Elevated preoperative serum interleukin-6 level is predictive for worse postoperative outcome after soft tissue sarcoma surgery

Laan, P. van der; Graaf, W.T.A. van der; Reijers, S.J.M.; Schrage, Y.M.; Hendriks, J.J.H.; Haas, R.L.; ... ; Houdt, W.J. van

European Journal of Surgical Oncology 49 (2023) 106926

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Elevated preoperative serum interleukin-6 level is predictive for worse postoperative outcome after soft tissue sarcoma surgery

P. van der Laan [a, b], W.T.A. van der Graaf [b, c], S.J.M. Reijers [a], Y.M. Schrage [a], J.J.H. Hendriks [b], R.L. Haas [d, e], D. van den Broek [f], N. Steeghs [b], W.J. van Houdt [a, *]

[a] Department of Surgical Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands
[b] Department of Medical Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands
[c] Department of Medical Oncology, Erasmus MC Cancer Institute, Dr. Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands
[d] Department of Radiotherapy, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands
[e] Department of Radiotherapy, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands
[f] Department of Laboratory Medicine, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 18 January 2023
Received in revised form
14 April 2023
Accepted 2 May 2023
Available online 03 May 2023

Keywords:
Soft tissue sarcoma
Interleukin-6
Inflammation
Textbook outcome
Surgical outcome

ABSTRACT

Background: The pro-inflammatory cytokine interleukin-6 (IL-6) plays a role in cancer development and progression, but research into the predictive value of IL-6 on postoperative outcome in soft tissue sarcoma (STS) is scarce. The purpose of this study is to investigate the predictive value of serum IL-6 level for the achievement of assumed (post)operative outcome after STS surgery, the so-called textbook outcome.
Methods: Preoperative IL-6 serum levels were collected in all patients with a STS at first presentation between February 2020 and November 2021. Textbook outcome was defined as a R0 resection, no complications, no blood transfusions, no reoperation within the postoperative period, no prolonged hospital stay, no hospital readmission within 90-days, and no mortality within 90-days. Factors associated with textbook outcome were determined by multivariable analysis.
Results: Among 118 patients with primary, non-metastatic STS, 35.6% achieved a textbook outcome. Univariate analysis showed that smaller tumor size ($p = 0.026$), lower tumor grade ($p = 0.006$), normal hemoglobin (Hb, $p = 0.044$), normal white blood cell (WBC) count ($p = 0.018$), normal C-reactive protein (CRP) serum level ($p = 0.002$) and normal IL-6 serum level ($p = 1.5 \times 10^{-5}$) were associated with achieving textbook outcome after surgery. Multivariable analysis showed that elevated IL-6 serum level ($p = 0.012$) was significantly associated with not achieving a textbook outcome.
Conclusions: Increased IL-6 serum level is predictive for not achieving a textbook outcome after surgery for primary, non-metastatic STS.

1. Introduction

Soft tissue sarcoma (STS) is a rare type of cancer that develops from mesenchymal tissue and accounts for <1% of all malignant tumors [1]. STS is a heterogeneous group of tumors that can occur at any anatomical site. For localized STS, treatment consists of surgery, which can be combined with (neo)adjuvant radiotherapy or chemotherapy.

The symptoms of a STS are diverse and depend on the size and location of the tumor. In some patients, these symptoms are accompanied by a poor performance status at presentation. These patients often have a large tumor, are in pain, show fatigue, weight loss and abnormal blood test results such as anemia and hypoalbuminemia. Interestingly, these patients also seem to have increased inflammatory blood parameters including C-reactive protein (CRP) and white blood cell (WBC) count.

The link between inflammation and cancer is widely accepted. Increasing evidence suggests that tumors are sometimes capable of inducing local and systemic inflammation that enhances their own

* Corresponding author.
E-mail addresses: p.vd.laan@nki.nl (P. van der Laan), w.vd.graaf@nki.nl (W.T.A. van der Graaf), s.reijers@nki.nl (S.J.M. Reijers), y.schrage@nki.nl (Y.M. Schrage), joris.hendriks@radboudumc.nl (J.J.H. Hendriks), r.haas@nki.nl (R.L. Haas), da.vd.broek@nki.nl (D. van den Broek), n.steeghs@nki.nl (N. Steeghs), w.v.houdt@nki.nl (W.J. van Houdt).

https://doi.org/10.1016/j.ejso.2023.05.001

growth [2,3]. Blood markers to assess systemic inflammation, such as CRP, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been extensively studied as prognostic markers in cancer [4–6].

