ORIGINAL RESEARCH

The prognostic value of pretreatment inflammatory biomarkers in primary angiosarcoma

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Background: Recent studies have suggested a significant relationship between inflammatory indexes such as the neutrophil-to-lymphocyte ratio (NLR) and survival outcomes in various cancers. The aim of the present study was to evaluate the prognostic value of 6 pretreatment inflammatory markers in patients with primary angiosarcoma (AS) which is a rare and highly malignant type of soft tissue sarcoma.

Methods: Fifty-six patients diagnosed with primary AS at West China Hospital between August 2009 and July 2016 were retrospectively enrolled. The value of each biomarker was calculated for its correlation with patients' overall survival.

Results: The low tumor grade, tumor size <5 cm, metastatic status, surgical treatment and low level of monocyte-to-lymphocyte ratio, NLR and lactate dehydrogenase (LDH) were correlated with better survival outcome in univariate analyses. In multivariate analyses, high levels of NLR (HR 2.673, 95% CI 1.253–5.703, *p*=0.011) and LDH (HR 2.964, 95% CI 1.464–5.998, *p*=0.003) were selected as independent prognostic factors.

Conclusion: This study identifies the elevated pretreatment levels of NLR and LDH as prognostic markers in patients with primary AS.

Keywords: inflammatory biomarker, prognosis, angiosarcoma

Background

Angiosarcoma (AS) is a rare and highly malignant type of soft tissue sarcoma derived from vascular endothelial cells. It accounts for only 1–4% of all soft tissue sarcomas.[1,2] Clinical symptoms vary considerably based on the primary sites including the skin, soft tissue and viscera. For example, patients with cutaneous ASs usually present bruise-like patches, violaceous nodules or plaques,[3] whereas symptoms of visceral ASs include abdominal pain, hepatosplenomegaly or anemia.[4]

The prognosis for primary AS is generally poor. Previous studies have addressed the poor prognosis of AS of the face and scalp (ASFS) which is a particular subgroup of sarcomas characterized by high frequencies of local recurrence or distant metastasis, with a 5-year survival rate of 11.1–53.8%.[5] Due to a low rate of clinical suspicion and unusual clinical presentation, a significant portion of patients present inoperable AS or metastasis at the time of initial diagnosis.[4,6,7] Surgery was considered the initial treatment, but was also observed with high rates of local recurrence.[8] Although the most effective treatments for the primary AS should vary according to individuals, the multimodal treatment (surgery followed by chemotherapy and/or radiotherapy) is considered the optimal option.[3,9] However, the majority of patients will ultimately develop distant metastases even after treatment, with local or systemic failure approaching 70% of all cases of

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complete resections.[4,10–13] It was reported that the rupture of cystic metastases in the lung would cause repeated pneumothorax and hemothorax and was the major cause of death.[14,15]

Several tumor biomarkers such as platelet-derived growth factor receptor-β and vascular endothelial growth factor receptor-2 have been investigated about their correlations with AS prognosis.[16] However, detecting these biomarkers as routine clinical tests is not feasible due to the high cost and absence of standardization system. Therefore, it is intriguing to identify a set of accessible biomarkers to predict prognosis before treatment. Recently, pretreatment systemic inflammatory indexes including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) have been reported to be associated with the prognosis of soft tissue sarcomas.[17–19]

Owing to the extreme rarity of this tumor, reports on clinicopathological features and prognostic factors of primary angiosarcoma (PAS) are limited and most of them are case reports or small case series, of which the selection bias makes the results difficult to interpret. Gen Suzuk et al have investigated the role of 3 inflammatory markers in prognosis of 17 patients with AS.[20] Our study aims to identify a set of accessible biomarkers in patients' peripheral blood and clarify their relationships with the overall survival (OS). To the best of our knowledge, this is the first study to analyze the 6 pretreatment inflammatory indexes including NLR, PLR, MLR, systemic immune-inflammation index (SII), lactate dehydrogenase (LDH) and ALP, in a relatively large clinical setting of 56 patients with this rare sarcoma.

