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European Journal of Surgical Oncology 50 (2024) 108530

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Interleukin-6 in relation to early recurrence in primary, localized soft tissue sarcoma: An addition for existing risk classification systems?

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ARTICLE INFO

Keywords:
Soft tissue sarcoma
IL-6
Inflammation
Early disease recurrence

ABSTRACT

Background: Several inflammatory markers have gained interest as prognostic factors for cancer. The aim of this study is to evaluate the inflammatory markers interleukin-6 (IL-6), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as predictive markers for aggressive behavior and early recurrences in primary, localized soft tissue sarcoma (STS).
Methods: 115 STS patients were retrospectively reviewed. IL-6 and CRP blood levels, NLR and PLR were obtained prior to treatment. Early recurrence was defined as disease relapse (local or distant) within the first year after surgery. Cox regression analysis was used to identify prognostic factors for early recurrence.
Results: IL-6 elevation was associated with a higher tumor grade, increased size, tumor necrosis and a higher mitotic count. NLR elevation was associated with a higher tumor grade, PLR elevation with a larger tumor size. Early recurrences were found in 24 patients (21 %). Univariable analysis revealed that tumor grade ($p = 0.029$), tumor size ($p = 0.030$, >10 cm vs < 5 cm), tumor depth ($p = 0.036$), necrosis on imaging ($p = 0.008$), mitotic count ($p = 0.045$, ≥20 mitoses vs 0–9 mitoses), and IL-6 level ($p = 0.044$) were associated with early recurrence. The factors age at diagnosis, tumor location, necrosis at pathology, (neo)adjuvant radio- or chemotherapy, resection margin, CRP level, NLR and PLR were not related to early disease recurrence.
Conclusions: Increased inflammatory markers in STS are associated with an aggressive phenotype. STS patients with elevation of IL-6 may be at risk for early disease recurrence.

1. Introduction

Soft tissue sarcomas (STS) comprise a heterogeneous group of tumors that consists of over 70 different subtypes [1]. Despite advances in imaging and multimodality therapy, disease recurrence remains a major problem in the management of STS patients. After treatment of primary extremity STS, approximately 33 % of patients experience disease recurrence [2]. Recurrence rates in primary retroperitoneal sarcoma are even more common, with rates up to 50 % [3]. Approximately three-quarters of the relapses occur within the first two years after primary treatment [4–6]. Due to limited treatment options, the prognosis of patients with recurrent STS remains unfavorable.

To improve outcomes of STS patients, it is crucial to identify factors that predict biological behavior and the risk for disease recurrence. Some well-known prognostic factors have already been established in previous studies, such as specific histological subtypes, histological grade, age and tumor size [4,7–9]. Predictive tools that incorporate these factors, such as SARCULATOR and PERSARC, are increasingly being used by clinicians to generate individualized treatment and follow-up schedules for each patient [10,11]. The addition of novel prognostic factors might be helpful in improving individual risk assessment of STS patients.

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https://doi.org/10.1016/j.ejso.2024.108530
Received 17 April 2024; Received in revised form 13 June 2024; Accepted 3 July 2024
Available online 4 July 2024

It is well-known that the inflammatory response plays an important role in cancer development and progression [12]. Tumor-promoting inflammation is even established as one of the hallmarks of cancer [13]. Measurable parameters in the blood that reflect systemic inflammation, such as C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR) and cytokines have been identified as prognostic factors for survival in many cancer types [14–16]. While the exact pathophysiology of systemic inflammation and cancer is still not exactly clarified, there is a growing interest in the use of blood-based inflammatory markers since they have the advantage of being readily accessible, inexpensive and easy to obtain. In STS, few studies have assessed the prognostic value of systemic inflammatory markers and showed that elevation of platelet-to-lymphocyte ratio (PLR), interleukin-6 (IL-6), CRP and NLR were related to decreased disease-free survival (DFS) in STS [17–20]. Moreover, further studies showed pretreatment CRP and NLR as independent factors for overall survival (OS) [21–23]. This suggests that pretreatment elevated inflammatory markers are adverse prognostic indicators in STS, and that they might be valuable for improving individualized treatment and surveillance. These markers might even be a useful addition to the already well-established prognostic factors for STS.

As NLR, PLR, CRP and IL-6 are regarded as representative indicators of systemic inflammation, the aim of this study was to evaluate these markers before treatment in their ability to predict early disease recurrence in primary, localized STS. In addition, the relation of these inflammatory markers with other, well-known negative prognostic factors was investigated.

