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ORIGINAL RESEARCH

Prognostic Value of the Aggregate Inflammation Systemic Index (AISI) in Patients with Diffuse Large B-Cell Lymphoma: A Multicenter Retrospective Study

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Background: The aggregate index of systemic inflammation (AISI, calculated as neutrophil count × monocyte count × platelet count/lymphocyte count) reflects systemic inflammatory status; however, its prognostic role in diffuse large B-cell lymphoma (DLBCL) remains underexplored. This study aimed to investigate the prognostic value of AISI in DLBCL.

Methods: A total of 1332 DLBCL patients (median age 62 years; 52.3% male) were included in this study. Patients were stratified based on AISI quartiles, and a cut-off value was determined using restricted cubic splines (RCS) analysis. The associations between AISI and Overall survival (OS) were assessed using Kaplan-Meier analysis and Cox proportional hazards models.

Results: Higher AISI levels were associated with adverse clinical features, including advanced Ann Arbor stage, poor performance status, and higher-risk categories of both the IPI and the NCCN-IPI. RCS analysis revealed a nonlinear relationship between AISI and OS, with an inflection point at 261.33. Kaplan-Meier analysis demonstrated that patients with AISI > 261.33 had significantly worse OS compared to those with AISI ≤ 261.33 ($P = 0.003$). Similarly, patients in the Q4 group had poorer OS than those in the lowest two quartiles (Q1-Q2) ($P = 0.008$). In fully adjusted Cox proportional hazards models (adjusted for age, sex, Ann Arbor stage, LDH, ECOG performance status, BMI, albumin, B symptoms, bone marrow involvement, central nervous system involvement, and liver/spleen involvement), high AISI level (> 261.33) were associated with increased mortality risk ($HR = 1.28$, 95% CI: 1.04–1.57, $P = 0.018$). Subgroup analyses indicated that the prognostic impact of AISI was particularly evident among patients classified as low risk by conventional prognostic systems.

Conclusion: Elevated AISI was associated with inferior OS in DLBCL patients and may potentially serve as a prognostic biomarker.

Keywords: aggregate index of systemic inflammation, diffuse large B-cell lymphoma, prognosis, risk stratification

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequently encountered subtype of non-Hodgkin lymphoma (NHL), characterized by aggressive clinical behavior and marked biological heterogeneity.[1,2] Although DLBCL can be cured with the standard treatment regimen of R-CHOP, approximately 30–40% of patients experience relapsed or refractory disease.[3,4] While scoring systems, such as the International Prognostic Index (IPI) and National Comprehensive Cancer Network IPI (NCCN-IPI) provide reference values for patient prognosis, they are primarily based on clinical

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characteristics and were not designed to capture host immune or inflammatory status.[5–7] Therefore, it is imperative to develop novel auxiliary prognostic indicators to refine risk stratification and guide treatment decisions.

Systemic inflammation is recognized as a significant contributing factor in tumor progression and therapeutic resistance.[8,9] Peripheral blood inflammatory indices (including NLR, PLR, SIRI, and SII) demonstrate prognostic value in various solid tumors owing to their operational simplicity and low cost.[10–13] In certain hematologic malignancies, related research is emerging but remains relatively limited. These markers facilitate clinical risk assessment by reflecting systemic signaling interactions between tumors and host immune responses. In DLBCL, systemic inflammation may influence disease progression through multiple biological mechanisms. Chronic inflammatory states can reshape the tumor microenvironment by promoting the infiltration and activation of immunosuppressive immune cells, such as tumor-associated macrophages, thereby facilitating immune evasion and lymphoma progression.[14]

The Aggregate Index of Systemic Inflammation (AISI) is a comprehensive inflammatory index that integrates counts of neutrophils, monocytes, platelets, and lymphocytes and can be calculated from routine blood tests. Previous studies have demonstrated that AISI is associated with patient prognosis in various solid tumors, such as lung cancer and colorectal cancer.[15–17] Neutrophils, monocytes, and platelets are involved in tumor-associated inflammation and progression, while lymphocytes reflect antitumor immune capacity. A higher AISI indicates a pro-inflammatory and immunosuppressive state, which may be associated with a worse prognosis.[18] However, research on AISI in DLBCL is scarce, and its prognostic role remains unestablished. This multicenter retrospective cohort study aims to evaluate the association between AISI and prognosis in DLBCL patients, explore its potential as an ancillary prognostic indicator, and provide clinical evidence to inform subsequent individualized treatment strategies.

