered distribution volumes, higher effective drug exposure per lean mass, and greater toxicity risk even when BMI is normal or elevated. In lymphoma, low skeletal muscle index has correlated with increased treatment-related adverse events and inferior survival, suggesting that lean mass better captures physiologic reserve than BMI alone. These insights argue for integrating cross-sectional body composition assessments when interpreting BMI-outcome relationships. [31–33]

Obesity can influence the pharmacokinetics and dosing of cytotoxics used in R-CHOP. Historically, dose capping or empiric dose reductions in patients with high BMI were common due to toxicity concerns, but evidence-based guidelines recommend full weight-based dosing to avoid compromising cure rates. Suboptimal dosing of doxorubicin or cyclophosphamide may attenuate R-CHOP efficacy; conversely, sarcopenic patients—regardless of BMI—may experience heightened toxicity at standard doses. Thus, BMI interacts with dosing practices and lean mass to shape both tolerability and effectiveness of therapy. [34–35,31]

Adipose depots may also create sanctuary niches affecting monoclonal antibody distribution and immune effector functions. While rituximab exposure correlates primarily with tumor burden and

10.48047/jocaaa.2024.33.06.102

patient-specific clearance factors, obesity-related changes in Fc-mediated cytotoxicity, complement activity, or cytokine milieu could modulate antibody-dependent cellular cytotoxicity. Coupled with obesity-related thrombocytosis and lymphopenia in some patients, these host factors could converge to influence both BMI and PLR signals captured in prognostic studies. Hypothesis-driven translational work interrogating these links remains a priority. [27–29,32]

Clinical Evidence for BMI as a Prognostic Factor in DLBCL

Across retrospective cohorts, higher BMI has frequently correlated with equal or better survival among patients with DLBCL treated in the rituximab era. In a large U.S. Veterans cohort, increased BMI was associated with improved overall survival independent of age and comorbidity, suggesting that metabolic reserve and full weight-based dosing may offset theoretical disadvantages of adiposity. Similar signals have been observed in non-Veterans cohorts, supporting that the relationship is not population-restricted. Collectively, these data underpin the frequently cited—though debated—“obesity paradox” in DLBCL outcomes [36,37].

Evidence from cooperative group and population datasets indicates that BMI effects may extend beyond a single study context. An analysis from U.S. Intergroup trials reported that overweight and mild obesity were not detrimental and, in some settings, associated with favorable outcomes, whereas underweight status consistently tracked with inferior survival. Earlier work in intermediate-grade B-cell NHL also suggested that extremes of BMI, particularly low BMI, portend worse prognosis—findings that align with clinical impressions of frailty and treatment intolerance [38,39].

Body-fat distribution appears to refine risk beyond BMI category. In patients receiving frontline R-CHOP, higher visceral adipose tissue quantified on imaging—rather than BMI per se—was associated with worse survival, highlighting that central adiposity may capture biologically adverse inflammation and endocrine signaling more precisely than a height-weight ratio. Conversely, loss of fat mass and cachexia, which can occur across BMI categories, has been linked to inferior outcomes in immunochemotherapy-treated DLBCL, reinforcing that dynamic changes in nutritional status matter [40,41].

The prognostic disadvantage of being underweight at diagnosis is among the most reproducible observations. Underweight patients experience higher rates of treatment-related toxicity, dose delays, and early discontinuation, culminating in inferior progression-free and overall survival. These effects likely reflect diminished physiologic reserve and coexistent sarcopenia—features not captured by BMI alone and that can coexist even in normal- or high-BMI patients. This underscores the need to interpret BMI within a broader assessment of body composition and fitness [21,31–33,38].

Interpretation of BMI-outcome studies requires attention to confounders and practice patterns. Historical dose capping or empiric reductions in obese patients could artifactually worsen outcomes, while guideline-concordant full weight-based dosing tends to neutralize such bias. Conversely,

10.48047/jocaaa.2024.33.06.102
sarcopenic patients (including those with normal or high BMI) may be functionally "overdosed" relative to lean mass and suffer excess toxicity. Standardizing dosing to actual body weight for obese patients and integrating body-composition measures where feasible may clarify BMI's independent prognostic contribution in DLBCL [34,35].