2. Methods

Adult patients with histologically-proved STS consecutively seen between March 2020 and March 2022 at a tertiary referral center in The Netherlands were included. Only primary, localized STS that were treated with surgery were included. Patients with benign tumors, desmoid tumors, well-differentiated liposarcoma and gastrointestinal stromal tumors were excluded from this study. Patients who presented after neo adjuvant treatment elsewhere, patients with synchronous other malignancies, metastasis at diagnosis, a R2 resection, recurrences or use of oral corticosteroids or purine antagonists or who had a significant delay in start of treatment (>90 days from first visit) were also excluded. Finally, a total of 115 patients were retrospectively enrolled in this study. This study was approved by the Institutional Review Board of The Netherlands Cancer Institute (IRBdm20-239).

Laboratory data, including IL-6, CRP, NLR and PLR, was obtained prior to treatment in all patients. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, whereas for PLR the absolute platelet count was divided by the absolute lymphocyte count. As there is no normal range of NLR and PLR, the median of each ratio was used to distinguish low versus high NLR or PLR. Blood IL-6 level was measured from serum by the Elecsys® IL-6 immunoassay on a cobas pro system (Roche Diagnostics). IL-6 elevation was defined as a value $\geq$ 7 ng/L, and CRP elevation as a value $\geq$ 8 mg/L, according to hospital standards. Clinical data was retrospectively collected from the patients' histories. Tumors were graded based on a pretreatment biopsy or untreated resection specimen according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system [24]. Since this grading system is less suitable for rhabdomyosarcoma, epithelioid sarcoma and clear cell sarcoma, these histologies were not graded. Tumor depth was assessed in relation to the deep fascia based on imaging. Both tumor depth and maximum tumor size were based on imaging data (MRI and/or CT), or on physical examination in case of a dermal sarcoma.

Data are presented as number (%) or median (IQR: interquartile range). The relationships between categorical variables were compared using the Pearson chi-square test. Continuous variables were expressed as medians and compared using the Mann-Whitney *U* test or Kruskal-Wallis test, where appropriate. DFS was defined as the time between date of surgery until the date of disease recurrence, either local or distant. DFS was censored at time of death or at 12 months follow-up if patient was alive and disease-free at that time.

Associations between clinical variables and DFS were analyzed by using Kaplan Meier curves and Cox-regression. The cox proportional hazards assumption was tested by log minus log plots. A value of $P < 0.05$ was considered as statistically significant. Because of the low number of events (n = 27 early recurrences) a multivariate analysis was not conducted since a low number of events per variable will lead to biased results and models that are not reliable. All analyses were performed using IBM SPSS statistical software (version 29.0). Figures were created in GraphPad Prism (version 9.3) and R (version 4.2.1).

3. Results

3.1. Patient demographics

A total of 115 STS patients were studied with a median age at diagnosis of 62 years (IQR: 51–71). The cohort consisted out of 60 males (52.2 %) and 55 females (47.8 %), diagnosed with various STS subtypes. Details are presented in Table 1. Median maximum tumor size was 7.5 cm (IQR: 5–13). The majority of tumors were larger than 5 cm (73.9 %), intermediate to high grade (72.6 %) and deeply seated (75.7 %). Median blood levels were 4.2 ng/L (IQR: 2.9–12.6) for IL-6, 5.0 mg/L (IQR: 1.0–33.0) for CRP, 2.7 (IQR: 2.1–4.3) for NLR and 167.0 (IQR: 134.6–221.9) for PLR.

3.2. Relationship between inflammatory markers and clinicopathological characteristics

IL-6 and CRP level, NLR and PLR were analyzed in relation to various clinicopathological factors, including FNCLCC tumor grade, tumor size, necrosis on imaging, necrosis at pathology, mitotic count, tumor depth, tumor location and resection margin. Results are shown in Table 2. Patients with elevation of blood IL-6 have tumors that are more often of higher grade ($p < 0.001$), are of larger size ($p < 0.001$) and have a higher mitotic count ($p = 0.018$). In addition, presence of necrosis on imaging and at pathological examination is more often seen in this group (for both $p = <0.001$). An elevation of NLR is related to higher-grade tumors ($p = 0.002$), whereas PLR elevation is associated with only a larger tumor size ($p = 0.030$). CRP did not show a relation with any of the clinicopathological variables. Median values of IL-6, CRP, NLR and PLR for different histopathologic subtypes are shown in Fig. 1. The level of IL-6 and NLR shows a significant variation among STS histology (IL-6: $p = 0.002$, NLR: $p = 0.004$) but not for PLR ($p = 0.052$) and CRP ($p = 0.188$). Highest levels of inflammation were seen for dedifferentiated liposarcoma, sarcoma not otherwise specified (sarcoma NOS) and undifferentiated pleomorphic sarcoma (UPS).