Materials and Methods

Study Population

This multicenter, retrospective cohort study included 1332 patients newly diagnosed with DLBCL between August 2008 and January 2025. Data were acquired from eight medical centers in the Huaihai Lymphoma Working Group (HHLWG). Inclusion criteria were: (1) diagnosis of DLBCL determined according to the WHO classification system for lymphoid malignancies.[19] (2) availability of complete clinical data. Exclusion criteria were: (1) age < 18 years. (2) diagnosis of primary central nervous system DLBCL. (3) presence of concurrent malignancies; (4) history of severe infectious diseases, autoimmune diseases, or chronic inflammatory diseases; and (5) incomplete medical records. All patients included were treated during the rituximab era and received regimens containing rituximab.

Definition of AISI

The AISI was calculated using the following formula, all counts in $\times 10^9$/L:

$$\text{AISI} = (\text{Neutrophil count} \times \text{Monocyte count} \times \text{Platelet count}) / \text{Lymphocyte count}.$$

Covariates

Baseline data, including age, gender (male, female), C-reactive protein (CRP), Epstein-Barr virus (EBV) DNA status, presence of B symptoms, bone marrow involvement (BM involvement), central nervous system involvement, liver/spleen involvement, Eastern Cooperative Oncology Group performance status (ECOG PS), IPI, NCCN-IPI, body mass index (BMI), platelet (PLT), red blood cell count (RBC), creatinine (Cr), total cholesterol (TC), triglyceride (TG), albumin (ALB), lymphocyte count (LYC), monocyte (MONO), hemoglobin (HB), neutrophil (NEU), lymphocyte count (LYC), WBC, FIB, and LDH were included. Disease staging for all patients was performed based on the Ann Arbor system.[20]

Follow-Up

Overall survival (OS) was calculated from the date of initial diagnosis to either death from any cause or the date of the last documented follow-up. Survival outcomes were ascertained through review of death certificates or via telephone contact with patients or their family members, when necessary. The final follow-up was completed in May 2025.

Statistical Analysis

Descriptive statistics were expressed as median with interquartile range (IQR) for continuous variables and frequency with percentage for categorical variables. Group comparisons were conducted using one-way ANOVA, chi-square test, or Kruskal–Wallis test, depending on data type and distribution. The relationship between AISI and clinical indicators was examined using Spearman's rank correlation analysis. Restricted cubic splines (RCS) analysis was applied to explore the nonlinear relationship between AISI and OS and to determine an optimal cut-off value. Survival outcomes were estimated by the Kaplan-Meier method, and group differences were evaluated using the Log rank test. Testing for interaction effects in pre-specified subgroups. Cox proportional hazards regression models were constructed to evaluate the prognostic value of AISI groupings for OS, with three levels of covariate adjustment: a crude model (Model 1); a minimally adjusted model (adjusted for age and gender; Model 2); and a fully adjusted model (adjusted for age, gender, Ann Arbor stage, ECOG PS, LDH, BMI, ALB, presence of B symptoms, BM involvement, CNS involvement, and liver/spleen involvement; Model 3). To assess the internal robustness and generalizability of the prognostic model, we randomly split the cohort into a training set (70%) and a validation set (30%). The multivariable Cox regression model (Model 3) was developed in the training set and applied to the validation set. Model discrimination was evaluated using Harrell's concordance index (C-index).

Interaction and subgroup analyses were performed to examine whether the association between AISI and OS was consistent across clinically relevant strata. Interaction effects were assessed by including multiplicative interaction terms between AISI groupings and predefined variables with established prognostic relevance in DLBCL, including age, gender, LDH level, ECOG PS, Ann Arbor stage, IPI, NCCN-IPI, EBV DNA status, and cell of origin. *P*-values for interaction were obtained using the likelihood ratio test by comparing models with and without interaction terms. In parallel, subgroup analyses were conducted across the same strata to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) within each subgroup.

