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Original Article

Analysis of risk factors affecting the prognosis of angiosarcoma patients: a retrospective study

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Abstract: This study aimed to identify prognostic factors influencing the survival of angiosarcoma patients and to explore the relationship between peripheral blood indicators and patient prognosis. A retrospective analysis was conducted on the clinical data collected from 105 angiosarcoma patients treated at China-Japan Union Hospital of Jilin University from January 2004 to April 2019, with an additional 50 patients included as external validation cohort. The median survival time for the study cohort was 1395 days, with 66.7% of patients (n=70) dying during the follow-up period. Significant differences were observed between the survival and death groups in age (P=0.022), primary tumor site (P=0.013), tumor size (P=0.008), and metastasis (P=0.018). Analysis of peripheral blood indicators showed that white blood cell (WBC) (P=0.006), platelet (PLT) (P=0.019), platelet-to-lymphocyte ratio (PLR) (P<0.001), and systemic immune-inflammation index (SII) (P=0.036) were significantly lower in the survival group, while lymphocyte (LYM) (P<0.001), albumin (ALB) (P<0.001), and prognostic nutritional index (PIN) (P<0.001) were significantly higher in the survival group. Multivariate Cox regression analysis identified SII (P=0.049, HR=0.551, 95% CI: 0.304-0.998), primary tumor site (P=0.001, HR=0.405, 95% CI: 0.235-0.699), metastasis (P=0.029, HR=1.864, 95% CI: 1.066-3.26), and chemotherapy (P=0.004, HR=0.434, 95% CI: 0.245-0.768) as independent prognostic factors affecting patients' 5-year survival. A nomogram model constructed based on these factors demonstrated high accuracy and stability in predicting 1-year, 3-year, and 5-year survival rates, with area under the curve (AUC) values of 0.836, 0.837, and 0.803, respectively, as validated by calibration curves and receiver operating characteristic (ROC) analysis. External validation further confirmed the model's reliability. Additionally, significant interactions were found between SII and primary tumor site (P=0.005) as well as chemotherapy (P=0.045). In conclusion, SII, primary tumor site, metastasis, and chemotherapy are crucial prognostic factors for angiosarcoma, and the developed nomogram provides a reliable tool for predicting survival outcomes.

Keywords: Angiosarcoma, prognostic factors, systemic immune-inflammation index, nomogram model, survival prediction

Introduction

Angiosarcoma is a rare but highly aggressive soft tissue sarcoma originating from endothelial cells, which can occur in any part of the body [1]. Due to its aggressive nature, angiosarcoma is highly malignant, and the prognosis is generally poor [2]. Current statistics indicate that the five-year survival rate for patients with angiosarcoma is approximately 10-50% [3]. Although the incidence is low, its high aggressiveness and recurrence rate cause significant patient suffering and present severe challenges for clinical treatment.

Currently, treatment methods for angiosarcoma, including surgical resection, chemotherapy, anti-angiogenic therapy, and immunotherapy, have advanced but still face substantial clinical limitations [4]. For localized angiosarcoma, complete surgical resection remains the primary approach; but achieving negative margins is challenging due to satellite lesions, leading to frequent recurrence [5-7]. For advanced cases, combined treatments are used, but the persistence of drug efficacy is limited, and tumors easily develop resistance, posing a major obstacle to improving patient prognosis.

Despite continuous advances in treatment strategies, the understanding of the biological characteristics, prognostic factors, and molecular mechanisms of angiosarcoma is still insufficient. Current studies have shown that clinical

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features such as tumor size, primary tumor site, and metastasis are closely related to patient prognosis [8]. Additionally, peripheral blood markers are emerging as valuable tools in disease prediction and diagnosis. For example, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and prognostic nutritional index (PNI) have been proven to be associated with prognosis in various types of cancer [9, 10]. One study [11] showed that changes in NLR, PLR, SII, and PNI before and after treatment were significantly related to the patients' pathological complete response rates. Another study [12] indicated that NLR, PLR, and lymphocyte-to-monocyte ratio (LMR) also have significant prognostic value in head and neck squamous cell carcinoma, with higher NLR and PLR associated with poorer survival rates, while lower LMR is related to better survival prognosis.

Given the aggressiveness and poor prognosis of angiosarcoma, this study aims to explore the factors affecting the prognosis of angiosarcoma patients and construct a corresponding prognostic model to provide reference for clinical treatment. Through this approach, we hope to gain a more comprehensive and in-depth understanding of the prognostic factors of angiosarcoma and provide more scientific guidance for clinical practice.

Methods and materials

Clinical data

A retrospective study was conducted on the clinical data collected from 105 angiosarcoma patients who were treated at China-Japan Union Hospital of Jilin University from January 2010 to April 2019 (**Table 1**). Additionally, 50 angiosarcoma patients treated at China-Japan Union Hospital of Jilin University during the same period were used as external validation cohort. Inclusion criteria: patients confirmed with angiosarcoma through pathological examination [13]; patients aged over 18; and patients with complete clinical data. Exclusion criteria: patient with congenital functional defects, severe cardiovascular, liver, or kidney diseases; patients who had received other experimental treatments; patients with acute inflammation or infection before surgery, radiotherapy, or chemotherapy; and patients with missing follow-up data. This study was approved by the Medical Ethics Committee of China-Japan Union Hospital of Jilin University.

Data collection

Relevant patient data were collected through the hospital's electronic medical record system. Baseline data included age, sex, primary site, tumor size, metastasis, lumen structure, nuclear atypia, cluster of differentiation 31 (CD31), cluster of differentiation 34 (CD34), tumor protein p53 (p53), history of surgery, history of radiotherapy, and history of chemotherapy. These data were obtained at the time of admission. Laboratory indicators included white blood cell (WBC), lymphocyte (LYM), neutrophil (NEUT), monocyte (MON), platelet (PLT), albumin (ALB), NLR, LMR, PLR, SII, and PIN. These indicators were collected one day before surgery, radiotherapy, and chemotherapy.

Peripheral blood indicators detection

Five milliliters of peripheral blood were collected from patients, and routine blood indicators were detected using an automatic blood cell analyzer (Mindray BC5000). The following formulas were used to calculate peripheral blood inflammation indicators: NLR = NEUT/LYM; LMR = LYM/MON; PLR = PLT/LYM; SII = (NEUT/LYM)PLT; PIN = ALB + (5LYM) [14].

Immunohistochemical analysis

Immunohistochemical staining was performed on all available cases with sufficient sample quantities. Formalin-fixed, paraffin-embedded tissue sections were cut into 3 μm thick slices. Immunocomplexes were detected using the DAKO EnVision detection system (Dako, Glostrup, Denmark). The criteria for immunohistochemical positivity for each antibody were as follows: CD31 and CD34 were considered positive if more than 10% of tumor cells were stained [15]; p53 was considered positive if ≥20% of cells were stained [16]. Staining intensity was assessed by comparison with internal positive controls (epidermis) or by visual confirmation of deep brown staining throughout the entire cell nucleus.