Controversies and Limitations in BMI-Related Outcomes

The prognostic role of BMI in DLBCL remains controversial due to inconsistencies in study design, population characteristics, and statistical adjustments. Many investigations are retrospective and rely on baseline BMI without accounting for changes during treatment, which may be clinically relevant. Weight loss during therapy—whether intentional or due to disease progression, toxicity, or cachexia—can confound associations between baseline BMI and survival outcomes. Additionally, BMI does not distinguish between lean and fat mass, and thus cannot differentiate sarcopenic obesity from metabolically healthy obesity, both of which may have distinct prognostic implications [42].

Cut-off points used to define BMI categories vary across studies and populations. While the World Health Organization (WHO) classification is most common, some Asian studies employ lower thresholds to reflect regional body composition differences, potentially affecting cross-study comparability. These inconsistencies complicate meta-analysis and may contribute to conflicting conclusions regarding the "obesity paradox" in lymphoma. Moreover, many studies inadequately adjust for comorbidities, socioeconomic factors, and performance status, which can influence both BMI and survival [19,36,43].

The "obesity paradox" itself is subject to methodological criticism. Reverse causation, whereby low BMI reflects underlying disease burden or pre-diagnosis weight loss, can create the appearance that higher BMI is protective. Inflammatory and metabolic changes in cancer can precede diagnosis by months or years, leading to cachexia and underweight status at presentation that portends poorer prognosis independent of BMI's true biological effect. Prospective studies with longitudinal BMI and body composition measurements are needed to disentangle these effects [44].

Another limitation is the lack of integration of BMI into existing prognostic models for DLBCL. The IPI and its variations remain dominant in clinical practice, and while BMI is easily measured, its independent contribution has yet to be validated in large, prospective, multi-center trials. Without standardized measurement protocols and consistent analytic frameworks, BMI will remain an adjunctive rather than definitive prognostic factor in this disease. Addressing these gaps will be crucial before BMI can be confidently incorporated into risk-adapted treatment algorithms [45].

Finally, the heterogeneity of R-CHOP delivery—including dose modifications, supportive care use, and access to salvage therapies—can influence BMI–outcome relationships across different health systems. This variability underscores the need for international collaborations that can control for treatment context while exploring BMI's prognostic value in a standardized manner [46].

10.48047/jocaaa.2024.33.06.102

Platelet-to-Lymphocyte Ratio and Systemic Inflammation

The platelet-to-lymphocyte ratio (PLR) is a composite biomarker derived from routine complete blood counts, calculated by dividing the absolute platelet count by the absolute lymphocyte count. It reflects two key biological processes with relevance to cancer prognosis: platelet-mediated tumor-promoting activities and lymphocyte-mediated anti-tumor immunity. A high PLR typically indicates both thrombocytosis and/or lymphopenia—conditions associated with systemic inflammation, tumor progression, and impaired immune surveillance [47].

Platelets contribute to cancer progression through multiple mechanisms. They can shield circulating tumor cells from immune recognition, facilitate tumor cell extravasation, and release pro-angiogenic and growth-promoting factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β). These mediators promote tumor cell survival, proliferation, and metastasis, and in hematologic malignancies, may influence the bone marrow microenvironment to favor malignant B-cell survival [48,49].

Conversely, lymphocytes—particularly cytotoxic T cells and natural killer cells—play a central role in anti-tumor immunity. Lymphopenia, whether due to tumor-related immune suppression, bone marrow infiltration, or treatment toxicity, has been consistently associated with inferior outcomes in multiple cancers. In DLBCL, low baseline lymphocyte counts have correlated with poor response to R-CHOP and reduced survival, supporting the notion that lymphocyte depletion is a marker of compromised host immunity [50,51].

Systemic inflammation is a hallmark of cancer and is closely linked to both thrombocytosis and lymphopenia. Pro-inflammatory cytokines such as IL-6 and IL-1β stimulate megakaryopoiesis, increasing platelet counts, while chronic immune activation and stress hormones can deplete lymphocyte populations. The PLR therefore integrates these opposing arms—tumor-promoting platelets and tumor-fighting lymphocytes—into a single, easily obtainable index that may outperform either parameter alone as a prognostic marker [52].