Missing data were handled using multiple imputation by chained equations (MICE), with 20 imputed datasets generated. Estimates from the imputed datasets were combined using Rubin's rules[21] to obtain pooled hazard ratios (HRs), confidence intervals (CIs), and *P*-values. A sensitivity analysis based on complete cases was also performed to assess the robustness of the findings. Statistical significance was defined as a two-sided *P*-value below 0.05. Analyses were conducted using R software (version 4.2.0, https://www.r-project.org).

Results

Baseline Characteristics

The cohort had a median age of 62 years, with 54.0% of patients older than 60 years and 52.3% being male (Table 1). Advanced-stage disease (Ann Arbor stage III/IV) was observed in 58.1% of cases. The median AISI value was 261.33. The 5-year OS rate reached 66.1%, with a median follow-up duration of 63 months (95% CI: 59.57–67.47).

Table 1 Baseline Characteristics of DLBCL Patients

Variables	Overall (n=1332)
Age (median [IQR])	62.00 [52.00, 70.00]
Age (%)	
≤60	613 (46.0)
>60	719 (54.0)
Gender (%)	
Male	696 (52.3)
Female	636 (47.7)
EBV DNA status (%)	
Negative	533 (69.6)
Positive	233 (30.4)

(*Continued*)

Table 1 (Continued).

Variables	Overall (n=1332)
B symptom (%)	
Absence	958 (73.3)
Presence	349 (26.7)
BM involvement (%)	
Absence	1083 (91.1)
Presence	106 (8.9)
Central nervous system involvement (%)	
Absence	1118 (92.4)
Presence	92 (7.6)
Liver/Spleen involvement (%)	
Absence	1017 (84.7)
Presence	184 (15.3)
ECOG PS (%)	
<2	820 (66.1)
≥2	420 (33.9)
Ann Arbor Stage (%)	
I/II	548 (41.9)
III/IV	761 (58.1)
IPI (%)	
LR/LIR	759 (59.2)
HIR/HR	524 (40.8)
NCCN-IPI (%)	
LR/LIR	641 (54.1)
HIR/HR	543 (45.9)
LDH (%)	
Normal	653 (52.9)
Elevated	581 (47.1)
BMI (median [IQR])	23.44 [21.30, 25.78]
WBC (median [IQR])	5.80 [4.54, 7.49]
NEU (median [IQR])	3.76 [2.69, 5.16]
LYC (median [IQR])	1.30 [0.90, 1.78]
MONO (median [IQR])	0.45 [0.32, 0.62]
PLT (median [IQR])	222.00 [170.00, 276.00]
AISI (median [IQR])	261.33 [129.47, 558.71]
RBC (median [IQR])	4.10 [3.66, 4.53]
HB (median [IQR])	122.00 [105.00, 136.00]
CRP (median [IQR])	8.13 [2.60, 36.65]
ALB (median [IQR])	39.70 [35.40, 43.50]
Cr (median [IQR])	59.00 [49.90, 70.00]
TG (median [IQR])	1.25 [0.91, 1.71]
TC (median [IQR])	4.33 [3.61, 5.04]
FIB (median [IQR])	3.48 [2.76, 4.41]

Abbreviations: AISI, aggregate index of systemic inflammation; ALB, albumin; BMI, body mass index; BM involvement, bone marrow involvement; CRP, c-reactive protein; Cr, creatinine; FIB, fibrinogen; HB, hemoglobin; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NCCN-IPI, National Comprehensive Cancer Network International Prognostic Index; LR, low risk; LIR, low intermediate risk; HIR, high intermediate risk; HR, high risk; TC, total cholesterol; TG, triglyceride.

Patients were divided into quartiles based on AISI levels. With increasing AISI, the proportions of male sex, advanced Ann Arbor stage (III/IV), high-risk categories of IPI and NCCN-IPI, and ECOG performance status ≥2 increased significantly, suggesting an association between elevated AISI and adverse clinical features. Similarly,

inflammatory markers such as WBC, CRP, and FIB were elevated across higher AISI quartiles. In contrast, BMI did not differ significantly among the groups (Supplementary Table 1).

Correlation of AISI with Clinical Parameters

AISI showed positive correlations with WBC ($r = 0.56$), CRP ($r = 0.29$), fibrinogen ($r = 0.34$), and LDH ($r = 0.16$), and a negative correlation with albumin ($r = -0.20$) (all $P < 0.001$). No significant associations were found with BMI, age, RBC, hemoglobin, creatinine, triglycerides, or total cholesterol (all $P > 0.05$, Figure 1).