Follow-up

All patients were followed up from the time of surgery, radiotherapy, or chemotherapy initiation. The follow-up period lasted for 5 years, with follow-ups every 3 months in the first year,

Table 1. Patient baseline data

Factors	n=105
Age	
<60	47
60-70	28
>70	30
Sex	
Male	57
Female	48
Primary Site	
Skin	51
Others	54
Tumor Size	
<5 cm	44
≥5 cm	61
Metastasis	
Present	34
Absent	71
Surgery	
Performed	29
Not Performed	76
Radiotherapy	
Performed	69
Not Performed	36
Chemotherapy	
Performed	49
Not Performed	56
Lumen structure	
≥50%	73
<50%	32
Nuclear anisotropy	
High	38
Low to medium	67
CD31	
Present	95
Absent	10
CD34	
Present	74
Absent	31
p53	
Present	67
Absent	38
WBC (10^9/L)	7.72±1.87
LYM (10^9/L)	1.78±0.59
NEUT (10^9/L)	3.44±1.30
MON (10^9/L)	0.36±0.14
PLT (10^9/L)	211.58±41.48
ALB (g/L)	38.47±8.10
NLR	2.16±1.14
LMR	6.18±4.68
PLR	134.78±58.63
SII	455.87±258.81

Note: CD31, Cluster of Differentiation 3; CD34, Cluster of Differentiation 34; p53, Tumor Protein p53; WBC, White Blood Cell; LYM, Lymphocyte; NEUT, Neutrophil; MON, Monocyte; PLT, Platelet; ALB, Albumin; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PIN, Prognostic Inflammatory Nutritional Index. These indicators were obtained from patients one day before surgery, radiotherapy, and chemotherapy.

every 4 months in the second and third years, and every 6 months thereafter.

Outcome measures

Primary outcomes: Prognostic factors affecting the 5-year survival of angiosarcoma patients were identified. A Nomogram model based on prognostic factors was constructed. The interaction between SII and prognostic factors was determined.

Secondary outcomes: Baseline data and laboratory indicators between the death and survival groups were compared. Survival curves for independent prognostic factors were plotted. The clinical value, stability, and predictive performance of the predictive model were validated using time-dependent Receiver Operating Characteristic (ROC) curves, calibration curves, Kaplan-Meier (K-M) survival curves, and Decision Curve Analysis (DCA).

Statistical analysis

Data were analyzed using R language (version 4.3.2). The "*stats*" package was used for statistical analysis of measurement data and count data [17]. Measurement data were tested for normal distribution; data conforming to normal distribution were expressed as mean ± standard deviation and analyzed using independent sample t-tests, while non-normally distributed data were expressed as interquartile range (IQR) and analyzed using Wilcoxon rank-sum tests. Count data were expressed as percentages (%) and analyzed using chi-square tests. The optimal survival cutoff values for laboratory indicators were determined using X-tile software. Univariate and multivariate Cox regression analyses were performed using the "*sur-*

Table 2. Comparison of baseline characteristics between the death and survival groups

Factors	Death Group (n=70)	Survival Group (n=35)	X^2 Value	*P* Value
Age				
<60	27	20	7.644	0.022
60-70	17	11		
>70	26	4		
Sex				
Male	39	18	0.173	0.678
Female	31	17		
Primary Site				
Skin	28	23	6.176	0.013
Others	42	12		
Tumor Size				
<5 cm	23	21	7.061	0.008
≥5 cm	47	14		
Metastasis				
Present	28	6	5.568	0.018
Absent	42	29		
Surgery				
Performed	18	11	0.381	0.537
Not Performed	52	24		
Radiotherapy				
Performed	48	21	0.761	0.383
Not Performed	22	14		
Chemotherapy				
Performed	29	20	2.315	0.128
Not Performed	41	15		

vival" package [18]. The predictive efficiency of risk scores for patient survival was assessed using the "*TimeROC*" package [19]. A Nomogram was constructed using the "*rms*" package [20], and its prognostic efficiency was further evaluated using Decision Curve Analysis (DCA) with the "*ggDCA*" package in R [21]. Kaplan-Meier survival curves were plotted for independent prognostic factors, and calibration curves were used to validate the model's performance. The interaction between SII and independent prognostic factors was analyzed using the "*visreg*" package. A two-sided *P*-value of less than 0.05 was considered statistically significant.

Results

Comparison of patient characteristics between the death and survival groups

All patients were followed for 5 years, with none lost to follow-up. The median survival time of the patients was 1395 days (1015.5-1774.5). During the follow-up period, 70 patients (66.7%) died. The patients were then grouped based on their survival status. Significant differences were observed between the death and survival groups in terms of age (P=0.022), primary site (P=0.013), tumor size (P=0.008), metastasis (P=0.018), and lumen structure (P=0.004) (**Table 2**).

Comparison of peripheral blood indicators between the death and survival groups

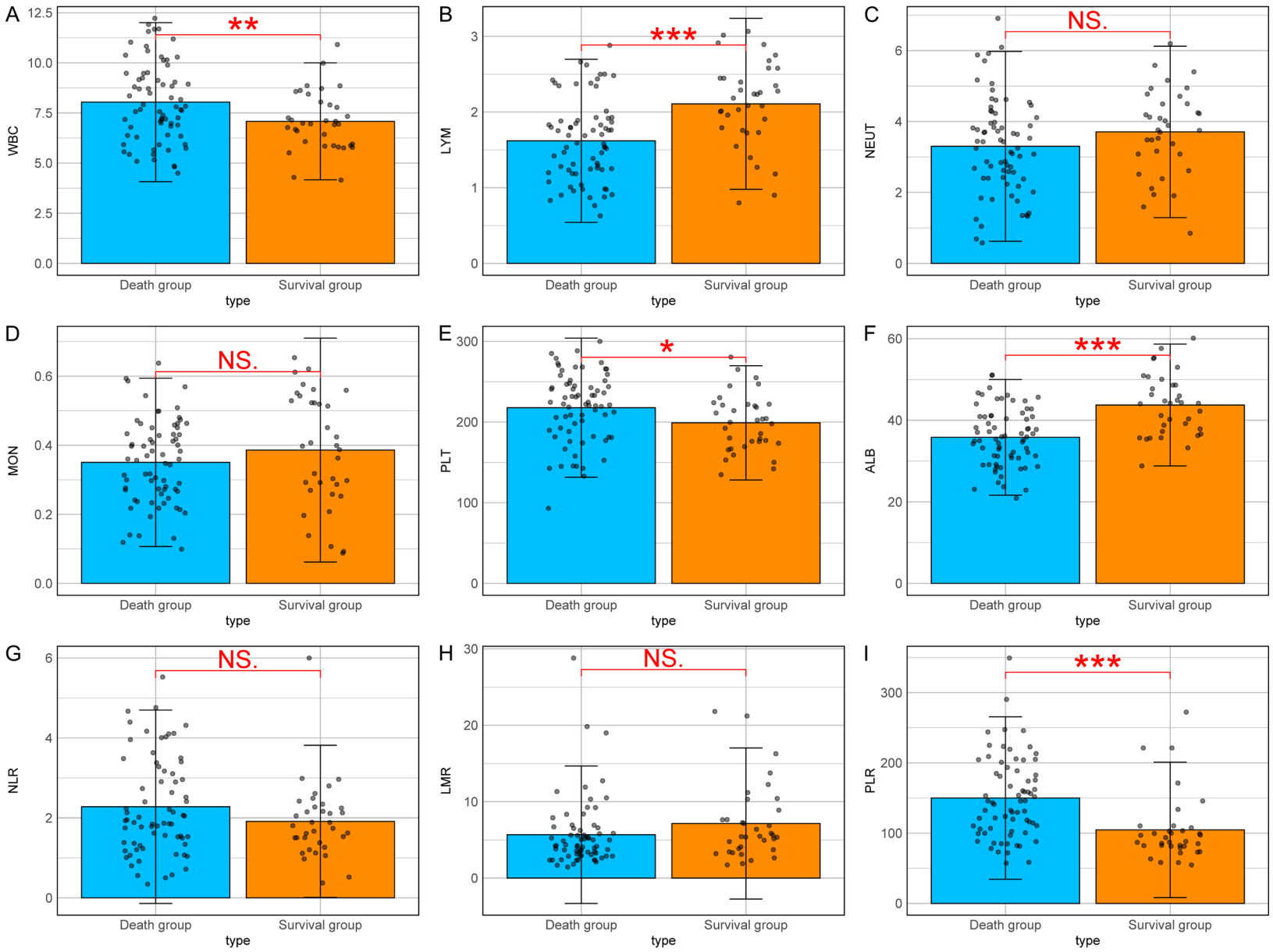
Peripheral blood indicators were collected one day before treatment (surgery, radiotherapy, or chemotherapy). Comparisons showed that WBC (P=0.006), PLT (P=0.019), PLR (P<0.001), and SII (P=0.036) were significantly lower, while LYM (P< 0.001), ALB (P<0.001), and PIN (P<0.001) were significantly higher in the survival group than those in the death group. However, there were no differences between the two groups in NEUT (P=0.120), MON (P=0.260), NLR (P=0.236), and LMR (P=0.056). The details are shown in **Figure 1A-K**.