3.3. Prognostic significance of inflammatory markers in STS

Median follow-up time was 24 months (range: 2–38). During the follow-up period, 37 patients (32 %) experienced disease recurrence, of which 24 (21 %) of recurrences occurred during the first year after surgery. Within this group of early recurrences, seven patients had a local recurrence, 14 had distant metastases and three patients had both manifestations. Most of patients with disease recurrence had a tumor of more than 5 cm that was deeply seated. Most tumors that recurred were intermediate to high grade (Table 3). Fig. 2 shows the Kaplan Meier curve for early disease recurrence between patients with high and low IL-6. Results of the univariable Cox regression analysis for early recurrence are shown in Table 4. Tumor grade (HR: 9.32, CI: 1.26–69.19, $p = 0.029$), tumor size (>10 cm vs < 5 cm, HR: 5.19, CI: 1.17–23.00, $p = 0.030$), tumor depth (HR: 8.47, CI: 1.14–62.79, $p = 0.036$), necrosis on imaging (HR: 3.03, CI: 1.33–6.91, $p = 0.008$), mitotic count (HR: 2.69, CI: 1.02–7.08, $p = 0.045$) and an elevated IL-6 level (HR: 2.28, CI:

Table 1
Baseline patient characteristics. Abbreviations: CRP: C-reactive protein; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; IL-6: interleukin-6; IQR: interquartile range; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Characteristics	Patients (n = 115)
Gender, n (%)	
Male	60/115 (52.2)
Female	55/115 (47.8)
Age at diagnosis (years), median [IQR]	62 [51.0–71.0]
Maximum tumor size in cm, median [IQR]	7.5 [4.8–12.5]
Maximum tumor size, n (%)	
< 5 cm	30/115 (26.1)
5–10 cm	43/115 (37.4)
>10 cm	42/115 (36.5)
FNCLCC tumor grade, n (%)	
1	31/113 (27.4)
2-3	82/113 (72.6)
Tumor depth, n (%)	
Superficial	28/115 (24.3)
Deep	87/115 (75.7)
Tumor location, n (%)	
Retroperitoneal, abdominal	33/115 (28.7)
Other	82/115 (71.3)
Tumor histology, n (%)	
Leiomyosarcoma	24/115 (20.9)
Sarcoma not otherwise specified (NOS)	22/115 (19.1)
Dedifferentiated liposarcoma	12/115 (10.4)
Myxoid liposarcoma	9/115 (7.8)
Undifferentiated pleomorphic sarcoma (UPS)	7/115 (6.1)
Angiosarcoma	7/115 (6.1)
Dermal sarcoma	6/115 (5.2)
Pleomorphic liposarcoma	3/115 (2.6)
Malignant peripheral nerve sheath tumor (MPNST)	3/115 (2.6)
Myxofibrosarcoma	3/115 (2.6)
Synovial sarcoma	3/115 (2.6)
Other	16/115 (13.9)
(Neo)adjuvant chemotherapy	19/115 (16.5)
(Neo)adjuvant radiotherapy	51/115 (44.3)
Necrosis on imaging, n (%)	
Absent	88/113 (77.9)
Present	25/113 (22.1)
Necrosis at pathology, n (%)	
Absent	63/112 (56.3)
Present	49/112 (43.8)
Mitotic count, n (%)	
0–9 mitoses	70/111 (63.1)
10–19 mitoses	21/111 (18.9)
≥20 mitoses	20/111 (18.0)
Resection margin, n (%)	
R0	100/115 (87.0)
R1	15/115 (13.0)
Serum inflammatory markers, median [IQR]	
IL-6 (ng/L)	4.2 [2.9–12.6]
CRP (mg/L)	5.0 [1.0–33.0]
NLR	2.7 [2.1–4.3]
PLR	167.0 [134.6–221.9]

1.02–5.09, p = 0.044) showed to be poor predictive values for early disease recurrence. The factors age at diagnosis, tumor location, necrosis at pathology, (neo)adjuvant radio- or chemotherapy, resection margin, CRP, NLR and PLR did not show any predictive value on univariable analysis.