The Nonlinear Relationship Between AISI and OS

RCS analysis revealed a nonlinear association between AISI and OS in patients with DLBCL, with a marked decline in OS observed when AISI exceeded the threshold of 261.33.

Prognostic Impact of AISI Stratified by Cut-Off and Quartiles

Patients were stratified into two groups based on the AISI cut-off value of 261.33. The 5-year OS rate was 68.9% in the low-AISI group (≤261.33) and 63.3% in the high-AISI group (>261.33, Figure 2A). When divided into quartiles (Q1-Q4), the 5-year OS rates were 68.9%, 68.9%, 65.1%, and 61.6%, respectively. A significantly lower OS was observed in Q4 compared to Q1 and Q2 ($P = 0.008$), whereas the difference between Q3 and Q4 was not statistically significant ($P = 0.135$, Figure 2B).

Cox regression analyses were performed to assess the prognostic impact of AISI on OS in DLBCL patients, using both quartile-based and cut-off-based groupings. When categorized by quartiles, univariate analysis showed that compared with the lowest quartile (Q1), the Q2 and Q3 groups had no significant differences in OS, whereas the Q4 group had significantly

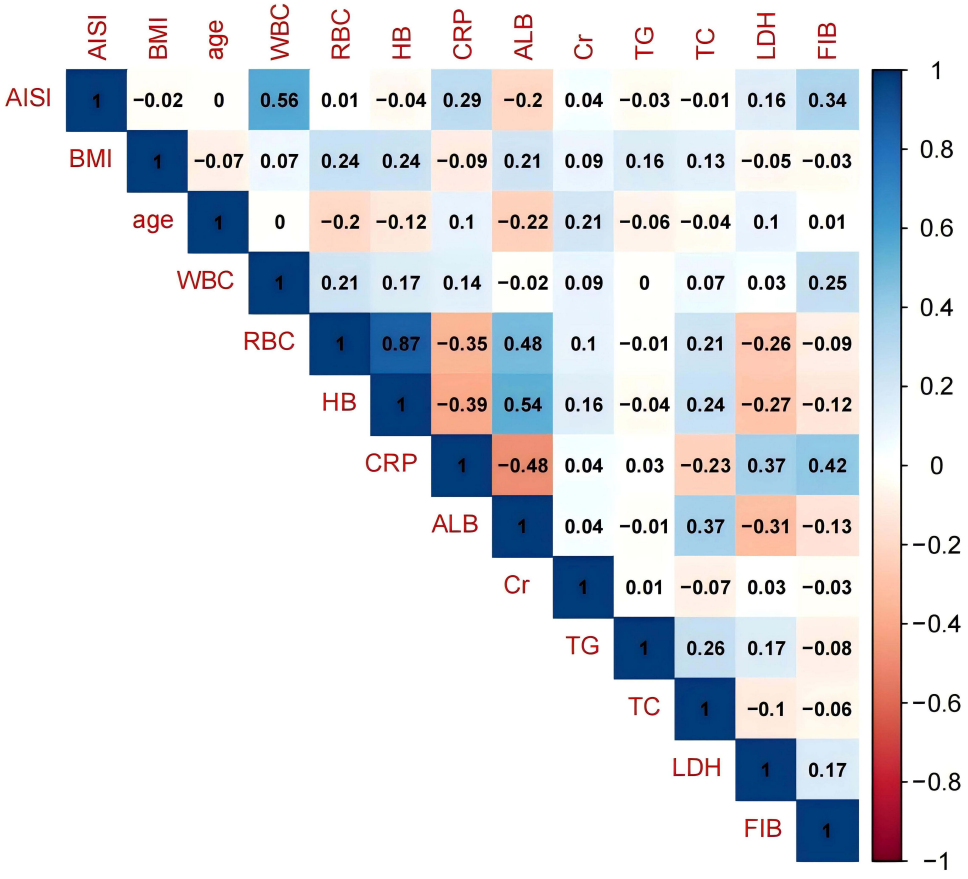

Figure 1 Correlation between AISI and Related Clinical Variables.
Abbreviations: AISI, aggregate index of systemic inflammation; ALB, albumin; BMI, body mass index; CRP, C-reactive protein; Cr, creatinine; FIB, fibrinogen; HB, hemoglobin; LDH, lactate dehydrogenase; TC, total cholesterol; TG, triglyceride.