In solid tumors, high PLR has been associated with inferior survival in gastrointestinal, breast, and lung cancers, and meta-analyses suggest it may be a broadly applicable marker of poor prognosis. Emerging evidence indicates similar prognostic value in hematologic malignancies, including DLBCL, where high PLR before treatment initiation has been linked to higher relapse rates and shorter overall survival. These findings support the rationale for exploring PLR as a component of integrated prognostic models in lymphoma [53,54].

Biological Rationale of PLR in Lymphomagenesis

The prognostic significance of PLR in DLBCL is grounded in the dual and often opposing roles of platelets and lymphocytes within the tumor microenvironment. Platelets are increasingly recognized as active participants in cancer biology rather than passive hemostatic elements. They release a

10.48047/jocaaa.2024.33.06.102

spectrum of growth factors, cytokines, and chemokines—such as VEGF, PDGF, and TGF-β—that can stimulate angiogenesis, promote tumor cell proliferation, and induce immune evasion. Platelets can also directly interact with malignant B cells, providing survival signals through adhesion molecules like P-selectin and integrins, and modulating endothelial permeability to facilitate lymphoma cell trafficking [48,49,55].

In parallel, lymphocytes—particularly CD8+ cytotoxic T cells and NK cells—are essential for recognizing and eliminating malignant cells. A reduced lymphocyte count, as reflected in a high PLR, indicates compromised cellular immunity, which may result from chronic inflammation, tumor-induced immune suppression, or bone marrow infiltration by lymphoma. In DLBCL, lymphopenia has been associated with impaired antibody-dependent cellular cytotoxicity (ADCC), which is a critical mechanism of action for rituximab, potentially diminishing the efficacy of R-CHOP immunochemotherapy [50,51,56].

The chronic inflammatory milieu characteristic of lymphoma progression can simultaneously elevate platelet counts and reduce lymphocyte levels. Cytokines such as IL-6 drive megakaryopoiesis, leading to thrombocytosis, while persistent immune activation, stress hormone release, and nutritional deficits can lead to lymphocyte depletion. This bidirectional effect exaggerates the PLR, potentially serving as a surrogate marker for tumor aggressiveness and host immunosuppression [52,57].

Preclinical evidence also suggests that platelets may shield lymphoma cells from shear stress and immune-mediated clearance in the circulation. By cloaking malignant B cells, platelets can reduce recognition by cytotoxic lymphocytes, thereby facilitating metastasis-like dissemination to extranodal sites. This protective mechanism is well established in solid tumors and is hypothesized to operate similarly in aggressive lymphomas, potentially contributing to advanced-stage disease presentations [48,49,55,58].

Taken together, these mechanisms suggest that a high PLR in DLBCL reflects not only tumor-driven systemic inflammation but also a shift in the balance between pro-tumor and anti-tumor forces within the host. This makes PLR a plausible and biologically relevant prognostic biomarker that could complement existing risk stratification systems in guiding clinical management [53,54].

Clinical Evidence for PLR in DLBCL

Multiple clinical studies have evaluated PLR as a prognostic biomarker specifically in patients with DLBCL, with most conducted in the rituximab era. In a pivotal retrospective cohort from China, Guo et al. analyzed baseline PLR in newly diagnosed DLBCL patients treated with R-CHOP and demonstrated that elevated PLR was significantly associated with lower complete remission rates, shorter progression-free survival (PFS), and inferior overall survival (OS). Importantly, PLR remained

10.48047/jocaaa.2024.33.06.102

an independent prognostic factor in multivariate analysis alongside the International Prognostic Index (IPI), suggesting its potential to add discriminatory power to established clinical models [53].

Similar findings were reported in other Asian cohorts, where high PLR at diagnosis consistently predicted poorer OS and PFS. Li et al. observed that elevated PLR was correlated with advanced stage, higher LDH, and poor performance status—features traditionally linked to worse outcomes in DLBCL. This association indicates that PLR may be capturing an element of systemic inflammation and immune suppression not fully reflected in the IPI, providing a biologically distinct layer of prognostic information [54,59].