Interleukin-6 (IL-6) is a pleiotropic cytokine produced by almost all stromal cells and immune cells in the body [7]. With its pro- and anti-inflammatory effects, IL-6 is an important regulator of the immune system, inflammation and hematopoiesis. Dysregulation of IL-6 has been linked to various disease conditions, such as chronic inflammation, autoimmune disease, infectious disease, and cancer [8,9]. Autocrine production of IL-6 is one of the strategies used by cancer cells to enhance proliferation, angiogenesis, survival, and invasion through the JAK/STAT3 pathway, resulting in aggressive tumor growth, poor prognosis and shorter survival [10–13]. IL-6 serum levels showed prognostic value in many cancer types, including lung, cervical, breast, colorectal, gastric, prostate and ovarian cancer [14–20].

Also in STS, an association between IL-6 serum levels and survival was found, which may be relevant for the prognosis and follow-up of STS patients [21,22]. However, the consequences of high IL-6 serum levels on short-term postoperative outcomes are not yet clear. The exploration of a subset of STS patients with high inflammatory markers suggests that there may be an association between these high inflammatory markers and poor performance status at presentation, which might negatively influence the postoperative outcome. Therefore, inflammatory markers like IL-6 could potentially provide useful information to guide treatment planning.

Recently, 'textbook outcome' is proposed as a novel composite measure to evaluate short-term outcomes among patients undergoing surgery [23–28]. It was originally developed to study the quality of care and hospital variation in outcome among colon cancer patients [29]. Textbook outcome represents an ideal postoperative course by combining multiple individual outcome parameters reflecting different domains of care. Textbook outcome covers the complete surgical process and not just one or two parameters such as complications, and is achieved when all desired short-term outcomes are met. This summary measure provides a powerful tool that estimates the quality of surgical procedures and how often the perioperative process is successful. With the textbook outcome tool, short-term surgical outcomes can be more accurately assessed and compared. Textbook outcome among patients undergoing surgery for STS was investigated previously and ranged from 35 to 56% depending on the type of surgery and textbook outcome definition [30–32]. Identification of parameters that predict the risk for decreased textbook outcome after STS surgery could potentially provide guidance to optimize the perioperative course and improve the postoperative outcome of STS patients.

In the present study, we aim to analyze the association between pre-operative IL-6 serum level and the achievement of a textbook outcome in patients with a primary, non-metastatic STS of any subtype or location.

2. Methods

2.1. Data acquisition and group definition

Data was collected for all patients with a STS presented in a tertiary referral center in the Netherlands between February 2020 and November 2021. Patient, tumor and treatment characteristics were retrospectively retrieved from the medical files. Patients with a benign tumor (e.g. desmoid fibromatosis, well-differentiated liposarcoma), a diagnosis other than STS, an active second malignancy, and concurrent use of oral corticosteroids or purine antagonists were excluded. The study was approved by the Institutional Review Board (IRBd20-239).

Maximum tumor size, tumor depth and presence of necrosis were obtained from baseline CT and MRI scans that were performed in the preoperative period with a maximum of 90 days between initial visit and start of treatment. Tumor depth was assessed in relation to the deep fascia. Histopathological diagnosis was confirmed by pathology review and tumor grading was determined using the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system [33]. This grading system is not suitable for gastrointestinal stromal tumors (GIST). GIST were therefore classified based on their mitotic count: $\leq$5 mitoses per 5 mm^2 was considered as 'low grade' whereas >5 mitoses per 5 mm^2 was considered as high grade. This cutoff is based on the Mietinnen criteria that are used for risk classification of GIST [34]. Blood results were prospectively collected at initial visit. Hospital standards were used for the cut-off values for blood test results, see Table 1. The cut-off value for IL-6 levels was according to hospital standard set at 7 ng/L. IL-6 levels were measured from serum by the Elecsys® IL-6 immunoassay on a cobas pro system (Roche Diagnostics). Postoperative complications were graded using the Clavien-Dindo Classification of Surgical Complications [35].

For textbook outcome analysis, only patients with a non-metastatic primary STS that were primarily treated with surgery were included. Patients that underwent a whoops resection or that had a significant delay in the start of treatment (>90 days between first visit and start of treatment) were excluded from the analysis.

2.2. Textbook outcome

The textbook outcome definition was based on STS studies by Wiseman et al. [30] and Lazarides et al. [31], and was defined as R0 resection, no $\geq$ grade 2 complications according to the Clavien-Dindo classification, no perioperative or postoperative blood transfusions, no reoperation within the postoperative period, no prolonged hospital stay – defined as a postoperative stay $\leq$50th percentile of the total cohort (with a median of 7 days and 3 days for retroperitoneal/trunk sarcomas and extremity STS, respectively) -, no hospital readmission within 90-days and no postoperative mortality within 90-days.