Methods
Patients
A total number of 56 patients diagnosed with PAS at West China Hospital between August 2009 and July 2016 were retrospectively enrolled in this study from our cancer database. The median follow-up time was 18.5 (11.05–32.55) months. The end date of follow-up was May 2017 or death. Patients meeting the following criteria were included: (1) patients were pathologically confirmed of AS; (2) patients with complete clinical information; (3) inflammatory biomarkers were obtained before any treatment.

Data extraction and follow-up
The demographics, laboratory tests and pathologic reports of patients were extracted from electronic medical records. Patient characteristics included the gender, age, tumor

size, tumor location and treatments. All biopsy or surgical specimens were reviewed by board-certified pathologists to determine the grade (low vs intermediate or high). The primary tumor was categorized by its location as head and neck, breast, viscera (organs and bones) and soft tissue (trunk and extremities).[3] For patients with multiple primary tumors, the size of the tumor was reported from the largest lesion available from surgeries or biopsies. The platelet, lymphocyte, monocyte and neutrophil counts, LDH and ALP were obtained from the last blood test before treatment and NLR, PLR, MLR and SII were calculated, respectively. The SII was calculated using platelet counts times NLR (P × NLR). Patients were retrospectively evaluated by telephone and outpatient follow-up. The OS was selected as primary endpoints. The OS was defined as the period from the date of pathologic diagnosis to death or last follow-up. Patients that are alive without progression were recorded as censored at the end of the follow-up.

Statistical analysis
NLR, PLR, MLR, SII, LDH and ALP were calculated with receiver operating curves (ROC) to determine the optimal cutoff values and then dichotomized into 2 categories: less than, and greater than or equal to the cutoff values. Survival curves were obtained by Kaplan–Meier survival analysis and compared among groups by log-rank test. Only variables revealing significant association on univariate analyses ($p<0.10$) were then performed with multivariate analyses. Multivariate analyses were performed using Cox proportional hazards regression, reported with 95% CIs to estimate the association between variables and survival outcome. All the statistical analyses were performed using SPSS version 21.0, and $p<0.05$ was considered statistically significant in multiple cox regression analyses.

Results
Baseline characteristics
This study analyzed 56 patients pathologically confirmed of AS treated at West China Hospital between 2010 and 2017. Table 1 presents the baseline characteristics of patients such as the age and gender distribution and of their primary tumors. The median OS was 21.00 (95% CI 10.465–31.535) months. Tumors larger than 5 cm on clinical assessment accounted for 51.8% of all tumors. Furthermore, the majority (62.5%) of the tumors were

Table 1 Baseline characteristics of 56 patients with angiosarcoma

Variables		No. of patients (%)
Age (year)	<65	41 (73.2)
	≥65	15 (26.8)
Median (year)	46	
Gender	Male	33 (58.9)
	Female	23 (41.1)
Tumor location	Head and neck	19 (33.9)
	Breast	6 (10.7)
	Viscera	22 (39.3)
	Soft tissue	9 (16.1)
Size (cm)	<5	27 (48.2)
	≥5	29 (51.8)
Grade	High	35 (62.5)
	Low & medium	21 (37.5)
Metastasis at diagnosis	Yes	16 (28.6)
	No	40 (71.4)
Surgery	Yes	38 (67.9)
	No	18 (32.1)
Chemotherapy	Yes	23 (41.1)
	No	33 (58.9)
NLR	<5.22	42 (75.0)
	≥5.22	14 (25.0)
PLR	<154	34 (60.7)
	≥154	22 (39.3)
MLR	<0.38	37 (66.1)
	≥0.38	19 (33.9)
SII (109/L)	<1048.5	44 (78.6)
	≥1048.5	12 (21.4)
LDH (U/L)	<184	36 (64.3)
	≥184	20 (25.7)
ALP (U/L)	<89.5	32 (57.1)
	≥89.5	24 (42.9)

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; LDH, lactate dehydrogenase.

classified as high grade (G3) according to pathology reports, whereas 37.5% of patients were recorded as low and medium grade (G1&G2). Sixteen patients (28.6%) were characterized as metastatic at initial diagnosis, and 40 patients (71.4%) were nonmetastatic. A total number of 22 (39.3%) tumors developed in the viscera included liver, spleen and bone. The head and neck (33.9%) was another common site for primary tumor. Six (10.7%) tumors occurred in the breast and in 9 (16.1%) cases in extremities or the trunk. Surgery was considered the first treatment option with certain indications and in this study, and most patients (67.9%) had undergone surgeries. Twenty-three patients (41.1%) received chemotherapy treatment whereas 33 patients (58.9%) did not.