Optimal cutoff values for X-tile software

Based on the comparison of peripheral blood data, significant differences in WBC, LYM, PLT, ALB, PLR, SII, and PIN were identified between the death and survival groups. For further Cox regression analysis, the optimal cutoff values for these seven indicators were determined using X-tile software (**Figure 2A-G**). The optimal cutoff values for WBC, PLT, PLR, SII, LYM, ALB, and PIN were 8.66, 1.93, 224, 35, 110.68, 536.82, and 45.5, respectively.

Analysis of prognostic factors affecting 5-year survival in angiosarcoma patients

Univariate Cox regression analysis was used to identify prognostic factors affecting the 5-year survival of angiosarcoma patients. The results showed that WBC, LYM, PLT, ALB, PLR, SII, PIN, age, primary site, tumor size, metastasis, and chemotherapy were prognostic factors affecting 5-year survival (P<0.05, **Figure 3**). Further multivariate Cox regression analysis identified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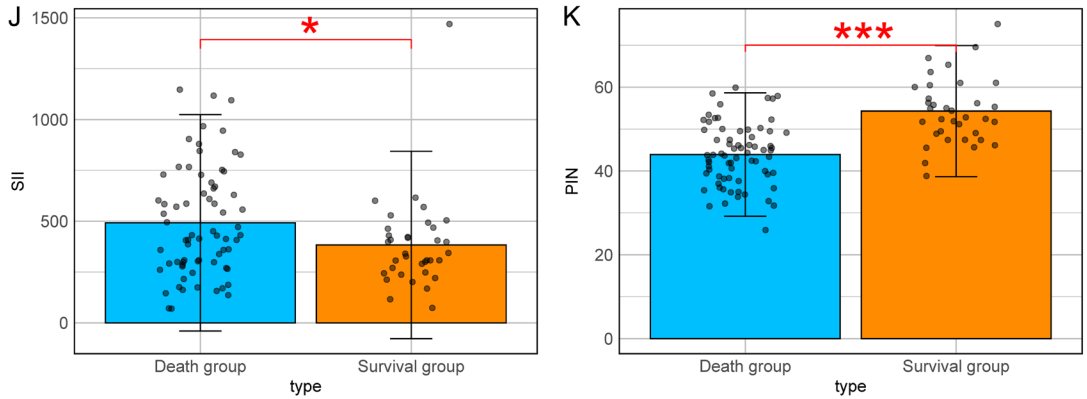

Figure 1. Comparison of peripheral blood indicators between the death and survival groups. A. Comparison of WBC between the death and survival groups. B. Comparison of LYM between the death and survival groups. C. Comparison of NEUT between the death and survival groups. D. Comparison of MON between the death and survival groups. E. Comparison of PLT between the death and survival groups. F. Comparison of ALB between the death and survival groups. G. Comparison of NLR between the death and survival groups. H. Comparison of LMR between the death and survival groups. I. Comparison of PLR between the death and survival groups. J. Comparison of SII between the death and survival groups. K. Comparison of PIN between the death and survival groups. Note: WBC, White Blood Cell; LYM, Lymphocyte; NEUT, Neutrophil; MON, Monocyte; PLT, Platelet; ALB, Albumin; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PIN, Prognostic Inflammatory Nutritional Index. nsP<0.05, *P<0.05, **P<0.01, ***P<0.001.

