Original article

Prognostic value of pretreatment anemia in patients with 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. While R-CHOP is the standard of care, treatment failure remains a challenge. Pretreatment anemia is a common paraneoplastic manifestation, yet its prognostic utility in Vietnamese patients remains under-investigated.

Materials and Methods: A combined prospective and retrospective study was conducted on 106 patients with CD20-positive DLBCL treated with first-line R-CHOP at Hue University of Medicine and Pharmacy Hospital, Hue Central Hospital and Da Nang Oncology Hospital from December 2022 to August 2025. Pretreatment anemia was classified according to NCI-CTCAE v5.0. Clinicopathological features, toxicity, treatment response, and survival were analyzed.

Results: The prevalence of pretreatment anemia was 32.1%, with the majority being Grade 1 (26.4%). Anemia was significantly associated with B symptoms ($p = 0.034$) and older age ($p = 0.039$). Regarding efficacy, non-anemic patients had approximately 12 times higher odds of responding (Odds Ratios = 11.897; 95% CI: 1.33 - 106.34, $p = 0.014$). Toxicity analysis showed a 3.8% treatment-related mortality rate due to severe infections. There was no statistically significant difference in overall survival or progression-free survival ($p > 0.05$).

Conclusion: Pretreatment anemia is a robust and easily accessible predictor of poor early treatment response in Vietnamese patients with DLBCL treated with R-CHOP. Anemic patients have significantly lower odds of achieving remission. While long-term survival benefits were obscured by treatment-related toxicity in this cohort, the strong link between hemoglobin levels and therapeutic efficacy suggests that anemia should be integrated into risk stratification.

***Keywords**: Diffuse Large B-Cell Lymphoma; Anemia; R-CHOP; Prognosis.*

1. INTRODUCTION

Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of malignancies, ranking as the 10th most common cancer globally [1]. According to GLOBOCAN 2022, in Vietnam, NHL ranks as the 13th most common cancer, accounting for 3,516 new cases (1.9% of total cancer cases) and 2,211 deaths annually. Within this group, Diffuse Large B-Cell Lymphoma (DLBCL) is the predominant subtype, with incidence rates mirroring global trends [1]. The R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) has significantly improved outcomes; however, population-based and real-world data indicate that a substantial proportion of patients still are not cured. Depending on the cohort, approximately 23% to 40% of patients experience relapsed or refractory disease following curative-intent R-CHOP therapy [2-4].

Risk stratification primarily relies on the International Prognostic Index (IPI) [5]. However, host factors such as systemic inflammation and hematologic reserve are increasingly recognized as critical in DLBCL. Pretreatment anemia, frequently related to cancer-associated inflammatory cytokines—especially IL-6—is an independent adverse prognostic factor [6]. In parallel, hypoxia-driven activation of HIF-1α pathways in DLBCL and other cancers promotes tumor survival, immune evasion, and chemoresistance [7, 8], suggesting that inflammatory anemia and hypoxic signaling may converge to influence treatment response, even though anemia has not yet been formally validated as a direct surrogate of tumor hypoxia in DLBCL.

While international studies have identified anemia as an adverse prognostic factor [9-11], data in the Vietnamese population have not yet been reported or studied. This study aims to determine the prevalence and severity of pretreatment anemia, analyze the toxicity profile, and to investigate the effect of pretreatment anemia on treatment response and survival in Vietnamese DLBCL patients.

2. MATERIALS AND METHODS

2.1. Study Population: A total of 106 patients diagnosed with de novo DLBCL were enrolled in this multicenter observational study from December 2022 to August 2025. Eligible patients were those with histopathologically confirmed CD20-positive DLBCL who received first-line treatment with at least three cycles of the R-CHOP regimen. Patients were excluded if they presented with primary central nervous system lymphoma, HIV-associated lymphoma, concurrent malignancies, or incomplete medical records preventing adequate data extraction.

2.2. Methods: This study employed a combined prospective and retrospective design. Pretreatment anemia was defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, where Grade 0 represents normal hemoglobin (≥ Lower Limit of Normal [LLN]), Grade 1 is mild anemia (< LLN - 10.0 g/dL), Grade 2 is moderate (8.0 - < 10.0 g/dL), and Grade 3 represents severe anemia (< 8.0 g/dL). Treatment-related toxicities were also graded using NCI-CTCAE v5.0. Treatment response was evaluated using the Lugano classification. Responses were categorized as "Responders" (Complete Response [CR] and Partial Response [PR]) versus "Non-Responders" (Stable Disease [SD] and Progressive Disease [PD]). Survival outcomes included Overall Survival (OS) and Progression-Free Survival (PFS).