2.3. Statistical analysis

Descriptive statistics were presented as median (IQR) for continuous variables and frequency (%) for categorical variables. Baseline patient, tumor and treatment characteristics and textbook outcome were evaluated using Mann-Whitney *U* test for continuous data and the Pearson chi-square test and Fisher's exact test, as appropriate, for categorical data. Spearman's rank correlation coefficient was used to compare correlations between IL-6 levels and variables that were expected to be related to IL-6 level. Results were considered statistically significant if the p-value was <0.05. A multivariable logistic regression model was created to determine associations between baseline characteristics and the occurrence of a textbook outcome. First, associations of baseline variables that were likely to be associated with the occurrence of a textbook outcome were tested by univariate analysis. The association with the occurrence of textbook outcome was tested for the following variables: gender, age at diagnosis, temperature, body mass index (BMI), ASA classification, histology, tumor size, location, tumor depth, tumor grade, necrosis on imaging, neoadjuvant systemic therapy, neoadjuvant radiotherapy, hemoglobin (Hb), leukocytes, NLR, PLR, albumin, CRP, and IL-6. Only significant variables at univariate analysis were entered in the logistic regression model. Statistical analysis was performed using IBM SPSS statistical software version 27.0. Figures were created using GraphPad Prism version 9.0.2.

Table 1
Baseline characteristics (median (IQR) or n (%)). Abbreviations: ASA: American Society of Anesthesiology, BMI: body mass index, CRP: C-reactive protein, Dediff. liposarcoma: Dedifferentiated liposarcoma, GIST: gastrointestinal stromal tumor, Hb: hemoglobin, IL-6: interleukin 6, Max: maximum, MPNST: malignant peripheral nerve sheath tumor, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, sarcoma NOS: sarcoma not otherwise specified, SFT: solitary fibrous tumor, UPS: Undifferentiated Pleiomorphic Sarcoma, WBC count: white blood cell count.

Variable	IL-6 < 7 ng/l	IL-6 ≥ 7 ng/l	p-value	Total
N	80 (67.8)	38 (32.2)		118
Demographics				
Gender, n (%)			0.284	
Male	40 (50)	23 (60.5)		63 (53.4)
Female	40 (50)	15 (39.5)		55 (46.6)
Age at first visit, n (%)			0.015	
<50 years	26 (32.5)	3 (7.9)		29 (24.6)
50–70 years	39 (48.8)	25 (65.8)		64 (54.2)
>70 years	15 (18.8)	10 (26.3)		25 (21.2)
Patient and tumor characteristics				
Temperature (median, IQR)	36.6 (36.2–36.8)	36.8 (36.2–37.2)	0.233	36.6 (36.2–36.9)
BMI, n (%)			<0.001	
Normal (18.5–24.9)	43 (55.8)	7 (18.9)		50 (43.9)
Overweight (25–29.9)	18 (23.4)	22 (59.5)		40 (35.1)
Obesity (>29.9)	16 (20.8)	8 (21.6)		24 (21.1)
ASA classification, n (%)			0.025	
1	42 (52.5)	10 (26.3)		52 (44.1)
2	30 (37.5)	23 (60.5)		53 (44.9)
3	8 (10)	5 (13.2)		13 (11)
Histology, n (%)			0.007	
GIST	18 (22.5)	3 (7.9)		21 (17.8)
Leiomyosarcoma	11 (13.8)	8 (21.1)		19 (16.1)
Sarcoma NOS	6 (7.5)	7 (18.4)		13 (11)
Dediff. liposarcoma	5 (6.3)	7 (18.4)		12 (10.2)
Myxoid liposarcoma	8 (10)	0		8 (6.8)
UPS	2 (2.5)	5 (13.2)		7 (5.9)
Dermal sarcoma	4 (5)	1 (2.6)		5 (4.2)
Angiosarcoma	4 (5)	1 (2.6)		5 (4.2)
MPNST	3 (3.8)	1 (2.6)		4 (3.4)
Myxofibrosarcoma	1 (1.3)	2 (5.3)		3 (2.5)
Synovial sarcoma	3 (3.8)	0		3 (2.5)
Pleiomorphic liposarcoma	1 (1.3)	1 (2.6)		2 (1.7)
SFT	1 (1.3)	0		1 (0.8)
Other	13 (16.3)	2 (5.3)		15 (12.7)
Max. tumor size, n (%)			<0.001	
<5 cm	30 (37.5)	3 (7.9)		33 (28)
5–10 cm	33 (41.3)	10 (26.3)		43 (36.4)
>10 cm	17 (21.3)	25 (65.8)		42 (35.6)
Location, n (%)			0.619	
Retroperitoneal, intra-abdominal, pelvic	34 (42.5)	18 (47.4)		52 (44.1)
Other	46 (57.5)	20 (52.6)		66 (55.9)
Tumor depth, n (%)			0.364	
Superficial	16 (20)	5 (13.2)		21 (17.8)
Deep	64 (80)	33 (86.8)		97 (82.2)
Tumor grade, n (%)			<0.001	
Low	34 (44.7)	1 (2.8)		35 (31.3)
High	42 (55.3)	35 (97.2)		77 (68.8)
Necrosis on imaging, n (%)			0.003	
No	68 (86.1)	22 (61.1)		90 (78.3)
Yes	11 (13.9)	14 (38.9)		25 (21.7)
Neoadjuvant systemic therapy, n (%)			0.540	
No	63 (78.8)	28 (73.7)		91 (77.1)
Yes	17 (21.3)	10 (26.3)		27 (22.9)
Neoadjuvant radiotherapy, n (%)			0.150	
No	57 (71.3)	22 (57.9)		79 (66.9)