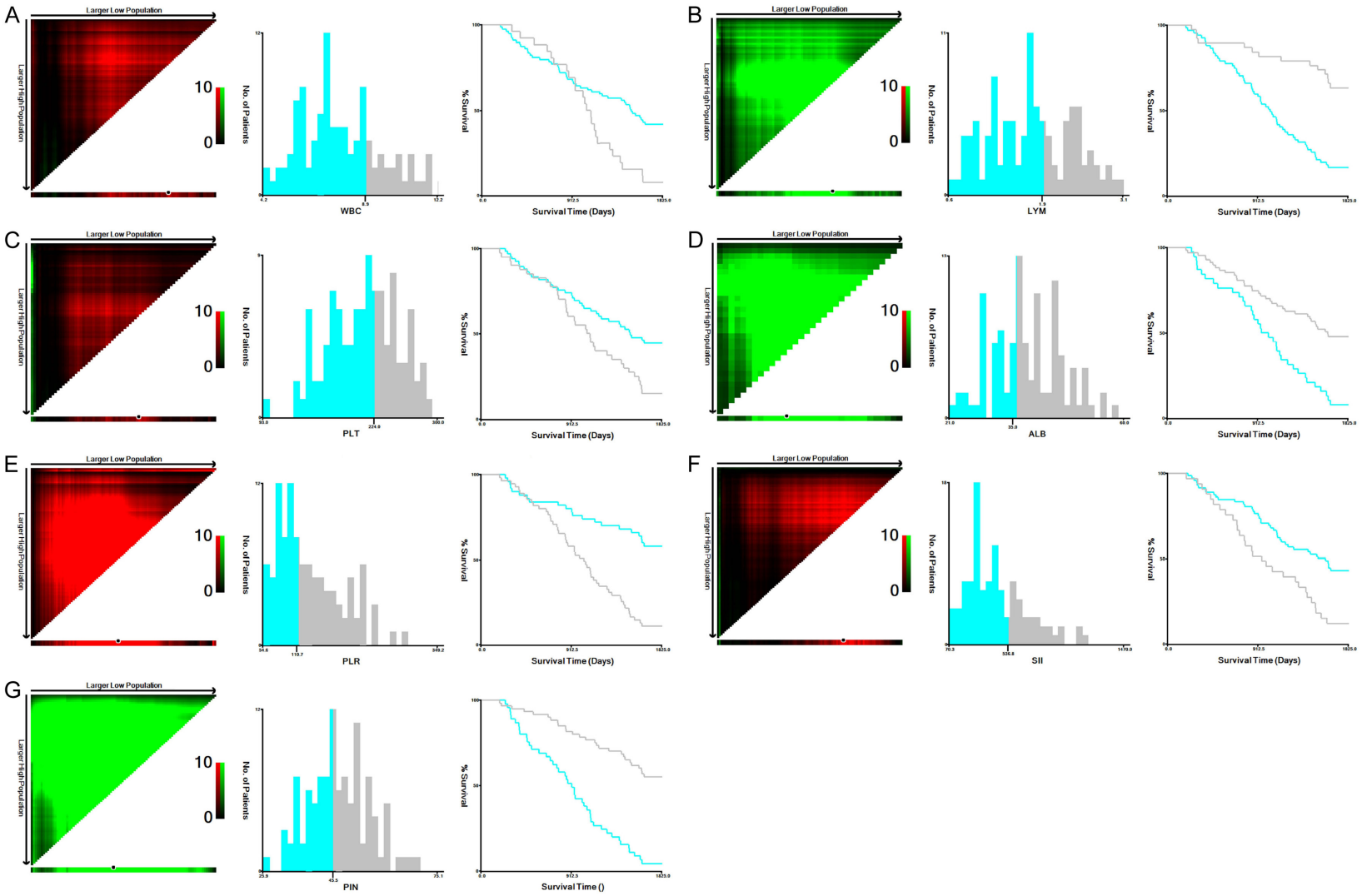

Figure 2. Determination of optimal cutoff values for 7 peripheral blood indicators using X-tile software. A. Optimal cutoff value for WBC: 8.96. B. Optimal cutoff value for LYM: 1.93. C. Optimal cutoff value for PLT: 224. D. Optimal cutoff value for ALB: 35. E. Optimal cutoff value for PLR: 110.68. F. Optimal cutoff value for SII: 536.82. G. Optimal cutoff value for PIN: 45.5. Note: WBC, White Blood Cell; LYM, Lymphocyte; PLT, Platelet; ALB, Albumin; LMR, Lymphocyte-to-Monocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PIN, Prognostic Inflammatory Nutritional Index.

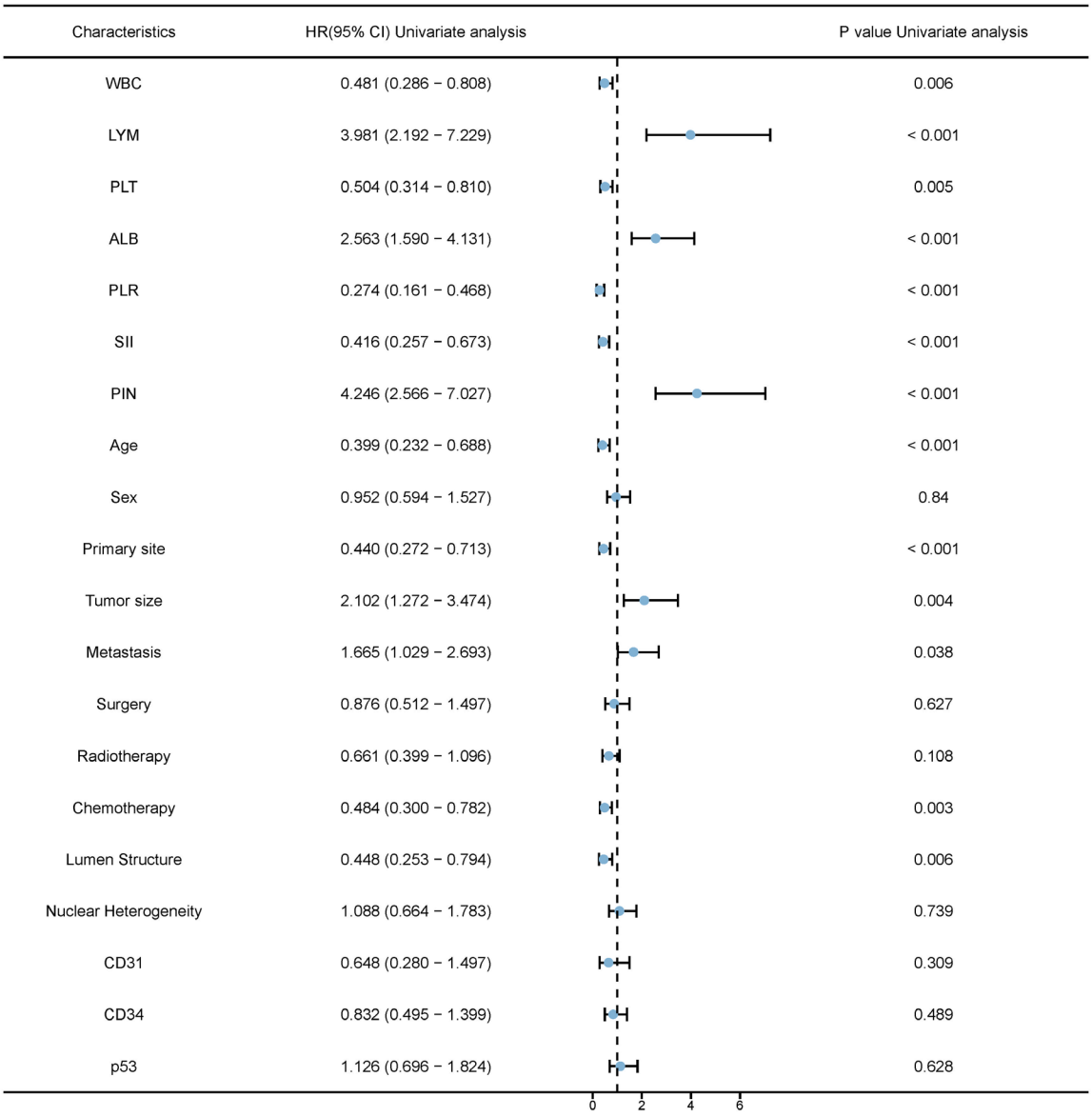

Figure 3. Univariate Cox regression analysis of prognostic factors affecting 5-year survival of angiosarcoma patients. Note: WBC, White Blood Cell; LYM, Lymphocyte; PLT, Platelet; ALB, Albumin; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PIN, Prognostic Inflammatory Nutritional Index.

SII (P=0.029, HR=0.518, 95% CI: 0.287-0.935), primary site (P=0.001, HR=0.398, 95% CI: 0.229-0.693), metastasis (P=0.021, HR=1.931, 95% CI: 1.102-3.384), and chemotherapy (P=0.003, HR=0.413, 95% CI: 0.231-0.739) as independent prognostic factors for 5-year survival in angiosarcoma patients (**Figures 4**, **5**).

Construction and validation of the nomogram model

Based on these four prognostic factors, we constructed a Nomogram model (**Figure 6**). Calibration curves were generated to assess the accuracy of the model in predicting 1-year, 3-year, and 5-year survival, showing good discrimination (**Figure 7A**). To provide an unbiased estimate of the model's performance, an internal validation was performed using a bootstrap resampling process with B=1000. The calculated C-index was 0.745 (0.720-0.769). DCA was used to compare the performance of the risk model with each prognostic factor (SII, primary site, metastasis, and chemotherapy). The prognostic model showed better net benefits at 1, 3, and 5 years compared to individual prognostic factors (**Figure 7B-D**). Comparing the