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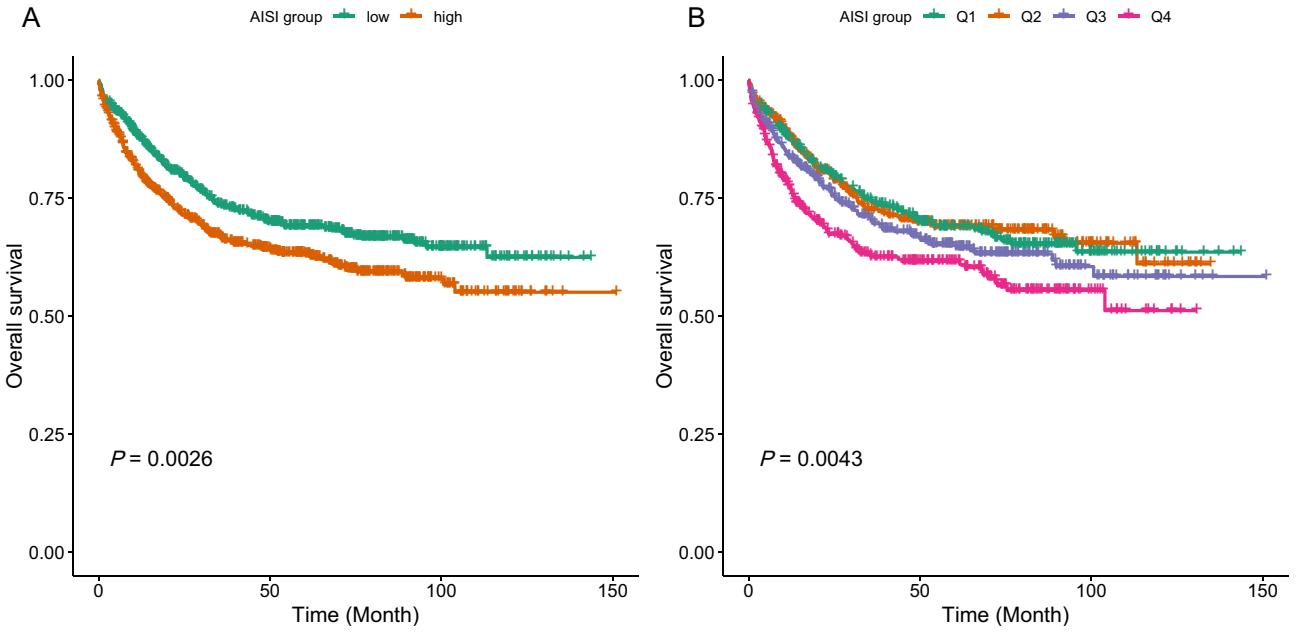

Figure 2 Kaplan-Meier curves for overall survival (OS) of DLBCL patients. (**A**) AISI groups were divided by the cut-off value; (**B**) AISI groups were divided into quartiles.

lower OS. This association remained significant in the fully adjusted model. Linear trend tests across quartiles further supported a positive association between higher AISI levels and increased mortality (*P* for trend: 0.001 in Models 1 and 2; 0.014 in Model 3). Similarly, when AISI was dichotomized using the cut-off value of 261.33, patients in the high-AISI group had significantly worse OS than those in the low-AISI group, both in the unadjusted model and after full adjustment for confounding factors (Table 2). In the training set, the prognostic model (Model 3) achieved a C-index of 0.70 (95% CI: 0.66–0.72). When applied to the validation set, the model yielded a C-index of 0.72 (95% CI: 0.68–0.77).

To evaluate whether AISI provides incremental prognostic information beyond established prognostic indices, additional multivariable Cox regression models were constructed, including AISI together with IPI or NCCN-IPI, respectively, with both indices entered as categorical variables. After adjustment for NCCN-IPI, AISI remained significantly associated with overall survival (*HR* = 1.230, 95% CI: 1.014–1.494, *P* = 0.035), whereas a borderline association was observed after adjustment for IPI (*HR* = 1.205, 95% CI: 0.993–1.463, *P* = 0.059). Model discrimination was further assessed using Harrell's C-index. The C-index was 0.622 for the IPI-adjusted model and 0.644 for the NCCN-IPI-adjusted model.