(*continued on next page*)

Table 1 (*continued*)

Variable	IL-6 < 7 ng/l	IL-6 ≥ 7 ng/l	p-value	Total
Yes	23 (28.7)	16 (42.1)		39 (33.1)
Baseline clinical laboratory results				
Hb, n (%)			<0.001	
Male <8.5, Female <7,5 mmol/l	12 (15)	24 (63.2)		36 (30.5)
Male ≥8.5, Female ≥7.5 mmol/l	68 (85)	14 (36.8)		82 (69.5)
WBC count, n (%)			<0.001	
≤10,5 × 10^9/l	77 (96.3)	23 (60.5)		100 (84.7)
>10,5 × 10^9/l	3 (3.8)	15 (39.5)		18 (15.3)
NLR, (median, IQR)	2.3 (1.7–3.1)	4.2 (2.5–6.7)	<0.001	2.6 (1.9–4.03)
PLR, (median, IQR)	147.9 (114.6–172.3)	216.5 (145.3–297.7)	<0.001	161.2 (124.9–210.2)
Albumin, n (%)			<0.001	
<35 g/l	0	6 (15.8)		6 (5.1)
≥35 g/l	80 (100)	32 (84.2)		112 (94.9)
CRP, n (%)			<0.001	
<10 mg/l	63 (94)	3 (10)		66 (68)
≥10 mg/l	4 (6)	27 (90)		31 (32)

3. Results

3.1. Cohort characteristics

Data of 118 patients with primary, non-metastatic STS was collected for textbook outcome analysis. The cohort included 63 men and 55 women with a median age of 60 years (IQR 49.8–70.0). The majority of patients did not have a severe comorbidity (89%) defined as having an American Society of Anesthesiology (ASA) class 3 or greater. Patients were most commonly diagnosed with GIST (17.8%) and leiomyosarcoma (LMS, 16.1%). Median tumor size was 7.6 cm (IQR 4.5–12.6). Most tumors were deeply seated (82.2%) and of a high grade (68.8%). Neoadjuvant radiotherapy or neoadjuvant systemic therapy was given in 33.1% and 22.9% of the patients, respectively. Elevated IL-6 levels were found in 38 (32.2%) of the patients. All clinicopathological parameters are presented in detail in Table 1. Age at first visit ($p = 0.015$), BMI ($p < 0.001$), ASA classification ($p = 0.025$), histology ($p = 0.007$), tumor size ($p < 0.001$), tumor grade ($p < 0.001$), necrosis reported on imaging ($p < 0.003$), Hb ($p < 0.001$), WBC count ($p < 0.001$), NLR ($p < 0.001$), PLR ($p < 0.001$), albumin ($p < 0.001$) and CRP ($p < 0.001$) demonstrated to be different for the two IL-6 groups.

The correlations of IL-6 levels and clinical parameters of patients in the cohort are shown in Table 2. IL-6 serum levels showed a significant positive correlation with BMI ($\rho = 0.254$, $p = 0.006$), tumor size ($\rho = 0.378$, $p = <0.001$), WBC count ($\rho = 0.612$, $p = <0.001$), neutrophils ($\rho = 0.622$, $p = <0.001$), thrombocytes ($\rho = 0.520$, $p = <0.001$), NLR ($\rho = 0.499$, $p = <0.001$), PLR ($\rho = 0.413$, $p = <0.001$), and showed a strong positive correlation with CRP levels ($\rho = 0.795$, $p = <0.001$). Negative correlations with IL-6 levels were found for hemoglobin in males but not in females (male: $\rho = -0.612$, $p = <0.001$; female: $\rho = -0.204$, $p = 0.135$), and albumin level ($\rho = -0.649$, $p = <0.001$).

3.2. Factors associated with textbook outcome

Textbook outcome was achieved in 35.6% of the patients, as displayed in Fig. 1A. Reasons not to achieve textbook outcome were mostly readmission, complications and a prolonged hospital stay.