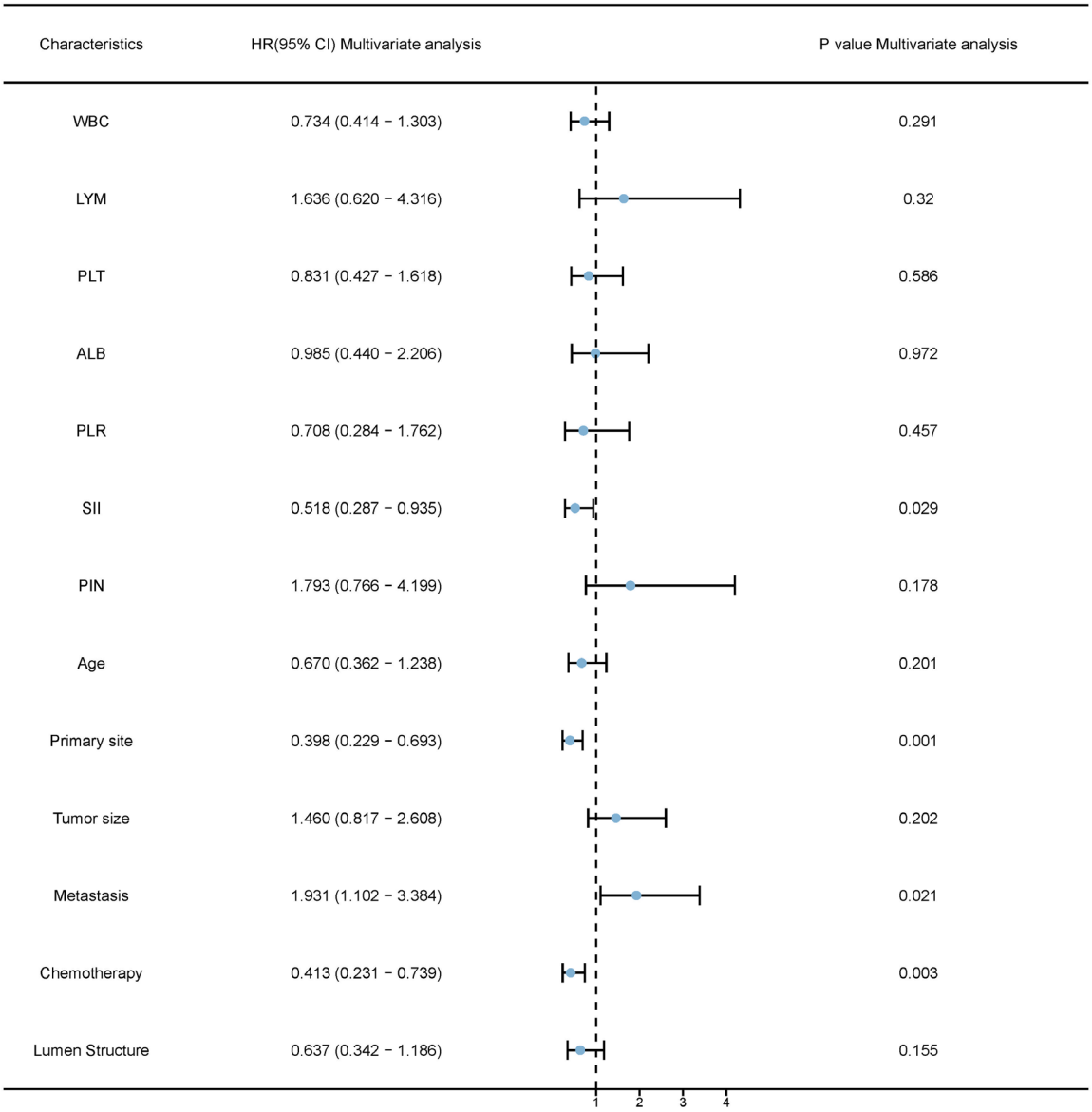

Figure 4. Multivariate Cox regression analysis of prognostic factors affecting 5-year survival of angiosarcoma patients. Note: WBC, White Blood Cell; LYM, Lymphocyte; PLT, Platelet; ALB, Albumin; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PIN, Prognostic Inflammatory Nutritional Index.

risk scores of each patient revealed that the death group's risk was significantly higher than that of the survival group (P<0.001, **Figure 7E**). The K-M survival curve showed that patients with risk score ≤-1.04 had significantly improved 5-year survival rates (P<0.001, **Figure 7F**). Finally, time-dependent ROC curve analysis further demonstrated that the AUC of the prognostic model in predicting 1-year, 3-year, and 5-year survival were 0.836, 0.837, and 0.803, respectively (**Figure 7G**).

Validation of the model with external data

To validate the clinical value of the model, data from an additional 50 angiosarcoma patients treated during the same period were collected. Comparison revealed no significant differences in primary site, metastasis, chemotherapy, and SII between the patient group and the validation group (all P>0.05, **Table 3**). Subsequently, we calculated the scores for each patient in the validation group based on the model formula.

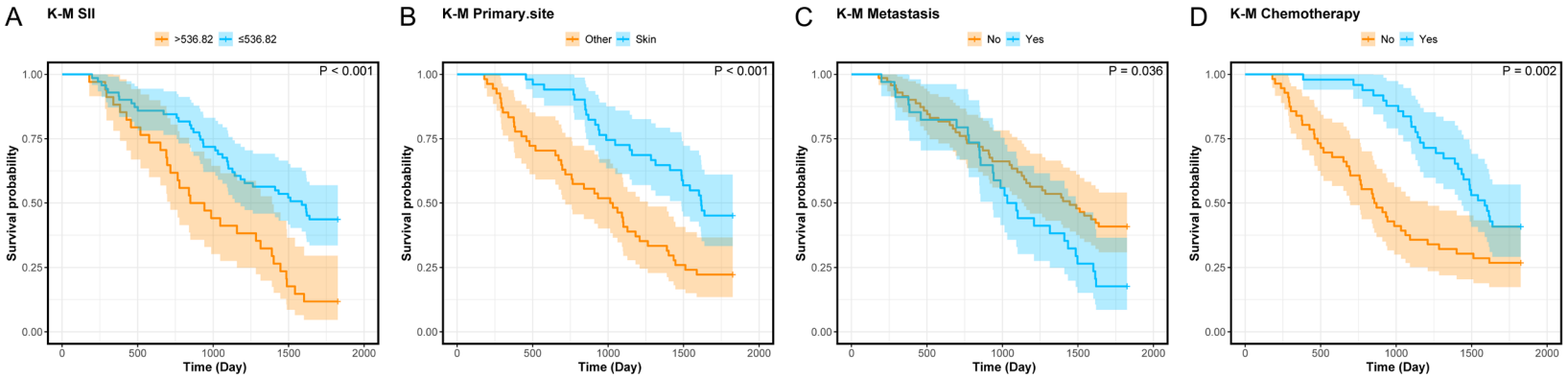

Figure 5. K-M survival curves for independent prognostic factors in predicting patient survival. A. K-M survival curves for patients with high and low SII values. B. K-M survival curves for patients with different primary tumor sites. C. K-M survival curves for patients with and without metastasis. D. K-M survival curves for patients receiving chemotherapy or not. Note: SII, Systemic Immune-Inflammation Index.