Cutoff values for inflammatory indexes

Of the 6 inflammatory indexes of patients enrolled in this study, the median values of NLR, PLR, MLR and SII were 2.56 (1.80–5.22), 126 (89–192), 0.29 (0.22–0.44) and 462.5 (252.8–937.0), respectively. LDH had a median value of 169.5 (145.5–249.0) IU/L and that of ALP was 86.0 (63.3–100.0) IU/L. The ROC was used to identify optimal cutoff value for indexes. The area under curve was presented in Table 2 and Figure 1. By analyzing the specificity and sensitivity of each value, the optimal cutoff

Table 2 Optimal cutoff values for each inflammatory marker

Marker	Median value	AUC	Optimal cutoff value
NLR	2.56 (1.80–5.22)	0.615	5.22
PLR	126 (89–192)	0.54	154
MLR	0.29 (0.22–0.44)	0.647	0.38
SII	462.5 (252.8–937.0)	0.573	1048.5
LDH	169.5 (145.5–249.0) IU/L	0.675	184
ALP	86.0 (63.3–100.0) IU/L	0.591	89.5

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; LDH, lactate dehydrogenase.
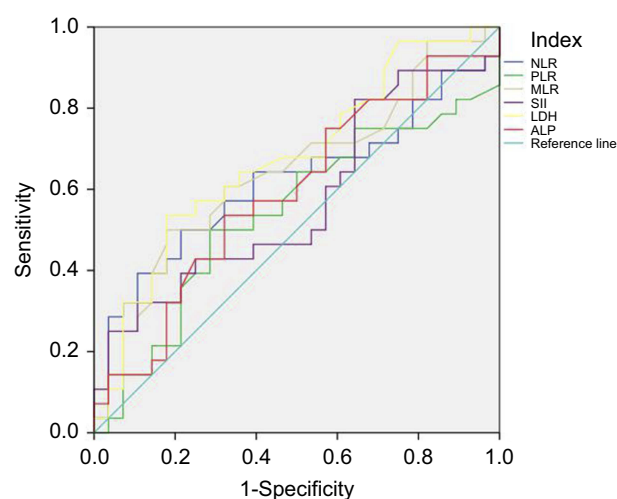

Figure 1 ROC of NLR, PLR, MLR, SII, LDH and ALP for patients' overall survival.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; LDH, lactate dehydrogenase; ROC, receiver operating curve.

values of NLR, PLR, MLR, SII, LDH and ALP were taken as 5.22, 154, 0.38, 1048.5, 184 and 89.5, respectively. Patients were therefore dichotomized into 2 categories: less than, and greater than or equal to the cutoff values.

Prognostic value of inflammatory indexes

The univariate analysis suggested that high levels of NLR were significantly correlated with poorer OS (p=0.001). Favorable OS was also observed in patients with lower levels of MLR (p=0.048). Compared to those with high LDH, the OS of LDH was markedly improved (37.6 months vs 12.3 months, p<0.001). Moreover, patients with high tumor grade had a poor prognosis with a median OS of 16.3 months compared with 51.7 months in patients with low & intermediate grade. While the metastatic status demonstrated significant relevance to survival in univariate analyses, with a median survival of 15.2 months in metastatic patients vs 37.6 months in nonmetastatic patients (p=0.010). The tumor size served as another potential predictor for poor prognosis with a median survival of 16.3 months in tumors ≥5 cm vs 31.5 months in tumors <5 cm. However, no significant difference in prognosis was identified between patients receiving surgery/chemotherapy or not. Similarly, age, gender, tumor location, PLR, SII and ALP were not correlated with OS. The Kaplan–Meier survival curves were also displayed to show the association of the grade, size, metastatic status, NLR, MLR, LDH and surgical treatment with patients' survival outcomes (Figure 2).