Factors contributing to textbook outcome were assessed by univariate and multivariable analysis. The univariate analysis showed that a smaller tumor size ($p = 0.026$), lower tumor grade ($p = 0.006$), normal Hb ($p = 0.044$), normal WBC count ($p = 0.018$), normal CRP ($p = 0.002$) and normal IL-6 ($p = 1.5 \times 10^{-5}$) were significantly associated with achieving a textbook outcome.

Table 2
Correlation of IL-6 (ng/l) with patient and tumor characteristics and clinical laboratory results. Abbreviations: BMI: body mass index, CRP: C-reactive protein, Hb: hemoglobin, IL-6: interleukin 6, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, WBC count: white blood cell count.

Variables	unit	n	Spearman ρ	p-value
Patient and tumor characteristics				
Preoperative temperature	°C	69	0.183	0.133
BMI at first visit	kg/m^2	114	0.254	0.006
Maximum tumor size	cm	118	0.378	<0.001
Baseline clinical laboratory results				
Hb	mmol/l			
Male		63	−0.619	<0.001
Female		55	−0.204	0.135
WBC count	x 10^9/l	118	0.612	<0.001
Neutrophils	x 10^9/l	118	0.622	<0.001
Thrombocytes	x 10^9/l	118	0.520	<0.001
NLR		118	0.499	<0.001
PLR		118	0.413	<0.001
CRP	mg/l	97	0.795	<0.001
Albumin	g/l	118	−0.649	<0.001

Fig. 1B displays the results of textbook outcome achievement in patients with normal IL-6 serum levels (48.8%) versus patients with elevated IL-6 serum levels (7.9%) ($p < 0.001$). For all individual outcomes that were included in the textbook outcome measure, patients with elevated IL-6 levels were less likely to achieve these outcomes. In particular, no transfusion ($p < 0.001$), no reoperation ($p = 0.012$, no readmission ($p = 0.011$), no complications ($p = 0.002$) and no prolonged hospital stay ($p < 0.001$) showed statistically significant differences for patients with elevated IL-6 levels compared to patients with normal IL-6 levels.

Table 3 reports the variables that were entered in the logistic regression model. Since CRP and IL-6 were strongly correlated ($\rho = 0.795$, $p = <0.001$), logistic regression was performed for both variables separately, each with tumor size, tumor grade, Hb and WBC count as covariates. By adding those variables in the

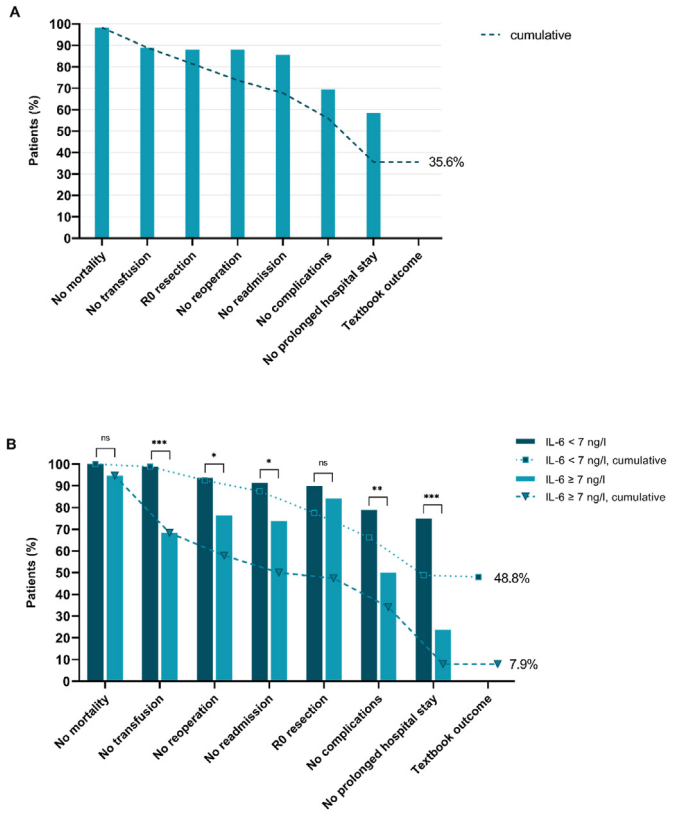

Fig. 1. A. Textbook outcome distribution (per item and cumulative) for patients with primary, non-metastatic STS that underwent resection. B. Textbook outcome distribution stratified by IL-6 groups. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

multivariable analysis, only a high IL-6 level (odds radio (OR) 0.139, confidence interval (CI) 0.027–0.730, $p = 0.020$) showed to be predictive for not achieving textbook outcome. None of the other variables included in multivariable analysis showed a significant effect on achieving textbook outcome.

