Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Association of Serum AXL and Gas6 Levels with Clinical Outcomes in Non-Hodgkin Lymphoma Patients with Post-Chemotherapy Infection

Lihua Wang[1], Yuan Zhang[1], Yan Guo[1], Man Yang[1], Youmei Zi[1], Xiankai Liu[1], Guoqing Lv[1], Yan Huang[1,2]

[1]Department of Hematology, The First Affiliated Hospital of Henan Medical University, Weihui, Henan, 453100, People's Republic of China; [2]Xinxiang Key Laboratory of Molecular Diagnosis and Treatment of Lymphoma, Xinxiang, Henan, 453000, People's Republic of China

Correspondence: Yan Huang, Department of Hematology, The First Affiliated Hospital of Henan Medical University, 88 Jiankang Road, Weihui, Henan, 453100, People's Republic of China, Email 17991966@qq.com

Purpose: To investigate the association between serum AXL, growth arrest-specific protein 6 (Gas6) levels, pathogen distribution, and prognosis in non-Hodgkin lymphoma (NHL) patients with post-chemotherapy infection.

Patients and Methods: This single-center observational cohort study included 102 NHL patients with post-chemotherapy infection. Infection sites, pathogens, and serum levels of AXL, Gas6, and procalcitonin (PCT) were assessed. All patients were followed for one year from infection diagnosis and divided into survival (n=79) and death (n=23) groups. Baseline characteristics, pathogen detection, and serum markers were compared between groups. Cox regression analysis was used to identify prognostic factors, and receiver operating characteristic curve analysis was performed to evaluate the predictive value of serum AXL and Gas6 levels.

Results: Among 102 patients, the most common infection site was the respiratory tract (58.82%). Of 108 isolated pathogens, Gram-positive bacteria accounted for 55.56%. Compared with the survival group, the death group had significantly higher proportions of elevated lactate dehydrogenase, International Prognostic Index (IPI) score ≥ 2, chemotherapy cycles ≥ 3, and B symptoms (all $P < 0.05$). Serum levels of AXL, Gas6, and PCT were also significantly higher in the death group (all $P < 0.05$). Multivariable Cox regression analysis identified B symptoms and elevated AXL and Gas6 as independent risk factors for poor prognosis ($P < 0.05$). ROC curve analysis showed that AXL and Gas6 had robust prognostic value, with sensitivities of 91.3% and 69.6%, specificities of 64.6% and 79.7%, and area under the curve (AUC) values of 0.829 and 0.820, respectively.

Conclusion: In this exploratory study, elevated serum AXL and Gas6 levels were associated with poor outcomes in NHL patients with post-chemotherapy infection, suggesting their potential as prognostic markers.

Keywords: AXL, Gas6, non-Hodgkin Lymphoma, chemotherapy, infection

Introduction

Non-Hodgkin lymphoma (NHL) comprises a highly heterogeneous group of malignant tumors of the lymphohematopoietic system, and its incidence has steadily increased in recent years.[1] Owing to immune dysfunction caused by the malignancy itself, together with myelosuppression and mucosal barrier injury induced by intensive chemotherapy, patients with NHL are particularly susceptible to infectious complications.[2,3] Post-chemotherapy infections are common and clinically significant.[4] These infections interrupt or delay antitumor treatment, compromising therapeutic efficacy. Moreover, they are a major cause of sepsis, multiple organ failure, and death, ultimately impairing long-term survival.[5]

Given this high infection burden, understanding the microbiological profile of infection in NHL patients is essential for timely and effective management. Current evidence suggests that bacterial infections predominate after chemotherapy in patients with NHL, with both Gram-positive and Gram-negative organisms contributing substantially; however, the distribution of specific pathogens and their antimicrobial resistance profiles varies across regions, institutions, and patient populations.[6,7] In addition, the increasing detection of fungal infections and multidrug-resistant organisms has made empirical

https://doi.org/10.2147/IDR.S595522
Received: 18 January 2026
Accepted: 12 May 2026
Published: 25 May 2026

anti-infective treatment more challenging.[8,9] Therefore, continuous surveillance of pathogen epidemiology in NHL patients within specific medical settings is necessary to optimize empirical antimicrobial strategies and improve clinical outcomes.

While defining the pathogen spectrum is important, microbiological data alone are often insufficient for early risk stratification, because culture results may be delayed, and clinical deterioration can occur rapidly in immunocompromised patients. Accordingly, there is a pressing need to identify circulating biomarkers that can sensitively reflect infection severity, inflammatory dysregulation, and prognosis at an early stage. In NHL patients, established prognostic factors such as the International Prognostic Index (IPI), lactate dehydrogenase (LDH), and B symptoms are well validated for tumor outcomes,[10] but their ability to predict infection-specific prognosis is limited. Integrating these clinical parameters with novel biomarkers may improve risk stratification in infected patients. In recent years, AXL, a receptor tyrosine kinase of the TAM family, and its high-affinity ligand, growth arrest-specific protein 6 (Gas6), have attracted increasing attention as potential indicators of systemic inflammation and adverse outcomes.[11–14] More importantly, accumulating evidence suggests that the AXL/Gas6 axis is mechanistically linked to infection biology rather than simply representing a nonspecific inflammatory signal.