In European populations, data are more limited but still supportive. A study from Turkey found that patients in the high PLR group had significantly shorter survival, with PLR demonstrating prognostic significance even when controlling for age, stage, and extranodal disease. Interestingly, the prognostic impact of PLR was most pronounced in intermediate-risk IPI groups, suggesting a role in refining prognosis for patients whose outcomes are otherwise uncertain under current models [60].

Beyond baseline assessment, dynamic changes in PLR during treatment may also hold prognostic relevance. Early declines in PLR after the first cycles of R-CHOP have been associated with improved outcomes, potentially reflecting effective control of both tumor burden and the inflammatory milieu. Conversely, persistently elevated PLR despite therapy may signal residual disease activity or inadequate immune recovery, identifying patients who could benefit from treatment intensification or novel therapeutic approaches [61].

Despite these promising observations, there is no universally accepted cut-off for defining “high” PLR in DLBCL, with thresholds ranging from 150 to over 300 across studies. Variability in laboratory methods, patient demographics, and treatment protocols further complicates direct comparison. Prospective, multi-center trials with standardized PLR measurement and cut-off determination are needed to validate its role before it can be integrated into routine prognostic assessment [53,54,60,61].

Comparative Prognostic Strength of PLR and BMI in DLBCL

Direct comparisons of PLR and BMI as prognostic markers in DLBCL are limited, but emerging evidence suggests they capture complementary aspects of host–tumor interaction. BMI primarily reflects nutritional status and metabolic reserve, which influence treatment tolerance and chemotherapy pharmacokinetics, while PLR reflects systemic inflammation and immune competence, both of which can drive tumor progression and impact treatment efficacy [19,36,53,54].

In a retrospective multi-institutional analysis, Han et al. stratified DLBCL patients treated with R-CHOP by both BMI and PLR categories. They found that underweight patients with elevated PLR had the poorest outcomes, with markedly shorter progression-free survival (PFS) and overall survival (OS) compared to other subgroups. Conversely, overweight or obese patients with low PLR tended to have

10.48047/jocaaa.2024.33.06.102

the most favorable prognosis. These findings highlight that the prognostic impact of BMI may be modified by inflammatory status, and vice versa [11,60].

Some studies have attempted to integrate BMI and PLR into combined scoring systems. For example, a Chinese cohort developed a composite risk score assigning points for underweight BMI (<18.5 kg/m^2) and high PLR (>150). Patients with both adverse factors exhibited significantly higher relapse rates and inferior OS, independent of IPI risk group. Such models may offer refined prognostic stratification, particularly in patients with intermediate IPI scores where clinical decision-making is less clear-cut [53,59].

The comparative strength of these biomarkers may also vary by molecular subtype. Preliminary data suggest that in non-germinal center B-cell-like (non-GCB) DLBCL, PLR may be a stronger predictor of outcome than BMI, possibly reflecting the more immunologically driven biology of this subtype. In contrast, in GCB DLBCL, nutritional reserve as measured by BMI may exert a greater influence on chemotherapy tolerance and survival. These subtype-specific differences remain to be validated in larger, molecularly annotated datasets [14,61].

While both markers are accessible and cost-effective, PLR may have an advantage in reflecting active disease biology, as it is more dynamic and can change rapidly with treatment response or disease progression. BMI, in contrast, is relatively stable over short intervals but may fail to capture acute biological changes. Integrating both parameters could harness the prognostic strengths of each, providing a more comprehensive patient risk profile [36,54,60].

Combined Prognostic Models (BMI + PLR) in DLBCL

The integration of BMI and PLR into a unified prognostic framework for DLBCL has gained interest as both parameters reflect distinct yet complementary host-related factors. BMI serves as a surrogate for nutritional status, metabolic reserve, and treatment tolerance, whereas PLR captures the inflammatory and immune status that can modulate tumor progression and therapeutic response. Combining these markers may therefore improve prognostic precision compared to using either alone [53,54,60,62].

Han et al. [62] demonstrated in a large retrospective cohort that combining BMI and PLR into a four-tiered risk matrix stratified patients into distinct survival groups beyond what the International Prognostic Index (IPI) could achieve. Underweight patients with high PLR had the poorest outcomes, while overweight/obese patients with low PLR had the most favorable prognosis. Intermediate combinations yielded proportional survival rates, indicating additive prognostic effects.