2.3. Statistical Analysis: Statistical analysis was performed using IBM SPSS Statistics 22.0, utilizing Chi-square or Fisher's Exact tests for categorical comparisons, Kaplan-Meier methods for survival estimation, and Odds Ratios (OR) for risk quantification, with statistical significance set at $p < 0.05$.

2.3. Ethical Statement: The study protocol was approved by the Institutional Ethics Committee of Hue University of Medicine and Pharmacy (Approval No. H2025/013, dated January 09, 2025).

3. RESULTS

3.1. Patient Characteristics

Table 1. Baseline Clinicopathological Characteristics by Anemia Status

Variable	Category	Non-Anemia (n = 72)	Anemia (n = 34)	P-value
Gender	Male	42 (58.3%)	19 (55.9%)	0.836
	Female	30 (41.7%)	15 (44.1%)	
Age (Mean ± SD)	Years	53.50 ± 14.0	59.32 ± 12.0	**0.039**
B Symptoms	Absent	63 (87.5%)	24 (70.6%)	**0.034**
	Present	9 (12.5%)	10 (29.4%)	
Stage	I-II	38 (52.8%)	15 (44.1%)	0.461
	III-IV	34 (47.2%)	19 (55.9%)	
IPI Score	0 - 1	40 (55.6%)	15 (44.1%)	0.431
	2 - 5	32 (44.4%)	19 (55.9%)	

As detailed in Table 1, pretreatment anemia was identified in 34 out of 106 patients, corresponding to a prevalence of 32.1%. Statistical analysis revealed a significant association between anemia and older age (mean 59.32 vs 53.50 years, $p = 0.039$) as well as the presence of constitutional B symptoms (29.4% vs 12.5%, $p = 0.034$). This correlation with B symptoms supports the hypothesis of an inflammatory etiology driving the anemia. Other variables such as gender, stage, and IPI score did not show statistically significant differences between the two groups.

3.2. Distribution of Pretreatment Anemia

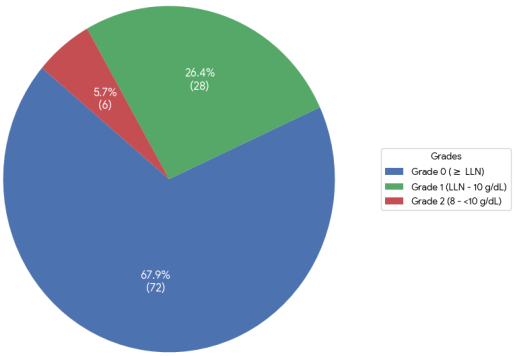

Figure 1. Distribution of Pretreatment Anemia Severity (NCI-CTCAE v5.0).

Figure 1 illustrates the distribution of anemia severity classified by NCI-CTCAE v5.0. The majority of the anemic cohort (28 patients, representing 26.4% of the total study population) presented with mild Grade 1 anemia. Moderate Grade 2 anemia was less frequent, observed in only 5.7% of cases. This distribution highlights that even mild perturbations in hemoglobin levels are the predominant presentation in this patient population.

3.3. Treatment Response

Table 2. Association between Pretreatment Anemia and Treatment Response

Response Group	Non-Anemia (n = 70)	Anemia (n = 34)	Total (N = 104)	Statistics
Responder (CR/PR)	69 (98.6%)	29 (85.3%)	98 (94.2%)	p = 0.014
Non-Responder (SD/PD)	1 (1.4%)	5 (14.7%)	6 (5.8%)	**OR = 11.897** (95% CI: 1.33 - 106.3)*

The impact of pretreatment anemia on immediate therapeutic efficacy is summarized in Table 2. Because two patients died from pneumonia in the setting of grade 4 febrile neutropenia, the remaining number of patients available for response evaluation was 104. There was a marked disparity in response rates between the two groups. Patients without anemia achieved an Overall Response Rate (CR/PR) of 98.6%, significantly higher than the 85.3% observed in the anemic group (p=0.014). The Odds Ratio of 11.897 indicates that non-anemic patients had nearly 12-fold higher odds of responding to induction therapy compared to their anemic counterparts, establishing anemia as a potent predictor of primary refractory disease.