Mechanistically, the AXL/Gas6 axis participates in multiple processes relevant to infection. By recognizing phosphatidylserine-containing membranes, it modulates host–pathogen interactions, facilitates apoptotic body clearance, and in some circumstances promotes the entry of enveloped pathogens through apoptotic mimicry.[15] AXL activation also restrains innate immune signaling through suppressor of cytokine signaling proteins and inhibition of Toll-like receptor and NF-κB, thereby limiting excessive inflammation but potentially impairing pathogen elimination.[16] In parallel, AXL/Gas6 regulates efferocytosis, endothelial integrity, and tissue repair, all of which are closely involved in the pathophysiology of severe infection and sepsis.[17] Thus, AXL/Gas6 may serve as a marker not only of inflammation, but also of the interaction among immune suppression, infection progression, and host tissue injury. This is particularly relevant in NHL patients receiving chemotherapy, who often experience profound immune dysregulation and are highly vulnerable to infection. Meanwhile, AXL/Gas6 has also been implicated in lymphoma-related immune modulation and tumor progression.[18–20] These features suggest that AXL/Gas6 may have dual clinical relevance in this setting, serving both as molecules involved in the immunosuppressive tumor microenvironment and as potential biomarkers of infection-related severity and prognosis.

Nevertheless, the scientific significance of AXL and Gas6 in post-chemotherapy infection among NHL patients remains unclear. Current studies have mainly focused on solid tumors, sepsis, and general inflammatory conditions, whereas evidence in hematologic malignancies is still scarce. In particular, it is unknown whether serum AXL and Gas6 are altered after infection in NHL patients receiving chemotherapy, whether these changes are associated with short-term prognosis, and whether they offer additional risk stratification value beyond conventional inflammatory markers. Clarifying these issues is essential for determining the clinical utility of AXL/Gas6 as infection-related biomarkers in this high-risk population. Methodologically, prognostic analyses in small cohorts are prone to overfitting. Thus, we adopted an exploratory approach that acknowledges sample size limitations and avoids overinterpretation of predictive performance.

Based on the above considerations, we hypothesized that serum AXL and Gas6 levels are significantly associated with infection severity and poor prognosis in NHL patients following chemotherapy, and that their dysregulation may reflect the combined effects of infection-driven inflammation and chemotherapy-related immune impairment. Therefore, the present study was designed to investigate pathogen distribution in NHL patients with post-chemotherapy infection at our center and to further evaluate the relationship between serum AXL and Gas6 levels and patient survival outcomes. Therefore, this study aimed to characterize infection sites and pathogen distribution and to evaluate the prognostic value of serum AXL and Gas6 levels in NHL patients with post-chemotherapy infection.

Methodology

Study Design and Participants

This was a single-center, observational cohort study. Only the first infection episode per patient was analyzed to avoid within-patient clustering effects. A total of 102 consecutive patients with non-Hodgkin lymphoma (NHL) who developed post-chemotherapy infections at the First Affiliated Hospital of Henan Medical University between July 2022 and

October 2024 were enrolled. Inclusion criteria were as follows: (1) meeting the diagnostic criteria for NHL according to the Chinese Guidelines for Lymphoma Treatment (2022 Edition);[21] (2) age >18 years; (3) receiving at least one cycle of systemic chemotherapy; and (4) confirmed diagnosis of infection during or after chemotherapy based on the Diagnostic Criteria for Nosocomial Infections.[22] Exclusion criteria were as follows: (1) comorbid Hodgkin lymphoma or other malignancies; (2) presence of active infection before chemotherapy; and (3) incomplete clinical or follow-up data. This study was approved by the Ethics Committee of the First Affiliated Hospital of Henan Medical University (No. EC-022-135), and written informed consent was obtained from all patients.

Data Collection and Pathogen Detection

Demographic characteristics (age, sex), disease characteristics (pathological type, clinical stage, B symptoms), treatment information (chemotherapy cycles), and IPIscores[23] were collected from the electronic medical record system. We collected specimens from infection sites (sputum, blood, urine, secretions) under sterile conditions, inoculated them onto appropriate culture media, and incubated them at 35°C for 24–48 hours. Suspected colonies were identified using the VITEK 2 COMPACT automated system (bioMérieux, France).

Blood Sampling and Serum Storage

Fasting venous blood was collected within 1–6 hours after the diagnosis of infection and before antibiotic administration. A single measurement was performed for each patient. After collection, blood samples were immediately sent to the hospital laboratory. An aliquot was used for routine testing, and the remaining blood was centrifuged at 3500 rpm (radius 10 cm) for 10 minutes to separate serum. The serum was then stored at −80°C until analysis of AXL and Gas6 levels.

Serological Marker Measurement

Serum procalcitonin (PCT) levels were measured by chemiluminescence immunoassay. Serum AXL levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (Jianglai Bio, Shanghai, China) according to the manufacturer's instructions. The AXL ELISA kit (JL17046) had a detection range of 0.312–20 ng/mL, a sensitivity of 0.16 ng/mL, and intra- and inter-assay coefficients of variation (CVs) both <10%. Serum Gas6 levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (Huamei Bio, Wuhan, China) according to the manufacturer's instructions. The Gas6 ELISA kit (CSB-EL009270HU) had a detection range of 0.78–50 ng/mL, sensitivity of 0.19 ng/mL, and intra- and inter-assay CVs both <10%. Elevated LDH was defined as >250 U/L,[24] consistent with the upper limit of normal in our laboratory.