Multivariate analysis was accordingly performed to identify any independent prognostic factors for AS. After being adjusted by other potential factors including the tumor grade, size, MLR and surgical history, high levels of pretreatment NLR (HR 2.673, 95% CI 1.253–5.703, p=0.011) and LDH (HR2.964, 95% CI 1.464–5.998, p=0.003) were proved to be independent predictors of poor survival outcomes (Table 3).

Discussion

To the best of our knowledge, this is the first study to explore the prognostic value of a set of pretreatment inflammatory indexes including NLR, PLR, MLR, SII, LDH and ALP, in a relatively large clinical setting of 56 patients with this rare sarcoma. There was only one study specifically targeting AS which evaluated the prognostic role of 3 serum markers in 17 patients with ASFS.[20] The OS of AS patients at any location was relatively short[21] and the major problem is the absence of treatment

standards. Based on the histopathology of PAS, some studies have suggested the concomitant use of antiangiogenic agents such as bevacizumab with chemotherapy[22] and that the molecular disorders like p53, PI3K, or mTOR pathways observed in PAS patients would be a future research direction.[23]

Consistent with previous studies,[24–27] the head and neck (33.9%) and viscera (organs and bones) were two most common sites for AS. One of the previous studies suggested that breast ASs had better survival than other parts of AS,[3] whereas in some other studies of breast AS,[28,29] such favorable survival could not be observed. Our results demonstrated the visceral AS was associated with the worst prognosis with a median OS of 14.6 months, which is in accordance with the research of Fayette et al.[4] Therefore, further studies are warranted to assess the correlation of tumor sites with AS prognosis. Interestingly, although our univariate analysis demonstrated that patients with high tumor grade had a poor prognosis with a median OS of 16.3 months compared with 51.7 months in patients with low & intermediate grade, the multivariate analysis failed to identify significant differences. This finding is in accordance with a previous study[11] in 1996 which reported the association of tumor grades with survival outcomes, but only in univariate analyses. However, some studies have suggested contrary results that the grade is not a prognostic factor for PAS.[30] Furthermore, the tumor size has been considered as a hallmark of AS prognosis, with previous evidence suggesting that tumor larger than 5 cm predicts poor prognosis.[11,31–34] We found that patients with tumors ≥5 cm had a median survival of 16.3 months vs 31.5 months of tumors <5 cm. Currently, the radical surgery remains the primary treatment modality for this highly malignant sarcoma, with other treatments such as chemotherapy or radiotherapy concomitantly used under certain circumstances. Our results showed the prolonged survival of patients receiving surgery (32.9 months vs 12.4 months without surgery). Although it was reported that the survival of malignant vascular tumors was related to complete surgical resection,[35] the aggressive nature of AS made it difficult to completely clear surgical margins.