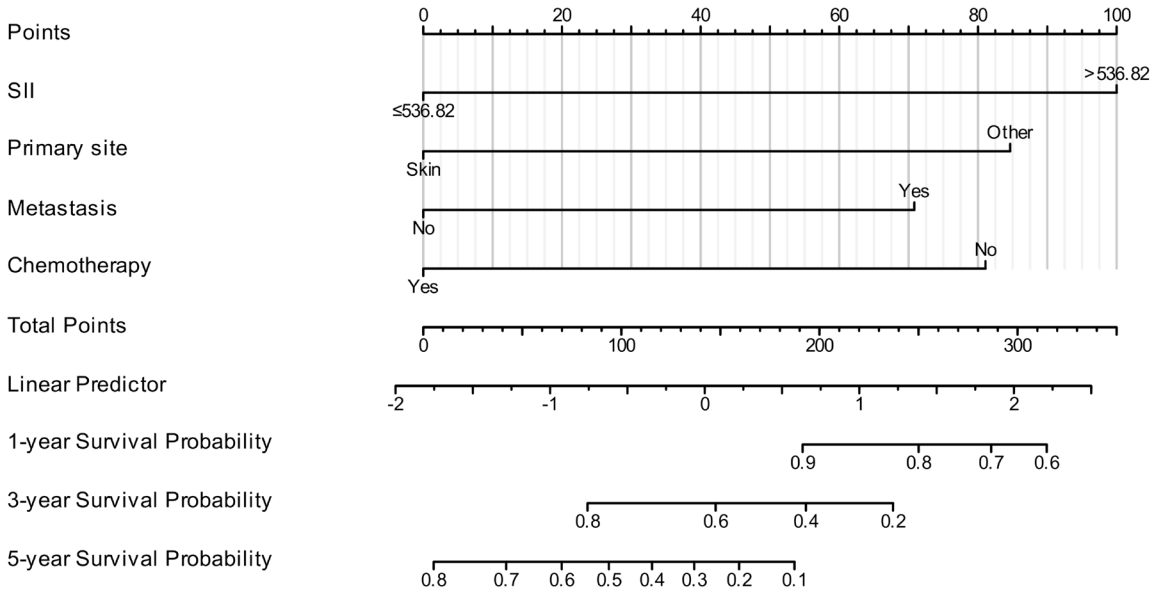

Figure 6. The Nomogram model for predicting 5-year patient survival. Note: SII, Systemic Immune-Inflammation Index.

The results showed that the calibration curves generated to assess the model's accuracy in predicting 1-year, 3-year, and 5-year survival had good discrimination (**Figure 8A**). The calculated C-index was 0.772 (0.739-0.806). DCA indicated that the prognostic model provided benefits for predicting 1-year, 3-year, and 5-year survival, with the greatest benefit observed at 3 years compared to individual factors (**Figure 8B-D**). By comparing the risk scores of each patient, it was found that the risk score of patients in the death group was significantly higher than that in the survival group (P<0.001, **Figure 8E**). The K-M survival curve showed that patients with risk ≤-1.04 had significantly improved the 5-year survival rates (P<0.001, **Figure 8F**). Finally, time-dependent ROC curve analysis further showed that the AUC for the risk model in predicting 1-year, 3-year, and 5-year survival were 0.818, 0.838, and 0.872, respectively (**Figure 8G**).

Interaction between SII and prognostic factors

At the end of the study, we analyzed the interaction between SII and other independent prognostic factors. Analysis showed that SII had significant interactions with primary site (P= 0.005) and chemotherapy (P=0.045) (**Figure 9A**, **9C**; **Table 4**). However, there was no interaction between SII and metastasis (**Figure 9B**).

Discussion

Angiosarcoma is a rare and highly aggressive soft tissue tumor, posing significant challenges in treatment and prognosis [22]. Despite advancements in treatment, the efficacy of surgery, chemotherapy, and anti-angiogenic therapy remains unsatisfactory [23]. Existing treatment options, although effective in some patients, still face issues such as long-term efficacy and drug resistance [24]. Additionally, the complex biological characteristics and molecular mechanisms of angiosarcoma make it difficult to establish reliable prognostic indicators and predictive models, hindering the accurate assessment of long-term patient survival [25]. These challenges highlight the urgent need to develop new treatment strategies and reliable prognostic models to improve patient outcomes and quality of life.

In this study, we retrospectively analyzed the clinical data and peripheral blood indicators of 105 angiosarcoma patients. The median survival time was 1395 days, with 70 patients (66.7%) dying during the follow-up period. Significant differences were observed between the survival and death groups in terms of age, primary site, tumor size, and metastasis. Younger patients, and those with skin-located tumors, smaller tumors, and absence of metastasis had significantly higher survival rates.

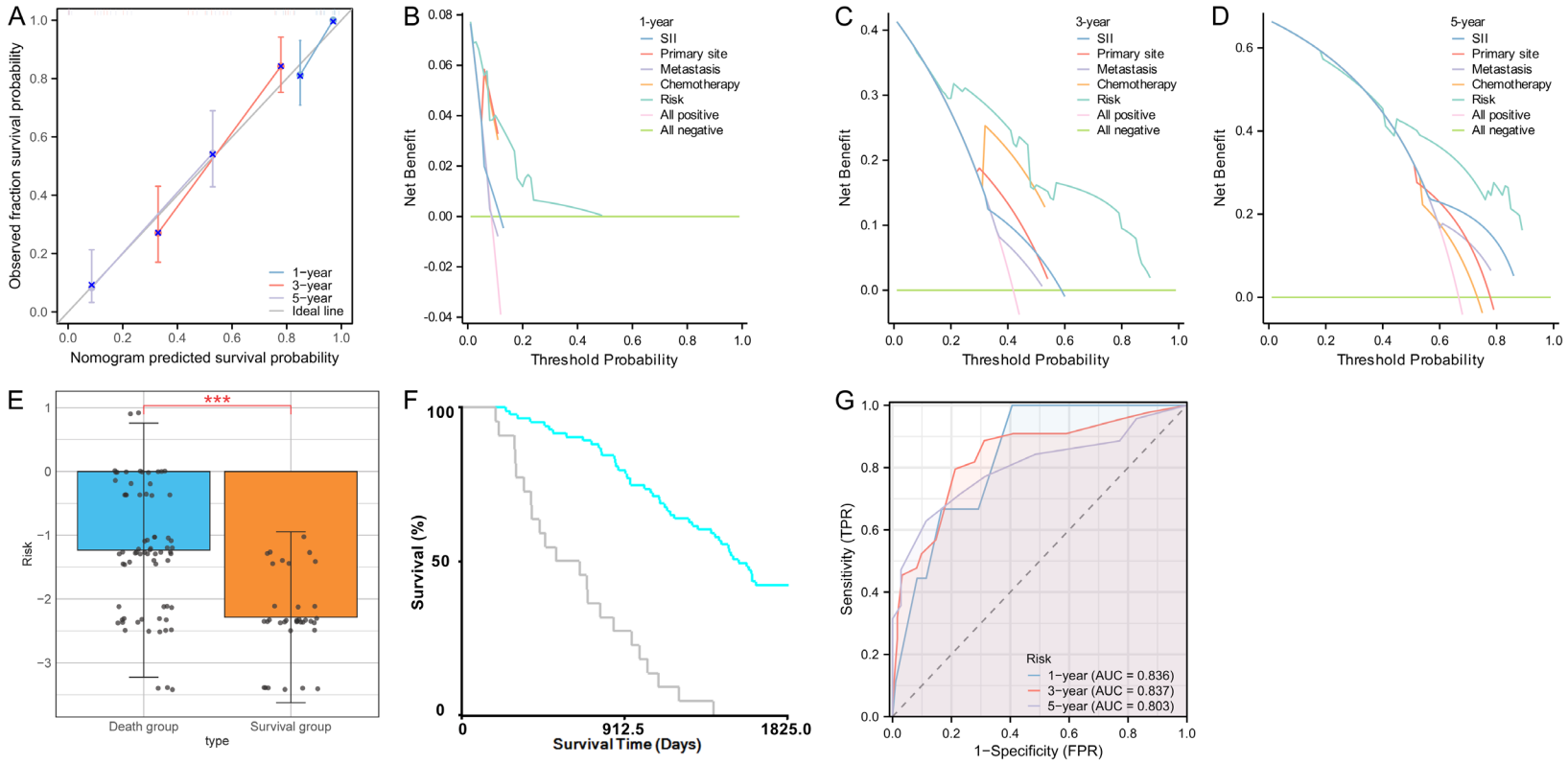

Figure 7. Nomogram model for predicting 5-year survival in angiosarcoma patients. A. Nomogram for predicting 5-year survival. B-D. DCA curves for validating the model's benefit rate in predicting 1-year, 3-year, and 5-year survival. E. Comparison of risk scores between death and survival patients. F. K-M survival curves of patients with high and low risk scores using optimal cutoff value calculated by X-tile software. G. Time-dependent ROC curves for validating the performance of the model in predicting 1-year, 3-year, and 5-year survival. Note: DCA, Decision Curve Analysis; ROC, Receiver Operating Characteristic; SII, Systemic Immune-Inflammation Index. ***P<0.001.