Follow-Up and Prognostic Grouping

All patients were followed for 1 year from the date of infection diagnosis through outpatient visits and telephone calls. Patients were divided into a survival group (n=79) and a death group (n=23) based on outcomes at the end of follow-up. For patients who died within the 1-year follow-up period, survival time was defined as the interval from the date of first infection to death, measured in weeks. For patients who survived, survival time was censored at 52 weeks.

Data Analysis

Data analysis was performed using SPSS 25.0 software. The normality of continuous variables, including age, AXL (ng/mL), Gas6 (ng/mL), and PCT (ng/mL), was assessed using the Kolmogorov–Smirnov test (or Shapiro–Wilk test for smaller sample sizes). Normally distributed continuous data are expressed as mean ± standard deviation (□x ± s), and comparisons between two groups were performed using an independent samples *t*-test. Categorical data are expressed as numbers (percentages) [n (%)], and group comparisons were conducted using the χ^2-test or Fisher's exact test, as appropriate. Univariable Cox proportional hazards regression analysis was performed to screen potential prognostic variables associated with overall survival. Variables with $P < 0.05$ in univariable analysis were entered into a forward stepwise multivariable Cox proportional hazards regression model, with entry and removal criteria set at $\alpha = 0.05$ and $\alpha = 0.10$, respectively. The proportional hazards assumption was assessed using Schoenfeld residuals. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. Due to the limited number of death events, the events-per-variable

ratio was calculated, and internal validation was performed using 1000 bootstrap resamples to obtain bias-corrected HRs and C-indices. Receiver operating characteristic curve analysis was used to evaluate the prognostic performance of serum AXL and Gas6 levels. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Distribution of Infection Sites and Pathogens

Among the 102 infected patients, the respiratory tract was the most common site of infection, accounting for 60 cases (58.82%), followed by the gastrointestinal tract in 13 cases (12.75%), urinary tract in 12 cases (11.76%), skin and mucous membranes in 12 cases (11.76%), and other sites in 5 cases (4.90%). A total of 108 pathogenic strains were isolated, including 60 Gram-positive bacteria (55.56%), 39 Gram-negative bacteria (36.11%), and 9 fungi (8.33%). The detection rates of *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Enterococcus faecalis* were significantly higher in the death group compared with the survival group ($P < 0.05$). There were no significant differences in the detection rates of *Pseudomonas aeruginosa* or fungi between the two groups ($P > 0.05$). Details are shown in Table 1.

Comparison of Clinical Characteristics and Serological Markers Between Prognostic Groups

The proportions of patients with elevated serum LDH, IPI score ≥ 2, chemotherapy cycles ≥ 3, and the presence of B symptoms were significantly higher in the death group than in the survival group ($P < 0.05$). There were no statistically significant differences between the two groups in terms of gender, age, pathological type, or tumor stage ($P > 0.05$). Regarding serological markers, serum levels of AXL, Gas6, and PCT were significantly higher in the death group than in the survival group ($P < 0.05$). Details are shown in Table 2.

Cox Regression Analysis of Factors Influencing Prognosis in NHL Patients

Univariable Cox regression analysis showed that pathological type, B symptoms, AXL levels, and Gas6 levels were significantly associated with overall survival, whereas sex, age, serum LDH, IPI score, chemotherapy cycles, and PCT were not significantly associated with overall survival. Among these factors, AXL levels exhibited the strongest prognostic significance, with an HR of 13.425 (95% CI: 3.980–45.280, $P < 0.001$). In contrast, sex, age, LDH, IPI

Table 1 Comparison of Major Pathogen Detection Rates Between the Death and Survival Groups in NHL Patients with Post-Chemotherapy Infection [n(%)]

Pathogen	Death Group (n=23)	Survival Group (n=79)	χ^2value	*P* value
Gram-negative Bacteria				
Overall	14 (60.87)	25 (15.19)	6.442	0.011
Klebsiella pneumoniae	8 (34.78)	12 (17.72)	4.338	0.037
Escherichia coli	7 (30.43)	9 (11.39)	4.884	0.027
Pseudomonas aeruginosa	3 (34.78)	3 (8.86)	2.751	0.097
Gram-positive Bacteria				
Overall	20 (86.96)	40 (50.63)	9.704	0.002
Staphylococcus aureus	14 (60.87)	20 (25.32)	10.133	0.001
Staphylococcus epidermidis	10 (43.48)	14 (17.72)	6.568	0.010
Enterococcus faecalis	6 (26.09)	6 (7.59)	5.868	0.015
Fungi				
Overall	2 (8.70)	7 (8.97)	0.002	0.967
Candida albicans	1 (4.35)	4 (5.06)	0.020	0.889
Aspergillus	1 (4.35)	3 (3.80)	0.014	0.905