4. Discussion

The present study suggests that blood inflammatory markers are indicators for aggressive STS tumors that could recur early. Specifically, elevation of IL-6, NLR and PLR were related to large tumors of high grade that often show necrosis and higher mitotic counts. In addition, univariable analysis of the follow-up data revealed that IL-6 elevation, but not CRP, NLR and PLR is associated with early disease recurrence.

Prognostication is of major importance for patients with cancer, as it informs many personal and clinical decisions. Various prognostic factors have been identified for STS in previous studies. The predictive and prognostic meaning of tumor grade according to the FNCLCC grading system is widely known and is whenever possible, applied to most STS cases [24,25]. This grading system distinguishes three grades based on tumor differentiation, mitotic count and necrosis. In our study, FNCLCC tumor grade could not be assessed for all cases and therefore tumor necrosis and mitoses were separately included. Next to histopathological factors, clinical factors such as age, tumor size, tumor depth and tumor location have been established as important factors for prognostication, and have been included in validated prognostic nomograms for STS [26–29]. The current data indicates that IL-6 elevation in STS may have prognostic implication as well.

Studies that investigated the role of inflammatory markers in STS show elevation of NLR, PLR, CRP or cytokines - either single or combined as inflammatory indexes - to be related to a poor prognosis [17–23]. Fiore et al. demonstrated the prognostic value of a combined measure comprising of NLR, hemoglobin, monocytes and PLR and propose this marker as a valuable addition to the already established prognostic STS nomograms [30]. Besides that blood-based inflammatory markers could improve the current prognostic models for STS, these serum markers could be useful for having a first impression of the characteristics of a tumor. Based on the current data, patients with elevated inflammation markers in blood often have large, high-grade tumors. Inflammatory markers in blood have the advantage that they are easy and quick to obtain, and thus could provide information even before imaging and biopsy have been assessed. Moreover, our study suggests IL-6 as predictive factor for early disease recurrence. This may indicate that patients with IL-6 elevation potentially benefit from more aggressive treatment, although the addition of (neo)adjuvant radiotherapy or chemotherapy did not lower the risk of early disease recurrence in the current dataset. Another option would be to intensify the follow-up strategy for patients with elevated IL-6 levels, to detect possible recurrences earlier.

IL-6 is a pleiotropic cytokine that is produced by various cells, including tumor cells [16]. IL-6 has been shown to be important in multiple cellular processes, including immune regulation, hematopoiesis and oncogenesis [31]. Systemically elevated IL-6 has been reported in patients with various types of cancer, and could be an indicator for worse prognosis [32–34]. These findings suggest that blocking IL-6 may be a therapeutic strategy for tumors in which IL-6 is overproduced. For STS, IL-6 serum levels and IL-6 expression in tumor tissue may have a role as predictive biomarker as they both show to be prognostic for survival in other studies [35,36]. Besides this, IL-6 levels have been linked to therapy response. Although IL-6 is one of the most important

Table 2
Relation of inflammatory markers with clinicopathological characteristics. Abbreviations: CRP: C-reactive protein; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; IL-6: interleukin-6; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