Table 2 Cox Regression Analysis of AISI for Overall Survival in DLBCL Patients, Stratified by Interquartile Range and Cut-off Values

AISI	Model 1		Model 2		Model 3	
	***HR* (95% CI)**	***P***	***HR* (95% CI)**	***P***	***HR* (95% CI)**	***P***
Q1	*Ref*	–	*Ref*	–	*Ref*	–
Q2	0.98 (0.74–1.30)	0.879	0.93 (0.70–1.23)	0.611	0.94 (0.70–1.27)	0.698
Q3	1.17 (0.89–1.54)	0.261	1.13 (0.86–1.48)	0.388	1.13 (0.85–1.51)	0.396
Q4	1.50 (1.15–1.95)	0.003	1.49 (1.14–1.94)	0.004	1.37 (1.03–1.81)	0.030
AISI ≤ 261.33	*Ref*	–	*Ref*	–	*Ref*	–
AISI > 261.33	1.34 (1.11–1.62)	0.003	1.34 (1.11–1.63)	0.003	1.28 (1.04–1.57)	0.018

Notes: Model 1: No adjustment. Model 2: Adjusted by age and gender. Model 3: Model 2+ Ann Arbor Stage, LDH, ECOG PS, BMI, ALB, B symptom, BM involvement, central nervous system involvement, liver/spleen involvement.
Abbreviations: ALB, albumin; BMI, body mass index; BM involvement, bone marrow involvement; CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase.

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Subgroup Analysis

Multivariate subgroup analyses were conducted according to age (≤60 vs>60 years), gender, LDH level (normal vs elevated), ECOG performance status (<2 vs ≥2), Ann Arbor stage (I/II vs III/IV), IPI and NCCN-IPI risk groups (low/low-intermediate vs high-intermediate/high), EBV DNA status (negative vs positive), and COO (GCB vs non-GCB). The association between higher AISI levels and worse OS appeared more pronounced among patients with limited-stage disease (Ann Arbor I/II), low or low-intermediate IPI, and low or low-intermediate NCCN-IPI risk categories (Figure 3).