Table 2 Comparison of Clinical Characteristics and Serum Biomarkers Between the Death and Survival Groups in NHL Patients with Post-Chemotherapy Infection

Clinical Indicator	Death Group (n=23)	Survival Group (n=79)	χ^2/t value	*P* value
Gender			0.133	0.715
Male	13 (56.52)	48 (60.76)		
Female	10 (43.48)	31 (39.24)		
Age (years, $\bar{x} \pm s$)	57.87±5.94	55.29±7.60	1.497	0.138
NHL pathological types			0.002	0.961
B-NHL	20 (86.96)	69 (87.34)		
T-NHL	3 (13.04)	10 (12.66)		
NHL staging			0.029	0.866
I~II	8 (34.78)	29 (36.71)		
III~IV	15 (65.22)	50 (63.29)		
Serum LDH			6.038	0.014
Normal	7 (30.43)	47 (59.49)		
Elevated	16 (69.57)	32 (40.51)		
IPI scores			4.104	0.043
<2	7 (30.43)	43 (54.43)		
≥2	16 (69.57)	36 (45.57)		
Chemotherapy Cycles			10.761	0.001
<3	8 (34.78)	57 (72.15)		
≥3	15 (65.22)	22 (27.85)		
B Symptoms			6.032	0.014
Yes	18 (78.26)	39 (49.37)		
No	5 (21.74)	40 (50.63)		
AXL (ng/mL)	4.896±0.651	3.862±0.805	5.639	<0.001
Gas6 (ng/mL)	23.774±3.566	19.019±3.755	5.403	<0.001
PCT (ng/mL)	4.458±0.798	3.737±0.829	3.703	<0.001

score, and chemotherapy cycles showed no significant correlation with overall survival (all $P > 0.05$). Variables with $P < 0.05$ (pathological type, B symptoms, AXL, and Gas6 levels) were included in the subsequent multivariate analysis (Table 3). The specific coding of categorical variables is shown in Supplementary Table 1. Subsequently, a multivariable Cox regression analysis was conducted. The overall model was statistically significant ($\chi^2 = 46.600$, $P < 0.001$). Three variables were retained in the final model: AXL, Gas6, and B symptoms. After adjusting for confounding factors, AXL (HR = 5.750, 95% CI: 2.300–14.390, $P < 0.001$), Gas6 (HR = 1.227, 95% CI: 1.082–1.390, $P < 0.001$), and B symptoms (HR = 5.537, 95% CI: 1.108–27.662, $P < 0.05$) remained independent prognostic factors. These results confirm that elevated AXL and Gas6 levels, as well as the presence of B symptoms, are independently associated with poor prognosis in NHL patients with post-chemotherapy infection (Table 4). Stepwise Regression Model Fitting Process is shown in Supplementary Table 2.

The analysis was performed using 1000 bootstrap resamples to obtain bias-corrected hazard ratios (HRs) and C-indices. The bias-corrected C-index after bootstrap resampling was 0.74 (95% CI: 0.65–0.82). The bias-corrected HRs and 95% confidence intervals (CIs) for each variable were as follows: B symptoms: HR = 4.21 (95% CI: 0.85–19.76); AXL: HR = 5.02 (95% CI: 1.89–13.28); Gas6: HR = 1.20 (95% CI: 1.03–1.39).

ROC curve analysis demonstrated that serum AXL and Gas6 had prognostic value for 1-year mortality (Figure 1). The optimal cutoff value for AXL was 4.045 ng/mL, yielding a sensitivity of 91.3%, a specificity of 64.6%, and an AUC of 0.829 (95% CI: 0.747–0.910, $P < 0.001$). For Gas6, the optimal cutoff was 22.425 ng/mL, with a sensitivity of 69.6%, a specificity of 79.7%, and an AUC of 0.820 (95% CI: 0.725–0.915, $P < 0.001$).

https://doi.org/10.2147/IDR.S595522

Table 3 Univariable Cox Regression Analysis of Prognostic Factors in NHL Patients with Post-Chemotherapy Infection

Variable	B	SE	Wald	P	HR	95% CI
Sex	−0.663	0.579	1.308	0.253	0.515	0.166–1.605
Age	0.069	0.04	2.968	0.085	1.071	0.991–1.158
Pathological Type	−2.028	0.84	5.822	0.016	0.132	0.025–0.683
Serum LDH	−1.264	0.689	3.365	0.067	0.282	0.073–1.090
IPI Score	−0.88	0.552	2.538	0.111	0.415	0.141–1.225
Chemotherapy Cycles	−1.189	0.615	0.094	0.759	0.828	0.248–2.765
B Symptoms	2.513	0.954	6.935	0.008	12.338	1.901–80.058
AXL (ng/mL)	2.597	0.62	17.53	<0.001	13.425	3.980–45.280
Gas6 (ng/mL)	0.234	0.081	8.396	0.004	1.264	1.079–1.480
PCT (ng/mL)	0.382	0.281	1.843	0.175	1.465	0.844–2.544

Table 4 Multivariable Cox Regression Analysis of Independent Prognostic Factors in NHL Patients with Post-Chemotherapy Infection

Variable	B	SE	Wald χ^2	P	HR	95% CI
B Symptoms	1.711	0.821	4.349	0.037	5.537	1.108–27.662
Gas6	0.204	0.064	10.232	0.001	1.227	1.082–1.390
AXL	1.75	0.468	13.993	<0.001	5.754	2.300–14.395

Discussion

Chemotherapy remains the cornerstone of systemic treatment for non-Hodgkin lymphoma (NHL). However, treatment-related immunosuppression significantly increases the risk of opportunistic infections, leading to treatment interruptions, increased complications, and worsened prognosis.[25] Therefore, investigating the pathogen characteristics and their association with prognosis in NHL patients with post-chemotherapy infections is essential for optimizing clinical management strategies. This study confirmed the prognostic impact of clinicopathological factors and revealed the potential value of serum AXL and Gas6 as prognostic biomarkers in such patients.