		IL-6			CRP			NLR			PLR		
	Total (n = 115)	<7 ng/L n = 74	≥7 ng/L n = 41	p-value	<8 mg/L n = 59	≥8 mg/L n = 43	p-value	<2.7 n = 51	≥2.7 n = 64	p-value	<166.7 n = 57	≥166.7 n = 58	p-value
FNCLCC tumor grade, n (%)				**<0.001**			0.166			**0.002**			0.490
1	31 (26.9)	30 (40.5)	1 (2.4)		13 (22.0)	15 (34.9)		21 (41.2)	10 (15.6)		17 (29.8)	14 (24.1)	
2-3	82 (71.3)	43 (58.1)	39 (95.1)		45 (76.3)	28 (65.1)		29 (56.9)	53 (82.8)		39 (68.4)	44 (75.9)	
Missing	2 (1.7)	1 (1.4)	1 (2.4)		1 (1.7)	0		1 (2.0)	1 (1.6)		1 (1.8)	1 (1.7)	
Maximum tumor size, n (%)				**<0.001**			0.910			0.136			**0.030**
<5 cm	30 (26.1)	25 (33.8)	5 (12.2)		15 (25.4)	12 (27.9)		17 (33.3)	13 (20.3)		18 (31.6)	12 (20.7)	
5–10 cm	43 (37.4)	32 (43.2)	11 (26.8)		23 (39.0)	15 (34.9)		20 (39.2)	23 (35.9)		25 (43.9)	18 (31.0)	
>10 cm	42 (36.5)	17 (23.0)	25 (61.0)		21 (35.6)	16 (37.2)		14 (27.5)	28 (43.8)		14 (24.6)	29 (50)	
Necrosis on imaging, n (%)				**<0.001**			0.116			0.744			0.465
Absent	88 (76.5)	65 (87.8)	23 (56.1)		40 (67.8)	36 (83.7)		39 (76.5)	49 (76.6)		46 (80.7)	42 (72.4)	
Present	25 (21.7)	9 (12.2)	16 (39.0)		17 (28.8)	7 (16.3)		12 (23.5)	13 (20.3)		11 (19.3)	14 (24.1)	
Missing	2 (1.7)	0	2 (4.9)		2 (3.4)	0		0	2 (3.1)		0	2 (3.4)	
Necrosis at pathology, n (%)				**<0.001**			0.133			0.054			0.317
Absent	63 (54.8)	49 (66.2)	14 (34.1)		28 (47.5)	27 (62.8)		32 (62.7)	31 (48.4)		33 (57.9)	30 (51.7)	
Present	49 (42.6)	23 (31.1)	26 (63.4)		29 (49.2)	15 (34.9)		16 (31.4)	33 (51.6)		21 (36.8)	28 (48.3)	
Missing	3 (2.6)	2 (2.7)	1 (2.4)		2 (3.4)	1 (2.3)		3 (5.9)	0		3 (5.3)	0	
Mitotic count, n (%)				**0.018**			0.171			0.091			0.065
0-9 mitoses	70 (60.9)	51 (68.9)	19 (46.3)		31 (52.5)	31 (72.1)		36 (69.8)	34 (53.1)		40 (70.2)	30 (51.7)	
10-19 mitoses	21 (18.3)	9 (12.2)	12 (29.3)		13 (22.0)	6 (13.9)		8 (15.1)	13 (20.3)		6 (10.5)	15 (25.9)	
≥20 mitoses	20 (17.4)	10 (13.5)	10 (24.4)		12 (20.3)	5 (11.6)		5 (9.4)	15 (23.4)		9 (15.8)	11 (19.0)	
Missing	4 (3.5)	4 (5.4)	0		3 (5.1)	1 (2.3)		2 (5.7)	2 (3.1)		2 (3.5)	2 (3.4)	
Tumor depth, n (%)				0.176			0.251			0.489			0.357
Superficial	28 (24.3)	21 (28.4)	7 (17.1)		12 (20.3)	13 (30.2)		14 (27.5)	14 (21.9)		16 (28.1)	12 (20.7)	
Deep	87 (75.6)	53 (71.6)	34 (82.9)		47 (79.7)	30 (69.8)		37 (72.5)	50 (78.1)		41 (71.9)	46 (79.3)	
Tumor location, n (%)				0.164			0.208			0.571			0.331
Retroperitoneal, abdominal	33 (28.7)	18 (24.3)	15 (36.6)		19 (32.2)	9 (20.9)		16 (31.4)	17 (26.6)		14 (24.6)	19 (32.8)	
Other	82 (71.3)	56 (75.7)	26 (63.4)		40 (67.8)	34 (79.0)		35 (68.6)	47 (73.4)		43 (75.4)	39 (67.2)	
Resection margin, n (%)				0.841			0.755			0.716			0.810
R0	100 (87.0)	64 (86.5)	36 (87.8)		52 (88.1)	37 (86.0)		45 (88.2)	55 (85.9)		50 (87.7)	50 (86.2)	
R1	15 (13.0)	10 (13.5)	5 (12.2)		7 (11.8)	6 (13.9)		6 (11.8)	9 (14.1)		7 (12.3)	8 (13.8)	