4. Discussion

Our study suggests a relation between systemic inflammation and a deteriorated post-operative outcome after resection of a primary, non-metastatic STS. Preoperative elevated serum IL-6 shows to be predictive for not achieving a textbook outcome after STS surgery. In our current cohort, patients with normal IL-6 levels achieved textbook outcome in 48.8% of cases, while only 7.9% of the patients with elevated IL-6 levels achieved textbook outcome.

Since previous studies proposed the prognostic relevance of IL-6 for various cancer types, we were interested to study the role of IL-6 in STS. To our knowledge, this is the first study in STS that investigates the relationship of IL-6 levels and postoperative outcome. Earlier studies reported an association between IL-6 elevation and worse survival among STS patients [21,36]. In a study by Rutkowski et al., IL-6 levels showed to be prognostic for survival and to correlate with clinicopathological features such as tumor size [22], which is in line with the findings in our study. An earlier study evaluated the relationship between cytokine serum levels and hematological alterations during routine blood tests in STS; neutrophilia, leukocytosis, thrombocytosis, and low hemoglobin levels were correlated with the elevation of IL-6 and other cytokines [37]. Abnormalities in hematological parameters were also found in our current study. Moreover, other inflammatory serum markers such as NLR, PLR, and CRP, were found to be important prognostic factors in STS as well [38–44].

Table 3
Univariate and multivariable analysis of demographic, clinical characteristics and textbook outcome of patients undergoing resection for primary, non-metastatic STS (n (%)).Abbreviations: CRP: C-reactive protein, Hb: hemoglobin, IL-6: interleukin 6, WBC count: white blood cell count.

Variable	**Missing (%)**	Textbook outcome		Univariate analysis	Multivariable analysis		
		No	**Yes**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Tumor size, n (%)	0			**0.026**			
<5 cm		15 (19.7)	18 (42.9)				
5–10 cm		30 (39.5)	13 (31)				
>10 cm		31 (40.8)	11 (26.2)				
Tumor grade, n (%)	5.1			**0.006**			
Low		16 (22.2)	19 (47.5)				
High		56 (77.8)	21 (52.5)				
Hb, n (%)	0			**0.044**			
Male <8.5, Female <7,5 mmol/l		28 (36.8)	8 (19)				
Male ≥8.5, Female ≥7.5 mmol/l		48 (63.2)	34 (81)				
WBC count, n (%)	0			**0.018**			
$\leq 10.5 \times 10^9$/l		60 (78.9)	40 (95.2)				
$>10.5 \times 10^9$/l		16 (21.1)	2 (4.8)				
CRP, n (%)	17.8			**0.002**			
<10 mg/l		36 (57.1)	30 (88.2)				
≥10 mg/l		27 (42.9)	4 (11.8)				
IL-6, n (%)	0			**1.5 x 10–5**			
<7 ng/l (reference)		41 (53.9)	39 (92.9)				
≥7 ng/l		35 (46.1)	3 (7.1)		0.115	0.021–0.623	0.012

To date, the underlying mechanisms leading to elevated IL-6 and the concurrent inflammatory processes in STS patients are not quite clear. One could speculate that the tumor microenvironment is the primary source of IL-6 production caused by the autocrine capacity of the tumor cells, supported by macrophages, myeloid-derived suppressor cells, $CD4^+$ T-cells and fibroblasts that secrete IL-6 in the tumor microenvironment [45]. There may be a link between tumor necrosis and an increased local IL-6 production, but if this is a causal relationship is not known [46]. Moreover, whether IL-6 that is secreted in the tumor microenvironment leads to an increased IL-6 serum level, or if this is the result of a systemic immune reaction is still unresolved [47]. In any case, the resulting systemic inflammation not only enhances tumor growth but is suggested to affect other processes as well.

This study utilized textbook outcome to assess IL-6 as a predictor for postoperative outcome among STS patients. Our textbook outcome definition was adapted based on previous studies, as a standardized definition has not been established for STS. Taken our entire study cohort together, textbook outcome was achieved in 35.6% of cases. This result is comparable to a study among retroperitoneal sarcomas by Wiseman et al. in which 34.9% of patients reached a textbook outcome [30]. Two other studies in STS show much higher rates for retroperitoneal (54%) and extremity (56%) STS [31,32]. This dissimilarity could be explained by a less strict textbook outcome definition composed out of fewer parameters, lacking the occurrence of complications, blood transfusions and reoperations. However, their importance should not be underestimated: Wiseman et al. showed complications and blood transfusions as two of the most frequent events preventing a textbook outcome for retroperitoneal sarcoma [30].