The values of neutrophil, platelet and lymphocyte, monocyte, LDH and ALP values can be easily obtained with minimally invasive procedures. Recently, these markers have been evaluated in many studies to predict the prognosis in patients with various types of cancer including hepatocellular carcinoma, renal cell carcinoma, lung cancer, urinary
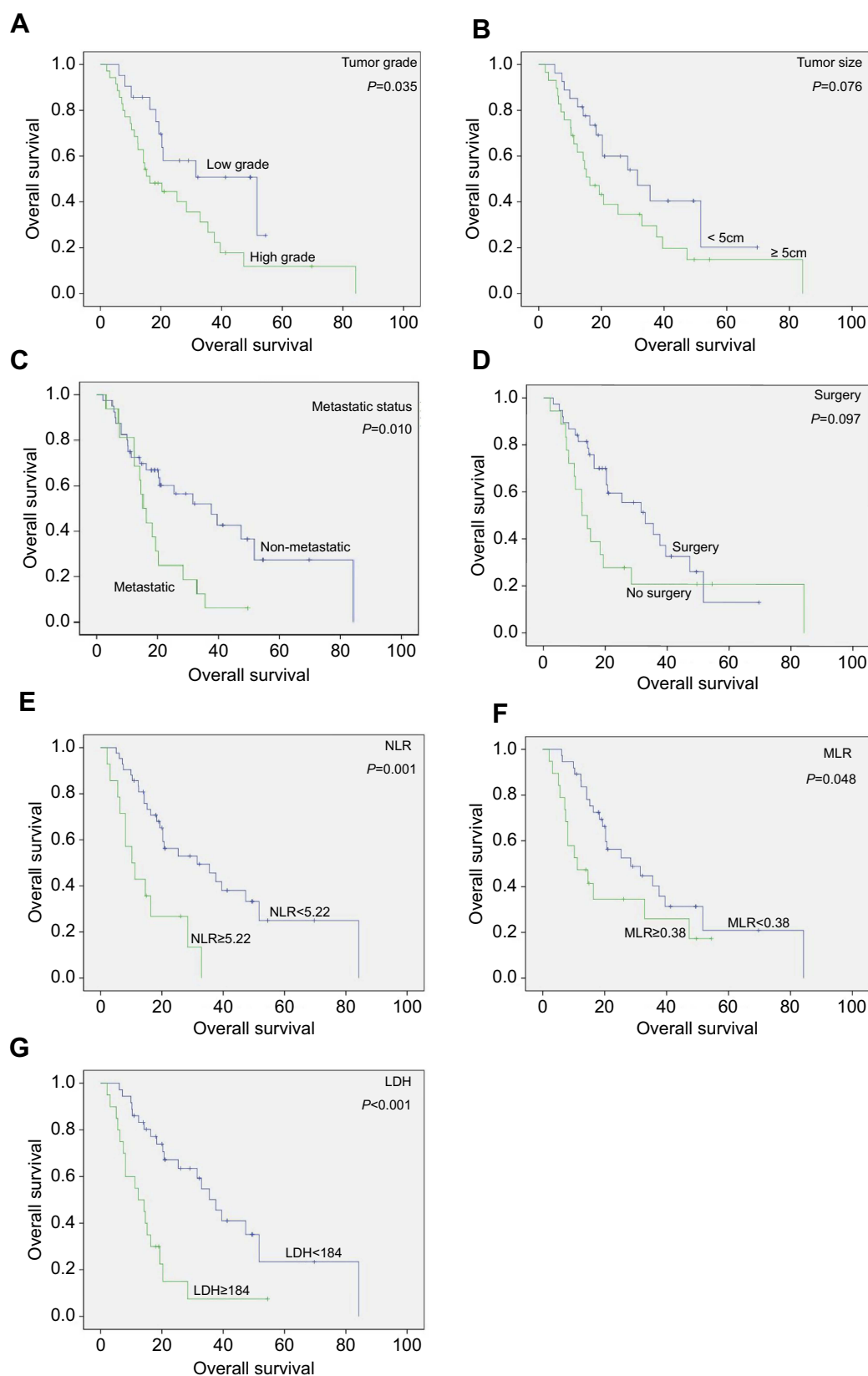
Figure 2 Kaplan–Meier curves comparing overall survival in patients with different clinicopathological features and marker levels: (**A**) tumor grade; (**B**) tumor size; (**C**) metastatic vs nonmetastatic patients; (**D**) surgery or no surgery; (**E**) low vs high; (**F**) low vs high; (**G**) low vs high.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; LDH, lactate dehydrogenase.