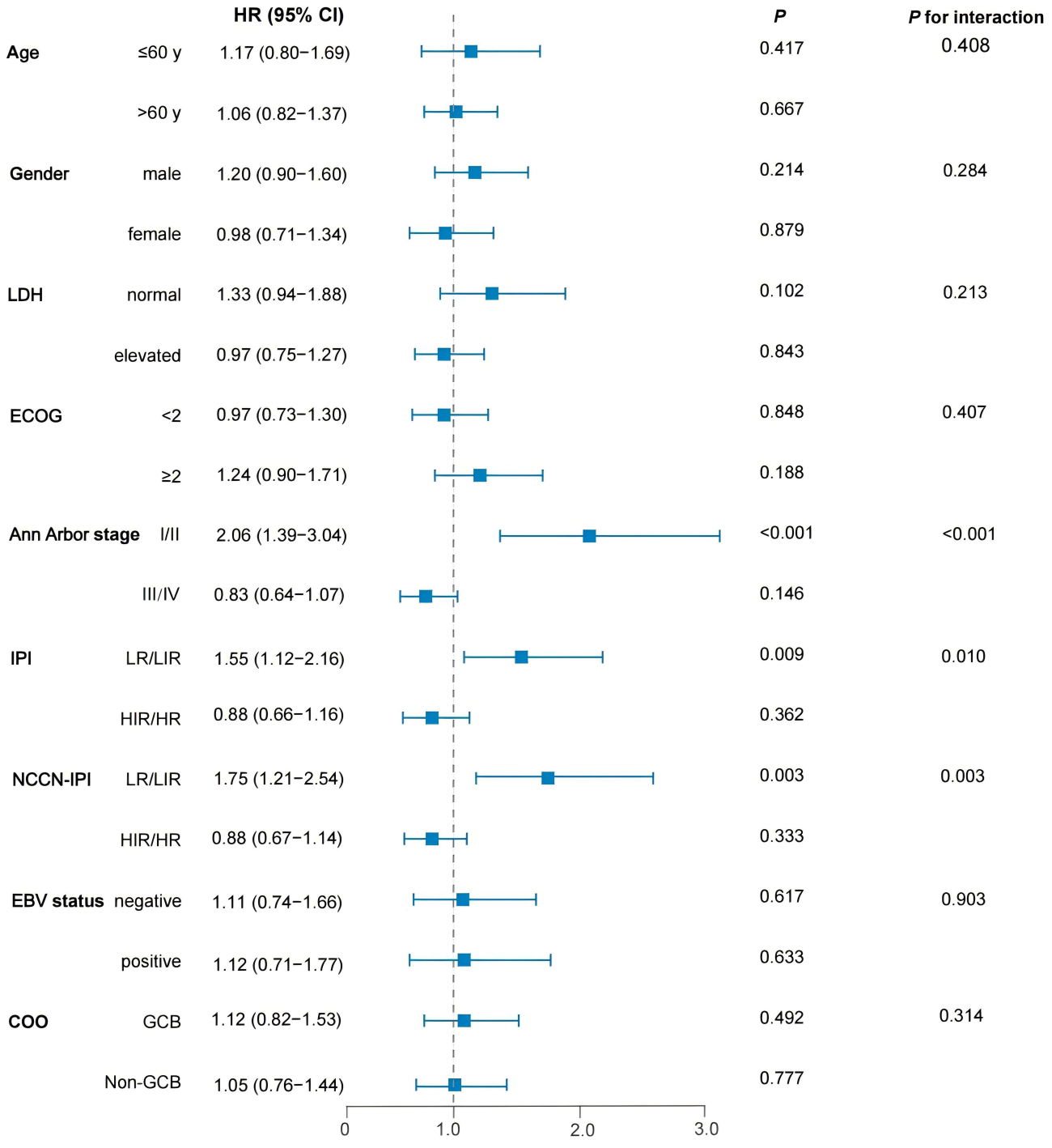

Figure 3 Forest plot of subgroup and interaction effects analyses.

Abbreviations: COO, cell of origin; ECOG, eastern cooperative oncology group; GCB, germinal center B cell; IPI, international prognostic index; LDH, lactate dehydrogenase; LR, low risk; LIR, low intermediate risk; HIR, high intermediate risk; HR, high risk; NCCN-IPI, National Comprehensive Cancer Network International Prognostic Index.

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To further explore the potential modifying effect of age, we performed an additional age-stratified analysis using finer age categories (60–69, 70–79, and ≥80 years). In these analyses, a significant association between elevated AISI and worse OS was observed in patients aged ≥80 years (n = 104; *HR* = 2.55, 95% CI: 1.49–4.39, $P < 0.001$).

Sensitivity Analyses

Sensitivity analyses excluding patients with missing data showed consistent results for the cut-off-based AISI grouping (HR = 1.33, 95% CI: 1.03–1.73; $P = 0.030$), while the association for the Q4 group did not reach statistical significance (HR = 1.41, 95% CI: 0.99–2.01; $P = 0.059$, Supplementary Table 2).

Discussion

In this multicenter retrospective study, we found that elevated AISI was associated with worse OS in patients with DLBCL. Both quartile- and cut-off-based analyses demonstrated that higher AISI levels correlated with increased mortality, even after adjustment for established prognostic factors. Notably, the highest AISI quartile (Q4) and the high-AISI group defined by the RCS-derived threshold (>261.33) showed consistently poorer survival outcomes. Subgroup analyses further suggested that AISI had greater prognostic discrimination in patients with limited-stage disease and lower IPI/NCCN-IPI risk categories. These findings support the potential utility of AISI as a readily available, inflammation-based prognostic biomarker in DLBCL.