Table 3. Comparison of the four prognostic factors between the patient group and the validation group

Factors	Patient group (n=105)	Validation group (n=50)	X^2 Value	*P* Value
Primary site				
Skin	51	27	0.399	0.527
Others	54	23		
Metastasis				
Performed	34	18	0.199	0.656
Not Performed	71	32		
Chemotherapy				
Performed	49	25	0.151	0.698
Not Performed	56	25		
SII				
>536.82	71	33	0.040	0.841
≤536.82	34	17		

Note: SII, Systemic Immune-Inflammation Index.

Regarding peripheral blood indicators, we found that the levels of WBC, PLT, PLR, and SII were significantly lower, while LYM, ALB, and PIN were significantly higher in the survival group than those in the death group. These results suggest that higher WBC, PLT, PLR, and SII, as well as lower LYM, ALB, and PIN, are associated with poorer prognosis in angiosarcoma patients. Further analysis showed that younger patients generally have better physiological states and immune functions, allowing them to more effectively resist disease progression when dealing with highly aggressive tumors [26]. A study by Young et al. [27] also found that anthracycline-based first-line chemotherapy was more effective in younger patients.

The primary site of the tumor significantly impacts prognosis. Tumors located in the skin are usually detected and treated earlier, while tumors in internal organs or deep tissues are often discovered at more advanced stages, making complete resection and disease control challenging [28]. Schlemmer et al. [29] found that late-stage soft tissue angiosarcoma patients treated with paclitaxel showed improved prognosis. Smaller tumors typically indicate earlier stage of disease, facilitating complete surgical resection easier and improving treatment outcomes [30]. Penel et al. [31] reported that patients with smaller tumor volumes had better prognosis after weekly paclitaxel treatment for unresected angiosarcoma. Patients without metastasis often have higher chances of being cured, while those with metastasis, especially multiple metastases, exhibit significantly poorer treatment outcomes and prognosis [32].

In terms of peripheral blood indicators, high levels of WBC, PLT, PLR, and SII usually indicate the presence of an inflammatory response and immune suppression, suggesting poor prognosis. Conversely, high LYM, ALB, and PIN levels reflect good immune status and nutritional condition, indicating better prognosis [33]. For example, Zhou et al. [12] found that preoperative peripheral blood NLR, PLR, and LMR were closely related to the prognosis of patients with head and neck squamous cell carcinoma. Luo et al. [34] reported that high SII is an independent predictor of low survival rates in diabetic acute myocardial infarction (AMI) patients, potentially aiding in patient risk stratification. These studies, consistent with our findings, emphasize the importance of peripheral blood indicators in assessing patient prognosis. Such indicators are important for doctors in evaluating patient prognosis, developing treatment plans, and monitoring treatment efficacy, and may serve as potential biomarkers for early diagnosis and prognosis evaluation.

To identify prognostic indicators affecting angiosarcoma patients, further analysis was conducted using Cox regression. Multivariate Cox regression results identified SII, primary site, metastasis, and chemotherapy as independent prognostic factors affecting 5-year survival in angiosarcoma patients. Validation showed that the Nomogram model constructed with these four factors performed well in predicting 5-year survival.

SII, which combines neutrophil, lymphocyte, and platelet counts, is a marker of systemic inflammation and immune status [35]. Previous studies by Wang et al. [36] found that elevated SII values usually indicate an enhanced inflammatory response and immune suppression, which are closely related to tumor progression

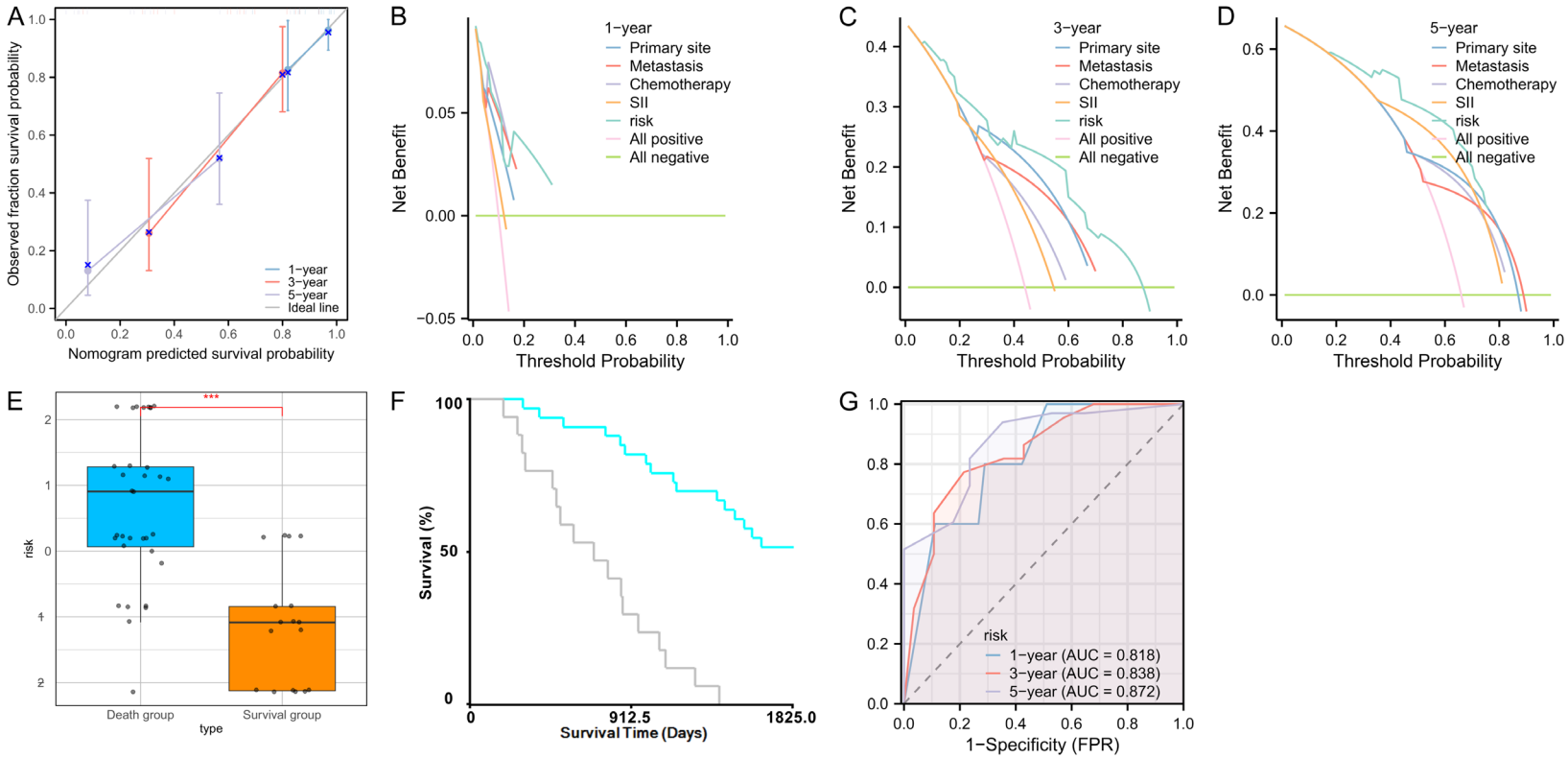

Figure 8. External validation of the prognostic model. A. Calibration curves for validating the stability of the model in predicting 1-year, 3-year, and 5-year survival. B-D. DCA curves for validating the model's benefit rate in predicting 1-year, 3-year, and 5-year survival. E. Comparison of risk scores between death and survival patients. F. K-M survival curves of patients with high and low risk scores using optimal cutoff value calculated by X-tile software. G. Time-dependent ROC curves for validating the performance of the model in predicting 1-year, 3-year, and 5-year survival. Note: DCA, Decision Curve Analysis; ROC, Receiver Operating Characteristic; SII, Systemic Immune-Inflammation Index. ***P<0.001.