3.4. Side Effects

Table 3. Treatment-Related Side Effects (CTCAE v5.0)

Adverse Event Type	Grade / Classification	Frequency (n)	Percentage (%)
Anemia (During treatment)	Grade 0 (Normal)	38	35.8%
	Grade 1 (Mild)	41	38.7%
	Grade 2 (Moderate)	16	15.1%
	Grade 3 (Severe)	11	10.4%
Neutropenia	Grade 1	8	7.5%
	Grade 2	15	14.2%
	Grade 3	26	24.5%
	Grade 4	30	28.3%

Leukopenia	Grade 1	14	13.2%
	Grade 2	28	26.4%
	Grade 3	25	23.6%
	Grade 4	13	12.3%
Infections (Fatal) *(Specific Causes)*	Grade 5 (Death)	**4**	**3.8%**
	Pneumonia	2	1.9%
	Sepsis	1	0.9%
	Febrile Neutropenia	1	0.9%

Table 3 details the hematological and infectious toxicities recorded during the treatment course. While 32.1% of patients entered the study with baseline anemia, treatment-emergent anemia was also common. Grade 4 neutropenia was the most prevalent severe toxicity, affecting 28.3% of the cohort. Crucially, the study recorded a treatment-related mortality rate of 3.8% (4 deaths), with causes attributable to severe infections including pneumonia, sepsis, and febrile neutropenia.

3.5. Survival Analysis

Table 4. Mean Survival Times (Kaplan-Meier Estimates)

Survival Metric	Group	Mean Time (Months)	95% CI	P-value (Log-rank)
Overall Survival (OS)	Non-Anemia	27.73 ± 1.08	25.6 - 29.8	0.345
	Anemia	25.20 ± 1.75	21.8 - 28.6	
Progression-Free (PFS)	Non-Anemia	20.09 ± 1.07	18.0 - 22.2	0.220
	Anemia	19.35 ± 2.10	15.2 - 23.5	

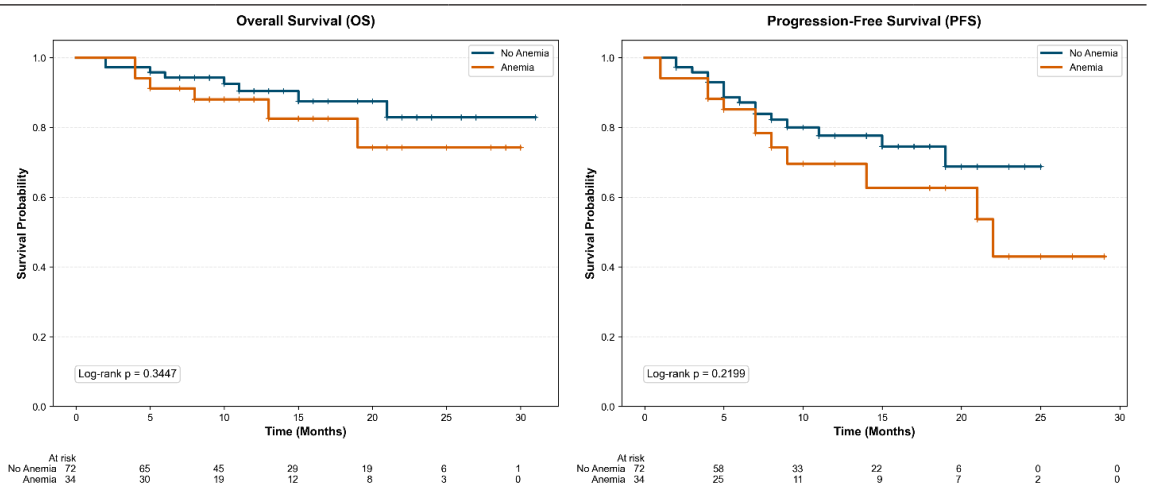

Figure 2. Kaplan-Meier Survival Estimates stratified by Pretreatment Anemia.
(A) Overall Survival (OS); (B) Progression-Free Survival (PFS).

The survival outcomes at the time of study completion are presented in Table 4 and visualized in the Kaplan-Meier curves in Figure 2. Although the mean Overall Survival (OS) was numerically longer in the non-anemic group (27.73 months) compared to the anemic group (25.20 months), this difference did not reach statistical significance (Log-rank p = 0.345). Similarly, Progression-Free Survival (PFS) showed no significant separation between the groups (p = 0.220). As seen in Figure 2, while the survival curve for non-anemic patients trends higher, the overlap suggests that long-term outcomes in this specific cohort may be influenced by other factors.