Table 3 Univariate and multivariate analysis of factors associated with overall survival in patients with laryngeal cancer

Variables		Median OS (months)	Univariate analysis		Multivariate analysis	
			95% CI	*p*	HR (95% CI)	*p*
Age (year)	<65	20.7	11.755–29.645	0.630		
	≥65	18.3	0.000–43.347			
Gender	Male	32.9	9.306–56.494	0.227		
	Female	20.3	14.375–26.225			
Location	Head and neck	32.9	10.903–54.897	0.138		
	Breast	25.3	9.745–40.855			
	Viscera	14.6	10.923–18.277			
	Soft tissue	20.7	8.434–32.966			
Size (cm)	<5	31.5	14.322–48.678	0.076*		
	≥5	16.3	9.950–22.650			
Grade	High	16.3	8.238–24.362	0.035*		
	Low and intermediate	51.7	16.434–86.966			
Metastasis	Yes	15.2	11.868–18.532	0.010*		
	No	37.6	19.028–56.172			
Surgery	Yes	32.9	19.045–46.755	0.097*		
	No	12.4	8.450–16.350			
Chemotherapy	Yes	28.4	11.258–45.542	0.897		
	No	20.7	9.827–31.573			
NLR	<5.22	31.5	12.155–50.845	0.001*	2.673 (1.253–5.703)	0.011*
	≥5.22	10.2	4.516–15.884			
PLR	<154	28.4	12.827–43.973	0.136		
	≥154	16.3	10.548–22.052			
MLR	<0.38	28.4	12.054–44.746	0.048*		
	≥0.38	11.2	2.327–20.073			
SII	<1048.5	31.5	16.134–46.866	0.103		
	≥1048.5	11.2	3.731–18.669			
LDH	<184	37.6	29.197–46.003	<0.001*	2.964 (1.464–5.998)	0.003*
	≥184	12.3	5.726–18.874			
ALP	<89.5	31.5	15.993–47.007	0.263		
	≥89.5	16.3	8.622–23.978			

Note: *Statistically significant *p*<0.1 in univariate analysis and 0.05 in multivariate analysis.
Abbreviations: OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; LDH, lactate dehydrogenase; SII, systemic immune-inflammation index.

cancer and colorectal cancer.[36–41] These markers such as NLR, PLR and MLR are believed to reflect the interplay between the systemic inflammatory responses with the tumor microenvironment. Elevated NLR, PLR and MLR are able to increase the resting energy expenditure, hypoalbuminemia and malnutrition, which ultimately leads to weight loss and tumor progression.[42,43] The exact mechanisms of this interaction remain incompletely defined. One possible explanation is that neutrophilia is related to the inhibition of cytotoxic activity of T cells and NK cells and at the same time lymphocyte infiltration has been shown to promote an effective antitumor cellular immune response.[44–46] In this study, the multivariate analyses identified pretreatment NLR (HR 2.673, 95% CI 1.253–5.703, *p*=0.011) and LDH (HR 2.964, 95% CI 1.464–5.998, *p*=0.003) levels as independent indicators for AS prognosis.

One limitation of the present study is the number of patients enrolled. Owing to its extreme rarity, previous reports on AS could only reach a relatively small patient group and their results often lack consensus. In this study, the reason why prognostic values of tumor grade and size failed to reach statistical significance in multivariate analyses might be the limited number of primary AS patients. Further studies involving larger patient groups are therefore required. In addition, we were unable to retrieve patients' TNM staging. Staging of AS follows the TNM system for soft tissue sarcoma by American Joint Committee on Cancer. However, because AS represents a unique type of all sarcomas, and there is no standardized treatment regime for each specific stage, TNM staging is of little benefit in clinical practice.[47]

Conclusion

In summary, AS is an extremely rare type of cancer with poor prognosis. This study identifies pretreatment serum levels of NLR and LDH as clinically useful markers to predict survival in patients with PAS. In addition, although survival curves suggested that patients with surgical treatment, low tumor grade and small tumor size have prolonged OS, the difference failed to reach statistical significance in multivariate analyses. Future studies involving larger patient groups with longer follow-up periods are warranted to verify the results.

Ethics approval and consent to participate

This retrospective study was approved by the institution ethics commission of Sichuan University, and due to its retrospective nature, a waiver of consent was granted for the proposed patient record review. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Abbreviations

NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; LDH, lactate dehydrogenase; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; ALP, alkaline phosphatase; AS, angiosarcoma; PAS, primary angiosarcoma; ASFS, angiosarcoma of the face and scalp; ROC, receiver operating curves; AJCC, American Joint Committee on Cancer.

Data sharing statement

All data generated or analyzed during this study are included in this article.

Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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