In our study, elevated AISI levels were associated with multiple adverse clinical features. These findings suggest that systemic inflammation may influence DLBCL progression and prognosis through several biological mechanisms. First, inflammatory mediators may directly promote the proliferation and survival of malignant B cells.[22] Lymphoma cells have been shown to recruit neutrophils via CXCL8, which then activate the NF-κB signaling pathway through APRIL-mediated stimulation of B-cell maturation antigen (BCMA) and TACI, thereby enhancing tumor growth.[23] Second, inflammatory mediators contribute to the formation of an immunosuppressive tumor microenvironment, thereby weakening antitumor immune responses and facilitating immune evasion by lymphoma cells.[24,25] In addition, they promote tumor angiogenesis and enhance the invasive and metastatic potential of malignant cells, further accelerating disease progression.[26,27] Moreover, chronic tumor-associated inflammation has been linked to treatment resistance and poor treatment tolerance, posing significant challenges for effective therapeutic planning and long-term disease control.[28–30]

The AISI serves as a practical tool for assessing systemic inflammatory status and can be readily obtained from routine blood tests in clinical settings.[31–33] Elevated AISI values reflect increased counts of neutrophils, monocytes, and platelets, along with decreased lymphocyte levels. These cellular components are all involved in tumor-related inflammatory and immune processes. Neutrophils are a major source of vascular endothelial growth factor (VEGF),[34] which plays a pivotal role in promoting tumor progression and angiogenesis.[35,36] Concurrently, a reduced lymphocyte count impairs immune surveillance, thereby weakening the host's antitumor immune response.[37–39] Monocytes infiltrate tumor tissues and differentiate into tumor-associated macrophages (TAMs), which regulate tumor immunity, angiogenesis, and metastasis.[40] Additionally, platelets interact with monocytes to form monocyte-platelet aggregates through various signaling pathways, which further drive inflammation and thrombogenesis, ultimately influencing lymphoma progression and patient outcomes.[41]

We confirmed a significant non-linear association between AISI and OS in DLBCL patients using restricted cubic splines. Patients with high AISI levels consistently exhibited poorer prognosis, as demonstrated in both cut-off- and quartile-based analyses. Importantly, these associations remained significant even after adjusting for a range of clinical covariates. Furthermore, subgroup analyses indicated that the prognostic value of AISI was particularly evident in patients with limited-stage disease and those classified as low- or intermediate-risk by IPI and NCCN-IPI, suggesting that AISI may help identify high-risk individuals who are underestimated by conventional risk stratification models. However, several limitations should be acknowledged. As a retrospective multicenter study, there is an inherent risk of selection bias and residual confounding. Moreover, the treatment regimens were not fully standardized across centers, which may introduce heterogeneity and partially influence survival outcomes. Additionally, although multiple imputation was used to address missing data, it may not fully account for the uncertainty associated with missingness, particularly for secondary endpoints such as progression-free survival, event-free survival, and cause-specific mortality. Due to

inconsistent documentation of disease progression across centers and incomplete cause-of-death data, these secondary endpoints could not be reliably assessed.

In conclusion, this study found that elevated AISI was associated with shortened OS in DLBCL. Patients with AISI levels exceeding 261.33 may benefit from closer monitoring and risk stratification. However, these findings require external validation in independent cohorts to confirm the generalizability of this threshold. Future prospective studies are warranted to validate these findings and to explore the utility of AISI in dynamic risk assessment and individualized management of DLBCL.

Abbreviations

AISI, aggregate index of systemic inflammation; ALB, albumin; BMI, body mass index; BM, bone marrow; CI, confidence interval; COO, cell of origin; CNS, central nervous system; CRP, c-reactive protein; Cr, creatinine; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FIB, Fibrinogen; GCB, Germinal Center B Cell; HB, hemoglobin; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LIR, low intermediate risk; LR, low risk; NCCN-IPI, National Comprehensive Cancer Network International Prognostic Index; TC, total cholesterol; TG, triglyceride.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author (Dr. Wei Sang, xyfylbl515@xzhmu.edu.cn) on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and study approval was obtained from the ethics committee of the affiliated Hospital of Xuzhou Medical University. Informed consent was obtained from each patient.

Consent for Publication

Consent for publication was obtained from the participants. All reasonable measures were taken to protect patient anonymity.

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Collaborators

The Huaihai Lymphoma Working Group (HHLWG) is composed of the following medical centers:

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5. The First Affiliated Hospital of Anhui Medical University: Qinhua Liu
6. The First People's Hospital of Yancheng: Yuqing Miao
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8. Wanbei General Hospital of Suzhou: Taigang Zhu
9. The Second Affiliated Hospital of Soochow University: Bingzong Li
10. The First Affiliated Hospital of Zhengzhou University: Xudong Zhang
11. The First People's Hospital of Changzhou: Weiying Gu
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18. Linyi People's Hospital: Shuo Zhang

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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