4. DISCUSSION

In this multicenter study of Vietnamese patients with de novo DLBCL, we observed a pretreatment anemia prevalence of 32.1%. This figure is lower than those reported in other Asian cohorts, such as Hong et al. (77.1%) [9] and Matsumoto et al. (47%) [11]. It is also slightly lower than Western cohorts reported by Troppan et al., where prevalence ranged from 38.3% to 48.8% [10]. This difference likely reflects the younger median age of our population compared to the older populations in the cited studies (majority >60 years in European studies).

We found a statistically significant association between anemia and the presence of B symptoms ($p = 0.034$). This aligns with the pathophysiology of cancer-related anemia described by Madeddu et al., where systemic inflammation mediated by cytokines such as IL-6 and TNF-α drives hepcidin synthesis, leading to functional iron deficiency and erythropoietin resistance [6]. The correlation between anemia and B symptoms in our cohort suggests that hemoglobin levels serve as a surrogate marker for the systemic inflammatory burden of the lymphoma, rather than merely reflecting bone marrow infiltration.

A pivotal finding of our study is the strong correlation between pretreatment anemia and immediate treatment failure. Non-anemic patients had an 11.9-fold higher likelihood of achieving an objective response (CR/PR) compared to anemic patients ($p = 0.014$). Notably, the majority of our anemic patients had mild (Grade 1) anemia. This contrasts with the findings of Hong et al., who reported that only moderate-to-severe anemia (Hb < 10 g/dL) was prognostic for survival, while Grade 1 anemia had outcomes similar to non-anemic patients [9]. However, our data resonates more closely with Troppan et al., who demonstrated that any degree of anemia (defined by WHO criteria) was an independent predictor of poor outcome and that adding hemoglobin levels to the R-IPI score improved risk stratification [10]. Our results suggest that even mild anemia may indicate a biological milieu hostile to chemotherapy efficacy in the Vietnamese population.

Despite the clear disparity in treatment response, we did not observe a statistically significant difference in OS or PFS ($p > 0.05$). This divergence from the findings of Matsumoto et al., who reported a hazard ratio of 2.27 for PFS in anemic patients [11], can be attributed to two factors: the smaller sample size of our cohort and the confounding effect of treatment-related toxicity.

The profound difference in response rates (98.6% vs. 85.3%) supports the hypothesis that anemia contributes to primary chemoresistance via tumor hypoxia. As detailed by Lee et al., anemia reduces oxygen delivery to the tumor microenvironment, stabilizing Hypoxia-Inducible Factor 1-alpha (HIF-1α) [7]. HIF-1α activation triggers multiple resistance mechanisms, including the upregulation of ATP-binding cassette (ABC) transporters (e.g., MDR1) which efflux chemotherapeutic agents like doxorubicin, and the induction of anti-apoptotic proteins such as Survivin and BCL-2. Furthermore, hypoxia-induced cell cycle arrest can protect tumor cells from antiproliferative agents in the R-CHOP regimen. Consequently, the anemic patients in our study likely harbored tumors that were physiologically "primed" to resist induction therapy, regardless of their IPI risk score.

The survival analysis in our study was confounded by a treatment-related mortality rate of 3.8%, primarily driven by severe infections (pneumonia, sepsis) in the context of Grade 4 neutropenia. In survival analysis, non-relapse deaths act as competing risks that can obscure disease-specific outcomes. While anemic patients were less likely to respond to therapy, the high background rate of infectious toxicity in both groups may have diluted the statistical separation in OS curves. This highlights the need for optimal supportive care, including G-CSF prophylaxis and rigorous infection monitoring, particularly in anemic patients who may already be immunocompromised.

Our study has limitations inherent to its design. The sample size (N = 106), while sufficient to detect differences in immediate response, was underpowered to detect smaller differences in long-term survival compared to the large cohorts of Troppan (N = 556) or Matsumoto (N = 185). Additionally, we did not assess serum cytokine levels (IL-6) or hepcidin, preventing a definitive confirmation of the inflammatory mechanism.

5. CONCLUSION

Pretreatment anemia is a robust and easily accessible predictor of poor early treatment response in Vietnamese patients with DLBCL treated with R-CHOP. Anemic patients have significantly lower odds of achieving remission, likely due to hypoxia-mediated chemoresistance mechanisms. While long-term survival benefits were obscured by treatment-related toxicity in this cohort, the strong link between hemoglobin levels and therapeutic efficacy suggests that anemia should be integrated

into risk stratification and that anemia correction or hypoxia-modifying strategies warrant further investigation.

Conflict of Interest: The authors declare no conflicts of interest.

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