Our present study reveals a relationship between decreased textbook outcome and cancer-associated systemic inflammation, as measured by IL-6 plasma levels. Univariate analysis showed tumor size, tumor grade, Hb, WBC count, CRP and IL-6 all to be associated with textbook outcome, however, after correction by multivariable analysis this effect was only found for IL-6. This suggests that IL-6 could provide valuable information to predict the preoperative course, and could help to increase awareness for postoperative complications. As an example, increased IL-6 levels in STS may function as a biomarker that could be used to identify patients that need immediate surgery or to select patients to undergo primary surgery without any neoadjuvant treatment, since the patient's condition may deteriorate during neoadjuvant therapy. Whether IL-6 functions simply as a marker for inflammatory tumors correlated with worsened postoperative outcomes or as a true inducer of the inflammatory process that leads to the development of those complications is not fully understood. The latter seems most reasonable, as it can be imagined that the immune system has a role in the pathogenesis of complications, particularly the ones of an inflammatory nature [48]. More studies are needed to confirm the role of IL-6 as a potential key player in inducing systemic inflammation in STS.

To improve outcomes after surgery, patients at risk for complications could be offered interventions to lower the risk of postoperative complications, such as preoperative prehabilitation programs that are composed of both exercise and a (immuno) nutritional program that has been studied for abdominal surgery [49–51]. Other interventions could include the dampening of the inflammation by the use of immunomodulatory drugs [52]. Selective IL-6 inhibitors such as tocilizumab demonstrated normalization of CRP levels in rheumatoid arthritis and Castleman disease and have been extensively studied for the treatment of COVID-19 associated hyperinflammation [53,54]. For ovarian cancer, tocilizumab was investigated to lower platinum drug resistance and improve the host immunity [55]. Treatment with tocilizumab resulted in lower IL-6 and CRP levels, but clinical efficacy in terms of oncological outcome was not demonstrated. Further studies are needed to investigate the role and cost-efficiency of this treatment strategy in cancer, but the availability of IL-6 inhibitors could make IL-6 a potentially interesting target.

This study has several limitations. The first limitation is the retrieval of retrospective data from the patients in the study, resulting in missing data and a lack of relevant data such as temperature, other cytokines in the blood, pain scores, and performance status. Second, 'tumor grade' was based on different classifiers: either mitotic count for GIST or the FNCLCC system for other STS, since there is no uniform classification system to apply on both histologies. Third, our cohort consists of tumors at different anatomic locations and this could be a disadvantage when choosing the most optimal resection margin for a textbook outcome definition since for retroperitoneal liposarcoma R0 and R1 are usually combined while this is not the case in extremity sarcoma. Also, different locations require different surgical strategies and this might impact textbook outcome, although neo adjuvant treatment, tumor location and tumor depth did not show any effect on textbook outcome in univariate analysis. Fourth, the different histologic STS subtypes that were pooled create a bias. However, the findings may be true for STS surgery in general.

In summary, this study reveals that increased IL-6 is an important predictor for worse postoperative outcome, determined by not achieving textbook outcome after surgery of a primary, non-metastatic STS. More prospective studies are needed to assess the clinical relevance of elevated IL-6 levels and whether this phenomenon can be used to better tailor treatment for STS.

CRediT authorship contribution statement

P. van der Laan: Conceptualization, Study design, Data curation, Quality control of data and algorithms, Formal analysis, and interpretation, Statistical analysis, Manuscript preparation, Writing – review & editing. **W.T.A. van der Graaf:** Conceptualization, Study design, Writing – review & editing. **S.J.M. Reijers:** Data curation, Writing – review & editing. **Y.M. Schrage:** Writing – review & editing. **J.J.H. Hendriks:** Data curation, Writing – review & editing. **R.L. Haas:** Writing – review & editing. **D. van den Broek:** Writing – review & editing. **N. Steeghs:** Study design, Writing – review & editing. **W.J. van Houdt:** Conceptualization, Study design, Data curation, Formal analysis, and interpretation, Manuscript preparation, Writing – review & editing.

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.

Acknowledgements

None.

References

[1] WHO Classification of Tumours Editorial Board. WHO classification of tumours of soft tissue and bone. fifth ed. IARC Press; 2020.
[2] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature Jul 24 2008;454(7203):436–44.
[3] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. Mar 19 2010;140(6):883–99.
[4] Faria SS, Fernandes Jr PC, Silva MJ, et al. The neutrophil-to-lymphocyte ratio: a narrative review. Ecancermedicalscience 2016;10:702.
[5] Zhou X, Du Y, Huang Z, et al. Prognostic value of PLR in various cancers: a meta-analysis. PLoS One 2014;9(6):e101119.