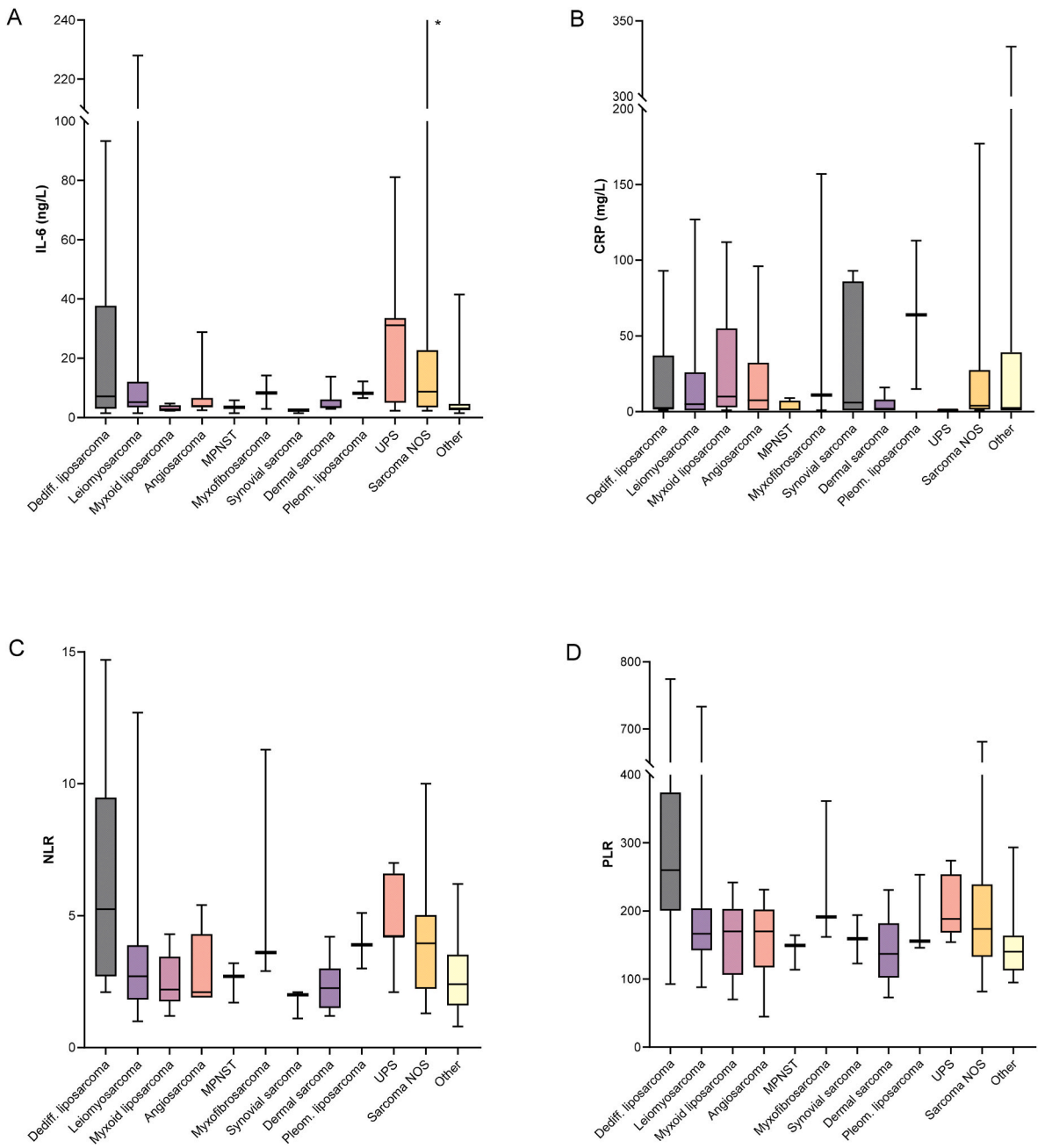

Fig. 1. Boxplots of median values for IL-6 (A), CRP (B), NLR (C) and PLR (D) among different STS subtypes. *: Upper whisker reaches to 445 ng/L. Abbreviations: Abbreviations: CRP: C-reactive protein; Dediff liposarcoma: dedifferentiated liposarcoma; IL-6: interleukin-6; MPNST: malignant peripheral nerve sheath tumor; NLR: neutrophil-to-lymphocyte ratio; Pleom. liposarcoma: pleomorphic liposarcoma; PLR: platelet-to-lymphocyte ratio; sarcoma NOS: sarcoma not otherwise specified; UPS: undifferentiated pleomorphic sarcoma.

pro-inflammatory cytokines, IL-6 could also exert anti-inflammatory properties. By the modulation of immune cells including T-cells, dendritic cells and macrophages, IL-6 signaling induces a pro-tumorigenic, immune-suppressive environment limiting the innate and adaptive immunity to respond to tumors [37]. This may explain why in recent melanoma studies IL-6 elevation showed to be related to poor responsiveness to chemotherapy and immune checkpoint blockade (ICB) [38–40]. IL-6 could be a promising therapeutic target to manipulate the immune-suppressive environment, either as monotherapy or in combination with ICB.