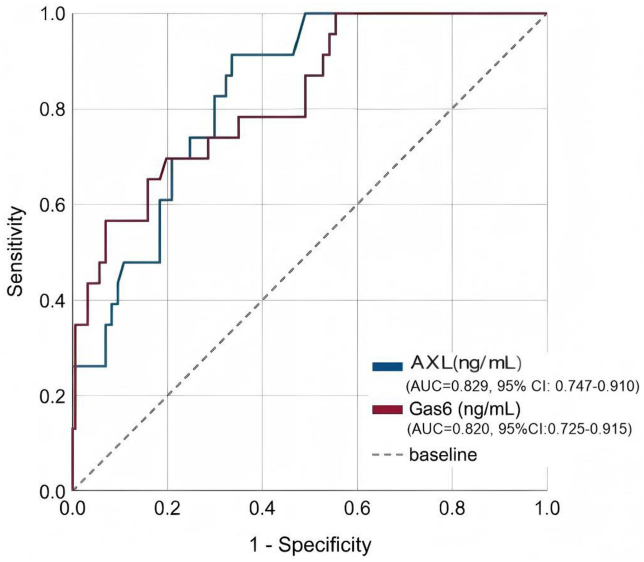

Figure 1 ROC curve of serum AXL and Gas6 levels for predicting patient prognosis. ROC curves of AXL: AUC 0.829 (95% CI: 0.747–0.910), cutoff 4.045 ng/mL, sensitivity 91.3%, specificity 64.6%. ROC curves of Gas6: AUC 0.820 (95% CI: 0.725–0.915), cutoff 22.425 ng/mL, sensitivity 69.6%, specificity 79.7%.

Pathogenic Characteristics of Infections

In this study, the respiratory tract was the most common site of infection in NHL patients after chemotherapy (58.82%), consistent with most reports.[26,27] This is mainly attributed to chemotherapy-induced mucosal barrier damage, granulocyte deficiency, and underlying pulmonary diseases. Gram-positive bacteria (55.56%) were predominant, with *Staphylococcus aureus* and *Staphylococcus epidermidis* being the most common. This is likely related to central venous catheter placement, disruption of skin and mucosal barriers, and exposure to the hospital environment.[28] Gram-negative bacteria (36.11%), particularly *Klebsiella pneumoniae* and *Escherichia coli*, are frequently associated with severe bloodstream infections and sepsis, presenting greater treatment challenges.[29] In univariate analysis, positivity for specific pathogens, including pneumonia-associated pathogens, was more frequent among fatal cases, suggesting that severe infection contributes to poor outcomes.

Heterogeneity of Lymphoma and Infection-Related Mortality

Non-Hodgkin lymphoma encompasses a diverse group of subtypes with distinct biological behaviors, treatment responses, and infectious risk profiles. For instance, aggressive subtypes such as diffuse large B-cell lymphoma (DLBCL) and peripheral T-cell lymphomas are associated with more profound immunosuppression from intensive chemotherapy regimens, whereas indolent lymphomas like follicular lymphoma may have a lower infection burden but still face increased risk after rituximab-based therapies.[30] The absence of subtype-specific analyses in the present study limits our ability to determine whether the prognostic value of AXL and Gas6 varies across different NHL entities. Moreover, infection-related mortality in NHL patients is multifactorial: direct septic complications, chemotherapy delay or dose reduction due to infection, and the interplay between systemic inflammation and lymphoma progression all contribute to poor outcomes.[31] In our cohort, fatal cases exhibited higher rates of pneumonia and bloodstream infections, but we could not disentangle the relative contributions of infection severity versus underlying lymphoma refractoriness. Future studies with larger sample sizes and predefined subtype stratification are needed to address these complexities.

Multidimensional Analysis of Prognostic Factors

Multivariable Cox regression analysis, after adjustment for confounding factors, identified B symptoms and elevated serum levels of AXL and Gas6 as independent risk factors for poor prognosis in NHL patients with post-chemotherapy infections. However, several statistical limitations must be acknowledged. With only 23 death events and an events-per-variable (EPV) ratio of 7.67 in the full Cox model, the risk of model instability and overfitting is substantial, even with stepwise selection to restrict the number of predictors.[32] Additionally, collinearity among the variables further compromises the stability of the effect estimate for B symptoms. Therefore, the identified risk factors, including AXL and Gas6, should be interpreted as exploratory rather than definitive, and their effect sizes may be overly optimistic. Future studies with larger sample sizes, along with LASSO regularization or external validation, are needed to confirm these findings.