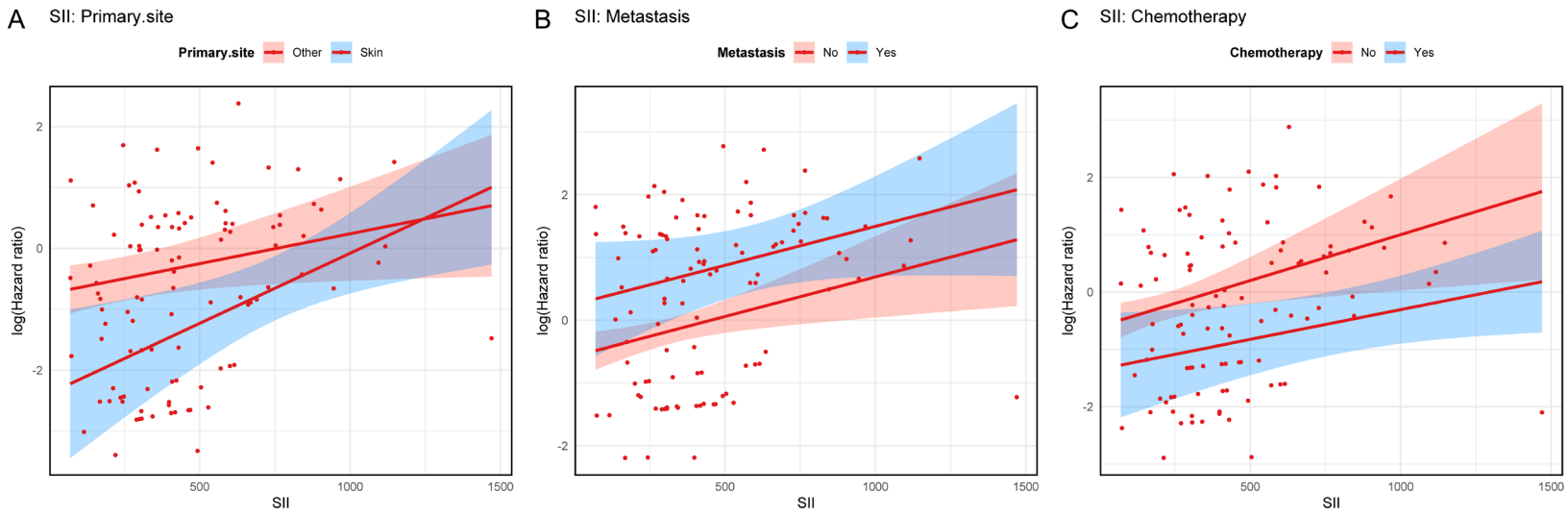

Figure 9. Interaction between SII and other three independent prognostic factors. A. Interaction between SII and primary tumor site. B. Interaction between SII and metastasis. C. Interaction between SII and chemotherapy. Note: SII, Systemic Immune-Inflammation Index.

Table 4. Interaction between SII and other three independent prognostic factors

Factor	Coefficient	Exp_Coefficient	Std_Error	z_value	*p*_value
Primary site: SII	0.002	1.002	0.001	0.005	0.005
Metastasis: SII	0.001	1.001	0.001	0.001	0.089
Chemotherapy: SII	0.001	1.001	0.001	0.001	0.045

Note: SII, Systemic Immune-Inflammation Index.

and metastasis. An inflammatory environment can promote tumor cell growth and metastasis while inhibiting antitumor immune responses, leading to poor prognosis [37]. Additionally, the primary tumor site significantly impacts prognosis. Tumors located in the skin are usually detected and treated earlier, while tumors in internal organs or deep tissues are often at an advanced stage when discovered, making complete resection and control difficult [28]. Ichiki et al. [38] found that tumors originating in the skin had better prognosis than those in other organs. Furthermore, metastasis is a key factor for poor prognosis. Patients without metastasis often have higher chances of being cured, while those with metastasis have significantly poorer treatment outcomes and prognosis due to the spread of tumor cells to other parts of the body, increasing the difficulty of treatment. Studies by Wang et al. [36] and Ichiki et al. [38] both confirmed that metastasis is an independent poor prognostic factor in multivariate analyses. Finally, chemotherapy is an important treatment for angiosarcoma. Ichiki et al. [38] found that patients receiving chemotherapy had their tumor burden effectively controlled, delaying disease progression and improving survival rates. The constructed Nomogram model, integrating these key factors, was confirmed with robustness and generalizability in predicting patients' long-term survival, providing important references for clinical decision-making.

In the final part of this study, we analyzed the interaction between SII and other prognostic factors to understand how SII influences prognosis across different clinical contexts. The analysis showed significant interactions between SII and primary site and chemotherapy, although no significant interaction was found between SII and metastasis. We speculate that the interaction between SII and primary tumor site may be due to the way different tumor locations affect local immune and inflammatory responses. Tumors in the skin are usually detected and treated earlier, with milder local inflammatory responses, so lower SII values may indicate better prognosis in these patients. For tumors in deep tissues, higher SII values reflect stronger systemic inflammatory responses and poorer prognosis. The interaction between SII and chemotherapy suggests that SII could be a potential predictor of chemotherapy efficacy. Higher SII values suggest stronger inflammatory responses and immune suppression during chemotherapy, indicating the need for more intensive monitoring and individualized treatment strategies. Conversely, patients with low SII values may tolerate chemotherapy better and have relatively better prognosis. Although metastasis is an independent poor prognostic factor, no significant interaction was observed between SII and metastasis, possibly because metastasis itself is a strong prognostic indicator, overshadowing the impact of SII, or because the systemic inflammatory state in metastatic patients is already at a high level, making changes in SII less influential on prognosis.

This study identified SII, primary tumor site, metastasis, and chemotherapy as independent prognostic factors affecting the 5-year survival of angiosarcoma patients. The constructed Nomogram model showed good performance in predicting 1-year, 3-year, and 5-year survival rates. Additionally, significant interactions were found between SII and primary tumor site and chemotherapy, indicating the important role of SII in prognosis in different clinical contexts.

Conclusion

This study retrospectively analyzed the clinical data and peripheral blood indicators of 105 angiosarcoma patients, identifying SII, primary tumor site, metastasis, and chemotherapy as independent prognostic factors affecting 5-year survival. The Nomogram model constructed based on these factors showed high accuracy and stability in predicting 1-year, 3-year, and 5-year survival rates. Additionally,

significant interactions between SII and primary tumor site and chemotherapy were observed, highlighting the importance of SII in prognosis under different clinical contexts.

Disclosure of conflict of interest

None.

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