There are several limitations of the present study that needs to be taken into account. First is the small sample size of the study. Because of the limited number of early recurrences, a multivariable analysis was not conducted. Performing a multivariable analysis with such low number of events will cause a too small ratio of events per variable, leading to less accuracy and precision of the model and affect their tests of statistical significance. Under such circumstances, a regression model could lead to unstable risk estimates and the suggestion of misleading results [41]. Prospective studies and larger dataset are therefore required to assess the value of IL-6 as a predictive marker in reliable multivariable models. Second, the cohort consisted out of a mixture of histological subtypes and tumor locations of STS while ideally this is analyzed in separate groups. However, because of the rarity of STS this would result in such small cohorts that it would be hard to draw conclusions. Therefore, subtypes and tumor locations were pooled as this is a well-established procedure in STS research. Third, NLR and PLR do not

Table 3
Characteristics of patients with early disease recurrence. Abbreviations: CRP: C-reactive protein; Dediff liposarcoma: dedifferentiated liposarcoma; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; IL-6: interleukin-6; MPNST: malignant peripheral nerve sheath tumor; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; sarcoma NOS: sarcoma not otherwise specified; UPS: undifferentiated pleomorphic sarcoma.

	Local recurrence (LR)	Distant metastases (DM)	Both LR and DM	All recurrences < 1 year	Total cohort
	n = 7	n = 14	n = 3	n = 24	n = 115
Gender, n (%)					
Male	2	10	2	14/24 (58.3)	60/115 (52.2)
Female	5	4	1	10/24 (41.7)	55/115 (47.8)
Maximum tumor size, n (%)					
< 5 cm	2	–	–	2/24 (8.3)	30/115 (26.1)
5–10 cm	3	5	1	9/24 (37.5)	43/115 (37.4)
>10 cm	2	9	2	13/24 (54.2)	42/115 (36.5)
FNCLCC tumor grade, n (%)					
1	–	1	–	1/23 (4.3)	31/113 (27.4)
2-3	7	12	3	22/23 (95.7)	82/113 (72.6)
Tumor depth, n (%)					
Superficial	1	–	–	1/24 (4.2)	28/115 (24.3)
Deep	6	14	3	23/24 (95.8)	87/115 (75.7)
Tumor location, n (%)					
Retroperitoneal, abdominal	1	4	–	5/24 (20.8)	34/115 (28.7)
Other	6	10	3	19/24 (79.2)	84/115 (71.3)
Tumor histology, n (%)					
Leiomyosarcoma	1	2	–	3/24 (12.5)	24/115 (20.9)
Sarcoma NOS	2	4	2	8/24 (33.3)	22/115 (19.1)
Dediff. liposarcoma	–	2	–	2/24 (8.3)	12/115 (10.4)
Myxoid liposarcoma	–	1	–	1/24 (4.2)	9/115 (7.8)
UPS	2	–	1	3/24 (12.5)	7/115 (6.1)
Angiosarcoma	–	1	–	1/24 (4.2)	7/115 (6.1)
Pleiomorphic liposarcoma	–	–	–	–	3/115 (2.6)
MPNST	1	–	–	1/24 (4.2)	3/115 (2.6)
Other	–	4	–	4/24 (16.7)	16/115 (13.9)
(Neo)adjuvant chemotherapy	1	3	2	6/24 (25.0)	19/115 (16.5)
(Neo)adjuvant radiotherapy	3	6	3	12/24 (50.0)	51/115 (44.3)
Elevated inflammatory markers, n (%)					
IL-6 (ng/L)	3	8	2	13/24 (54.2)	41/115 (35.7)
CRP (mg/L)	2	4	0	6/20 (30.0)	43/102 (42.2)
NLR	6	8	2	16/24 (66.7)	64/115 (55.7)
PLR	4	8	1	13/24 (54.2)	58/115 (50.4)

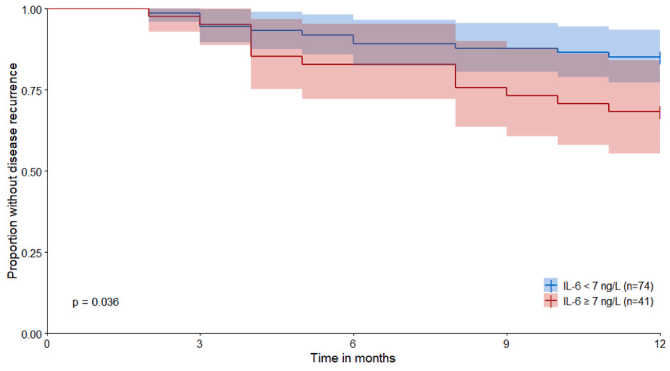

Fig. 2. Kaplan Meier curves of first year DFS for IL-6 groups. Abbreviations: IL-6: interleukin-6.

have a standard cut-off point. In our study, the median value was used to separate low from high NLR or PLR. In previous studies, various methods to define a cut-off value for these ratios were used including ROC-curve analyses, median values, institutional standards or previous studies [23]. This results in variable cut-offs that may results in different outcomes.