Beyond statistical considerations, tumor invasiveness remains a key prognostic determinant. Univariate analysis showed that elevated serum LDH, a high IPI score (≥ 2), and the presence of B symptoms were associated with poor prognosis, reflecting higher tumor burden and biological aggressiveness. Although LDH and IPI score did not retain independent significance in multivariate analysis (possibly due to overlap with factors such as AXL and Gas6 or limited sample size), B symptoms emerged as an independent prognostic factor. B symptoms (fever, night sweats, weight loss) not only indicate tumor activity but may also reflect systemic inflammation, which could exacerbate the hyperinflammatory state following infection and contribute to a worse prognosis.[33,34]

Prognostic Value of Novel Serum Markers AXL and Gas6 in the Context of Existing Literature

A key finding of this study is that elevated serum levels of AXL and Gas6 are strong independent predictors for poor prognosis. These results should be placed within the broader landscape of prognostic models for lymphoma. AXL and Gas6, components of the TAM receptor tyrosine kinase pathway, have emerged as regulators of tumor immunity, inflammation, and apoptosis. AXL has been reported to be abnormally overexpressed in various human malignancies

and is closely associated with systemic inflammatory responses.[35] In patients with NHL who develop infections after chemotherapy, elevated AXL levels may reflect an excessive inflammatory response, which can lead to widespread tissue injury and ultimately contribute to organ dysfunction and increased mortality. Gas6, a ligand of the TAM receptor family, plays a crucial role in the regulation of inflammation, immune homeostasis, and coagulation. Increased serum Gas6 levels may represent a compensatory mechanism aimed at suppressing excessive inflammation; however, persistently elevated levels may also indicate an immunosuppressive state or endothelial dysfunction, thereby contributing to an unfavorable clinical outcome.[36] The interaction between the AXL receptor and its ligand Gas6 has been shown to inhibit apoptosis and promote tumor progression through activation of the AKT and NF-κB signaling pathways.[37,38] Therefore, the concurrent elevation of AXL and Gas6 may define a high-risk pathophysiological state in infected patients, reflecting the coexistence of heightened inflammatory drive and dysregulated immune modulation, which together contribute to poor prognosis. Our findings add to the growing evidence that TAM pathway components could serve as complementary biomarkers to existing prognostic indices, particularly in the setting of post-chemotherapy infections.

Study Limitations and Future Directions

This study has several limitations. First, it was a single-center retrospective study with a small sample and few outcome events, resulting in a low EPV ratio in the Cox model. Although stepwise Cox regression limited the number of variables, model instability and overfitting remain concerns. Second, AXL and Gas6 were measured only at infection diagnosis, precluding assessment of their utility in guiding treatment response or monitoring dynamic changes during anti-infective therapy. Third, non-Hodgkin lymphoma (NHL) is heterogeneous; the lack of subgroup analyses by pathological subtype limits generalizability to specific NHL subtypes. Fourth, pathogen drug resistance data were not analyzed, which is a notable shortcoming given the rising threat of multidrug-resistant organisms in immunocompromised hosts. As emphasized by Koca and Eskazan, clinical prediction models require external validation across diverse populations and should incorporate dynamic response markers and machine learning to refine risk stratification.[39] Although such approaches were beyond our exploratory study, future prospective studies should evaluate serial AXL and Gas6 measurements alongside treatment response as dynamic biomarkers. Future multicenter, large-sample prospective studies with adequate power are needed to validate the prognostic efficacy of AXL and Gas6, to explore the value of their serial measurements in guiding anti-infective therapy and assessing treatment response.

Conclusion

The prognosis of NHL patients with post-chemotherapy infection is likely influenced by tumor burden, treatment-related factors, and infection characteristics. In this exploratory analysis with a small sample size and limited outcome events, higher serum AXL and Gas6 levels were associated with worse short-term prognosis. However, given the restricted number of events and concerns about model stability, these findings do not support clinical risk stratification and should be considered strictly hypothesis-generating. Further validation in larger, multicenter cohorts is required to assess their robust prognostic value.

Abbreviations

NHL, non-Hodgkin lymphoma (NHL); Gas6, growth arrest-specific protein 6; PCT, procalcitonin; IPI, International Prognostic Index (IPI).

Data Sharing Statement

The datasets are available from the corresponding author on reasonable request.

Ethical Statement

This study complies with the Declaration of Helsinki. All NHL-infected patients provided informed consent. This study was approved by the Ethics Committee of the First Affiliated Hospital of Henan Medical University (No. EC-022-135).

Acknowledgments

We gratefully acknowledge the staff of the Hematology Department, the First Affiliated Hospital of Henan Medical University, for their valuable assistance in case collection.

Funding

This work was supported by the 2025 Henan Provincial Hospital Fiscal Funding Audit and Allocation Mechanism Project (Project Code: 210020113).

Disclosure

The authors declare that they have no competing interests.