Zhou et al. [63] further refined this approach by developing a BMI–PLR composite score in newly diagnosed DLBCL patients receiving R-CHOP. In this model, patients received one point each for BMI <18.5 kg/m^2 and PLR >150. Those with scores of 0, 1, and 2 exhibited markedly different three-year progression-free survival (PFS) and overall survival (OS) rates. Importantly, the BMI–PLR score

10.48047/jocaaa.2024.33.06.102

retained independent prognostic significance in multivariate analysis, even after adjusting for IPI, stage, and LDH.

Such combined models may be particularly valuable in intermediate-risk IPI patients, where current stratification leaves uncertainty in clinical decision-making. In this subset, the BMI–PLR score helped identify individuals who might benefit from closer monitoring, more aggressive first-line therapy, or early consideration for clinical trials. Conversely, low-score patients might be candidates for therapy de-escalation strategies without compromising outcomes [62,63].

The practicality of integrating BMI and PLR into routine practice is high, as both are easily obtained from standard clinical assessments without additional cost. However, before widespread adoption, prospective validation across diverse populations and treatment settings is necessary. Cut-off standardization for PLR, as well as consensus on BMI thresholds in different ethnic groups, will be critical to ensure reproducibility and clinical applicability of these combined prognostic models [19,43,63].

Relationship to International Prognostic Index (IPI)

The International Prognostic Index (IPI) has been the cornerstone of clinical risk stratification in DLBCL for over three decades. Incorporating age, Ann Arbor stage, serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status, and number of extranodal sites, it effectively categorizes patients into low-, intermediate-, and high-risk groups. However, while the IPI remains robust in the R-CHOP era, it does not account for host-related biological parameters such as nutritional status or systemic inflammation, which may significantly influence prognosis [12,13,45].

Several studies have explored whether adding BMI and PLR to IPI scoring improves prognostic accuracy. Han et al. [62] showed that the combination of BMI and PLR provided further stratification within each IPI risk group, particularly in intermediate-risk patients, who often display heterogeneous outcomes under standard IPI classification. For example, intermediate-risk patients with both underweight BMI and elevated PLR had survival curves resembling those of high-risk IPI groups, suggesting that host-related metrics can unmask hidden risk within clinically similar cohorts.

Similarly, Zhou et al. [63] demonstrated that their BMI–PLR composite score retained independent prognostic value in multivariate models that included IPI, underscoring that these markers capture aspects of disease biology and patient resilience not encompassed by traditional risk factors. This aligns with the broader shift in oncology toward integrating host-immune and metabolic markers into prognostic frameworks to better individualize therapy [19,43,64].

Incorporating BMI and PLR into IPI-based models could be done in several ways: Additive Models – Adding one or more points for adverse BMI or PLR values to the traditional IPI score. Layered Stratification – Applying BMI–PLR classification within each IPI category to refine risk predictions.

10.48047/jocaaa.2024.33.06.102
Composite Indices – Creating a novel prognostic index that blends clinical, metabolic, and inflammatory markers into a single scoring system.

Prospective validation will be essential to determine which approach offers the greatest prognostic improvement without sacrificing simplicity. Given that IPI is universally known and used, integration of BMI and PLR would need to be straightforward to encourage adoption in routine clinical workflows [64,65].

Conclusion

Body Mass Index (BMI) and Platelet-to-Lymphocyte Ratio (PLR) are simple, cost-free, and routinely available measures that provide complementary insights into prognosis for patients with Diffuse Large B-Cell Lymphoma (DLBCL) treated with R-CHOP. BMI reflects nutritional status and treatment tolerance, while PLR captures systemic inflammation and immune competence. Both have been linked to survival outcomes, and their combined assessment may improve risk stratification beyond traditional tools such as the International Prognostic Index.

Integrating BMI and PLR into prognostic models could help identify patients who might benefit from tailored treatment intensity or closer monitoring. However, current evidence is largely retrospective, with variations in cut-offs, populations, and study designs limiting universal application. Standardization of measurement and prospective validation are essential before widespread adoption.

Overall, BMI and PLR hold promise as accessible prognostic markers that, when used together, could enhance personalized care in DLBCL, but further robust research is needed to confirm their role in clinical practice

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