Taken together, this study suggests that cancer-associated inflammation, particularly IL-6, has prognostic value in STS and thus should be considered in clinical decision making and treatment planning. Based on the current data, the presence of elevated inflammatory markers implies that those tumors have a risk of early recurrences and thus may require more aggressive treatment strategies. Serum inflammatory markers are simple to measure and available early in the diagnostic process. They could provide a valuable tool for a more accurate prediction of tumor behavior and prognosis. Whether IL-6 is most appropriate and how to incorporate this into the already established prognostic nomograms warrants further investigation.

Table 4
Cox regression analysis of early recurrences. Abbreviations: CI: confidence interval; CRP: C-reactive protein; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; HR: hazard ratio; IL-6: interleukin-6; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

			Recurrence <1 year	Univariable analysis	
		n	(n/total per group (%))	HR (95 % CI)	p-value
Age at diagnosis, years	≤62	60	10/60 (16.7)	Reference	
	>62	55	14/55 (25.5)	1.65 (0.73–3.72)	0.228
FNCLCC tumor grade	1	31	1/31 (3.2)	Reference	
	2–3	82	22/82 (25.9)	9.32 (1.26–69.19)	**0.029**
Maximum tumor size	<5 cm	30	2/30 (6.7)	Reference	
	5–10 cm	43	9/43 (20.9)	3.27 (0.71–15.11)	0.130
	>10 cm	42	13/42 (30.9)	5.19 (1.17–23.00)	**0.030**
Tumor depth	Superficial	28	1/28 (3.6)	Reference	
	Deep	87	23/87 (26.4)	8.47 (1.14–62.79)	**0.036**
Tumor location	Retroperitoneal, abdominal	33	5/33 (15.2)	Reference	
	Other	82	19/82 (23.2)	1.57 (0.59–4.21)	0.368
Necrosis on imaging	Absent	88	13/88 (14.8)	Reference	
	Present	25	10/25 (40.0)	3.03 (1.33–6.91)	**0.008**
Necrosis at pathology	Absent	63	10/63 (15.9)	Reference	
	Present	49	14/49 (28.6)	2.03 (0.90–4.57)	0.088
Mitotic count	0-9 mitoses	70	10/70 (14.3)	Reference	
	10-19 mitoses	21	7/21 (33.3)	2.48 (0.95–6.52)	0.093
	≥20 mitoses	20	7/20 (35.0)	2.69 (1.02–7.08)	**0.045**
(Neo)adjuvant chemotherapy	No	96	18/96 (18.8)	Reference	
	Yes	19	6/19 (31.6)	1.29 (0.49–3.39)	0.609
(Neo)adjuvant radiotherapy	No	64	12/64 (18.8)	Reference	
	Yes	51	12/51 (23.5)	0.41 (0.16–1.04)	0.061
Resection margin	R0	100	18/100 (18.0)	Reference	
	R1	15	6/15 (40.0)	2.50 (0.99–6.29)	0.052
IL-6	<7 ng/L	74	11/74 (18.9)	Reference	
	≥7 ng/L	41	13/41 (31.7)	2.28 (1.02–5.09)	**0.044**
CRP	<8 mg/L	59	14/59 (23.7)	Reference	
	≥8 mg/L	43	6/43 (14.0)	0.55 (0.21–1.43)	0.218
NLR	<2.7	51	8/51 (15.7)	Reference	
	≥2.7	64	16/64 (25)	1.69 (0.72–3.95)	0.225
PLR	<166.7	57	11/57 (19.3)	Reference	
	≥166.7	58	13/58 (22.4)	1.22 (0.55–2.71)	0.634

CRediT authorship contribution statement

P. van der Laan: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **W.T.A. van der Graaf:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **D. van den Broek:** Writing – review & editing. **H. van Boven:** Writing – review & editing. **B.C. Heeres:** Writing – review & editing. **Y. Schrage:** Writing – review & editing. **R.L. Haas:** Writing – review & editing. **N. Steeghs:** Conceptualization, Methodology, Writing – review & editing, Supervision. **W.J. van Houdt:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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