References

1. Iida T, Nozawa H, Sonoda H, et al. Upfront surgery for small intestinal Non-Hodgkin's Lymphoma. *Anticancer Res*. 2020;40(4):2373–2377. doi:10.21873/anticanres.14206
2. Kassar O, Kahla AB, Koubaa A, Kallel F, Amor IB, Elloumi M. Non-Hodgkin's lymphoma developed during imatinib mesylate treatment of chronic myeloid leukemia. *J Oncol Pharm Pract*. 2023;29(4):996–998. doi:10.1177/10781552221137700
3. St-Pierre F, Gordon LI. CAR T-cell therapy for relapsed/refractory non-Hodgkin's lymphoma: a comprehensive review. *Clin Adv Hematol Oncol*. 2022;20(5):309–318.
4. Bermudez MA, Grant KM, Rodvien R, Mendes F. Non-Hodgkin's lymphoma in a population with or at risk for acquired immunodeficiency syndrome: indications for intensive chemotherapy. *Am J Med*. 1989;86(1):71–76. doi:10.1016/0002-9343(89)90232-5
5. Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, Phase 1/2 study. *Lancet*. 2021;398(10306):1157–1169. doi:10.1016/S0140-6736(21)00889-8
6. Songthawee N, Chavananon S, Sripornsawan P, McNeil E, Chotsampancharoen T. Prevalence and risk factors of disseminated intravascular coagulation in childhood acute lymphoblastic leukemia. *Pediatr Res*. 2023;94(2):588–593. doi:10.1038/s41390-023-02475-8
7. Yagi K, Tao Y, Hara K, et al. Increased plasma plasmin-α2-plasmin inhibitor complex levels correlate with postoperative rebleeding after endoscopic surgery for spontaneous intracerebral hemorrhage. *Acta Neurochir*. 2020;162(12):3129–3136. doi:10.1007/s00701-019-04154-2
8. Li YH, Lu CH, Lin FH, et al. Plasma growth arrest-specific 6 protein and genetic variations in the GAS6 gene in patients with metabolic syndrome. *Metab Syndr Relat Disord*. 2019;17(1):22–28. doi:10.1089/met.2017.0143
9. Giovanella L, Garo ML, Ceriani L, Paone G, Campenni' A, D'Aurizio F. Procalcitonin as an alternative tumor marker of medullary thyroid carcinoma. *J Clin Endocrinol Metab*. 2021;106(12):3634–3643. doi:10.1210/clinem/dgab564
10. Durani U, Ansell SM. CD5+ diffuse large B-cell lymphoma: a narrative review. *Leuk Lymphoma*. 2021;62(13):3078–3086. doi:10.1080/10428194.2021.1953010
11. Tian Q, Guo H, Zhang M, et al. NETs activate the GAS6-AXL-NLRP3 axis in macrophages to drive morphine tolerance. *Cell Commun Signal*. 2025;23(1):181. doi:10.1186/s12964-025-02181-4
12. Di Stasi R, De Rosa L, D'Andrea LD. Therapeutic aspects of the Axl/Gas6 molecular system. *Drug Discov Today*. 2020;25(12):2130–2148. doi:10.1016/j.drudis.2020.09.022
13. Chen J, Wang Y, Li X, et al. IDHP mitigates LPS-induced cardiomyocyte injury via the GAS6/Axl-AMPK axis: a multi-target strategy counteracting inflammation, oxidative stress, and apoptosis. *Pharmaceuticals*. 2025;18(8):1188. doi:10.3390/ph18081188
14. Zhang S, Liu Y, Wang X, An N, Ouyang X. STAT1/SOCS1/3 are involved in the inflammation-regulating effect of GAS6/AXL in periodontal ligament cells induced by porphyromonas gingivalis lipopolysaccharide in vitro. *J Immunol Res*. 2021;2021:9577695. doi:10.1155/2021/9577695
15. Zdżalik-Bielecka D, Poświata A, Kozik K, et al. The GAS6-AXL signaling pathway triggers actin remodeling that drives membrane ruffling, macropinocytosis, and cancer-cell invasion. *Proc Natl Acad Sci U S A*. 2021;118(28):e2024596118. doi:10.1073/pnas.2024596118
16. Zhou G, Li H. AXL inhibits proinflammatory factors to relieve rheumatoid arthritis pain by regulating the TLR4/NF-κB signaling pathway. *Evid Based Complement Alternat Med*. 2023;2023:9758919. doi:10.1155/2023/9758919
17. Zhang L, Richard AS, Jackson CB, Ojha A, Choe H. Phosphatidylethanolamine and phosphatidylserine synergize to enhance GAS6/AXL-mediated virus infection and efferocytosis. *J Virol*. 2020;95(2):e02079–20. doi:10.1128/JVI.02079-20
18. Tanaka M, Siemann DW. Gas6/Axl signaling pathway in the tumor immune microenvironment. *Cancers*. 2020;12(7):1850. doi:10.3390/cancers12071850
19. Roy S, Bag AK, Dutta S, et al. Macrophage-derived neuropilin-2 exhibits novel tumor-promoting functions. *Cancer Res*. 2018;78(19):5600–5617. doi:10.1158/0008-5472.CAN-18-0562
20. Holtzhausen A, Harris W, Ubil E, et al. TAM family receptor kinase inhibition reverses MDSC-mediated suppression and augments Anti-PD-1 therapy in melanoma. *Cancer Immunol Res*. 2019;7(10):1672–1686. doi:10.1158/2326-6066.CIR-19-0008
21. Health Commission of The People's Republic of China N. National guidelines for diagnosis and treatment of malignant lymphoma 2022 in China (English version). *Chin J Cancer Res*. 2022;34(5):425–446. doi:10.21147/j.issn.1000-9604.2022.05.01
22. Kollef MH, Torres A, Shorr AF, Martin-Loeches I, Micek ST. Nosocomial Infection. *Crit Care Med*. 2021;49(2):169–187. doi:10.1097/CCM.0000000000004783
23. Garcia-Recio M, Wudhikarn K, Pennisi M, et al. The international prognostic index is associated with outcomes in diffuse large B cell lymphoma after chimeric antigen receptor T cell therapy. *Transplant Cell Ther*. 2021;27(3):233–240. doi:10.1016/j.jtct.2020.10.022
24. Resuli B, Walter J, Kauffmann-Guerrero D, et al. Distinct Clinical and Biological Features of Diffusely Metastatic Versus Bulky Localized Lung Cancer: real-World Outcomes from a University Cancer Center in Germany. *Cancers*. 2025;17(23):3728. doi:10.3390/cancers17233728

25. Na R, Laaksonen MA, Grulich AE, et al. Iatrogenic immunosuppression and risk of non-Hodgkin lymphoma in solid organ transplantation: a population-based cohort study in Australia. *Br J Haematol*. 2016;174(4):550–562. doi:10.1111/bjh.14083
26. Ma R, Li Y, Yin S, Gao Y, Zhao G. Interstitial pneumonia development after chemotherapy in B-cell non-hodgkin's lymphoma patients: clinical profiles and risk factors. *Am J Cancer Res*. 2024;14(9):4484–4494. doi:10.62347/BTGQ7302
27. Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a Phase 2 randomised study (ROMULUS). *Lancet Haematol*. 2019;6(5):e254–e265. doi:10.1016/S2352-3026(19)30026-2
28. Rafa O, Basile EJ, Ali A, Patel PD, Palatnic L. Atypical presentation of infective endocarditis with native aortic valve involvement secondary to *Staphylococcus aureus* bacteremia in the setting of non-hodgkin lymphoma. *Cureus*. 2022;14(9):e29012. doi:10.7759/cureus.29012
29. Guarana M, Nucci M, Nouér SA. Shock and early death in hematologic patients with febrile neutropenia. *Antimicrob Agents Chemother*. 2019;63(11):e01250–19. doi:10.1128/AAC.01250-19
30. Cordas Dos Santos DM, Tix T, Shouval R, et al. A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy. *Nat Med*. 2024;30(9):2667–2678. doi:10.1038/s41591-024-03084-6
31. Zając-Spychała O, Wachowiak J, Czyżewski K, et al. Hematopoietic stem cell transplantation does not increase the risk of infection-related complications for pediatric patients with Hodgkin and non-Hodgkin lymphomas: a multicenter nationwide study. *Transpl Infect Dis*. 2020;22(4):e13292. doi:10.1111/tid.13292
32. Fusar-Poli P, Stringer D, Durieux AMS, et al. Clinical-learning versus machine-learning for transdiagnostic prediction of psychosis onset in individuals at-risk. *Transl Psychiatry*. 2019;9(1):259. doi:10.1038/s41398-019-0600-9
33. Li Q, Ou Z, Lin J, et al. Specific labeling of outer membrane vesicles with antibiotic-conjugated probe reveals early bacterial infections in blood. *Nat Commun*. 2025;16(1):3535. doi:10.1038/s41467-025-58676-8
34. Wudhikarn K, Soh SY, Huang H, Perales MA. Toxicity of chimeric antigen receptor T cells and its management. *Blood Cell Ther*. 2021;4(Spec Edition):S1–S7. doi:10.31547/bct-2021-011
35. Zhao W, Fan J, Kulic I, et al. Axl receptor tyrosine kinase is a regulator of apolipoprotein E. *Mol Brain*. 2020;13(1):66. doi:10.1186/s13041-020-00609-1
36. Shiozawa Y, Pedersen EA, Taichman RS. GAS6/Mer axis regulates the homing and survival of the E2A/PBX1-positive B-cell precursor acute lymphoblastic leukemia in the bone marrow niche. *Exp Hematol*. 2010;38(2):132–140. doi:10.1016/j.exphem.2009.11.002
37. Kong L, Wu Z, Zhao Y, et al. Qigesan reduces the motility of esophageal cancer cells via inhibiting Gas6/Axl and NF-κB expression. *Biosci Rep*. 2019;39(6):BSR20190850. doi:10.1042/BSR20190850
38. Lee WP, Wen Y, Varnum B, Hung MC. Akt is required for Axl-Gas6 signaling to protect cells from E1A-mediated apoptosis. *Oncogene*. 2002;21(3):329–336. doi:10.1038/sj.onc.1205066
39. Koca O, Eskazan AE. Refining the risk stratification in advanced-stage classical Hodgkin lymphoma: a critical analysis of clinical prediction models. *Br J Haematol*. 2025;207(5):1744–1754. doi:10.1111/bjh.70115