[6] McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care May 2009;12(3):223–6.
[7] Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol 2015;16(5):448–57. May.
[8] Kishimoto T. IL-6: from its discovery to clinical applications. Int Immunol May 2010;22(5):347–52.
[9] Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat Rev Immunol Dec 2018;18(12):773–89.
[10] Kumari N, Dwarakanath BS, Das A, Bhatt AN. Role of interleukin-6 in cancer progression and therapeutic resistance. Tumour Biol 2016;37(9):11553–72. Sep.
[11] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357(9255):539–45.
[12] Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 2018;15(4):234–48. Apr.
[13] Grivennikov S, Karin M. Autocrine IL-6 signaling: a key event in tumorigenesis? Cancer Cell 2008;13(1):7–9. Jan.
[14] Silva EM, Mariano VS, Pastrez PRA, et al. High systemic IL-6 is associated with worse prognosis in patients with non-small cell lung cancer. PLoS One 2017;12(7):e0181125.
[15] Cai C, Peng X, Zhang Y. Serum IL-6 level predicts the prognosis and diagnosis in cervical cancer patients. Int J Womens Health 2022;14:655–63.
[16] Salgado R, Junius S, Benoy I, et al. Circulating interleukin-6 predicts survival in patients with metastatic breast cancer. Int J Cancer 2003;103(5):642–6. Feb 20.
[17] Knüpfer H, Preiss R. Serum interleukin-6 levels in colorectal cancer patients–a summary of published results. Int J Colorectal Dis 2010;25(2):135–40. Feb.
[18] Szczepanik AM, Scislo L, Scully T, et al. IL-6 serum levels predict postoperative morbidity in gastric cancer patients. Gastric Cancer Aug 2011;14(3):266–73.
[19] Nguyen DP, Li J, Tewari AK. Inflammation and prostate cancer: the role of interleukin 6 (IL-6). BJU Int 2014;113(6):986–92. Jun.
[20] Browning L, Patel MR, Horvath EB, Tawara K, Jorcyk CL. IL-6 and ovarian cancer: inflammatory cytokines in promotion of metastasis. Cancer Manag Res 2018;10:6685–93.
[21] Hagi T, Nakamura T, Iino T, et al. The diagnostic and prognostic value of interleukin-6 in patients with soft tissue sarcomas. Sci Rep Aug 29 2017;7(1):9640.
[22] Rutkowski P, Kaminska J, Kowalska M, Ruka W, Steffen J. Cytokine serum levels in soft tissue sarcoma patients: correlations with clinico-pathological features and prognosis. Int J Cancer Aug 1 2002;100(4):463–71.
[23] Busweiler LA, Schouwenburg MG, van Berge Henegouwen MI, et al. Textbook outcome as a composite measure in oesophagogastric cancer surgery. Br J Surg May 2017;104(6):742–50.
[24] Heidsma CM, Hyer M, Tsilimigras DI, et al. Incidence and impact of Textbook Outcome among patients undergoing resection of pancreatic neuroendocrine tumors: results of the US Neuroendocrine Tumor Study Group. J Surg Oncol 2020;121(8):1201–8. Jun.
[25] Kalff MC, Vesseur I, Eshuis WJ, et al. The association of textbook outcome and long-term survival after esophagectomy for esophageal cancer. Ann Thorac Surg Oct 2021;112(4):1134–41.
[26] Levy J, Gupta V, Amirazodi E, et al. Textbook outcome and survival in patients with gastric cancer: an analysis of the population registry of esophageal and stomach tumours in ontario (PRESTO). Ann Surg Jan 1 2022;275(1):140–8.
[27] Ten Berge MG, Beck N, Steup WH, et al. Textbook outcome as a composite outcome measure in non-small-cell lung cancer surgery. Eur J Cardio Thorac Surg Jan 4 2021;59(1):92–9.
[28] van der Kaaij RT, de Rooij MV, van Coevorden F, et al. Using textbook outcome as a measure of quality of care in oesophagogastric cancer surgery. Br J Surg 2018;105(5):561–9. Apr.
[29] Kolfschoten NE, Kievit J, Gooiker GA, et al. Focusing on desired outcomes of care after colon cancer resections; hospital variations in 'textbook outcome. Eur J Surg Oncol 2013;39(2):156–63. . Feb.
[30] Wiseman JT, Ethun CG, Cloyd JM, et al. Analysis of textbook outcomes among patients undergoing resection of retroperitoneal sarcoma: a multi-institutional analysis of the US Sarcoma Collaborative. J Surg Oncol 2020;122(6):1189–98. Nov.
[31] Lazarides AL, Cerullo M, Moris D, Brigman BE, Blazer DG, Eward WC. Defining a textbook surgical outcome for patients undergoing surgical resection of intermediate and high-grade soft tissue sarcomas of the extremities. J Surg Oncol Oct 2020;122(5):884–96.
[32] Moris D, Cerullo M, Nussbaum DP, Blazer 3rd DG. Textbook outcomes among patients undergoing retroperitoneal sarcoma resection. Anticancer Res 2020;40(4):2107–15. Apr.
[33] Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. *Int J Cancer*. Jan 15 1984;33(1):37–42.
[34] Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130(10):1466–78. Oct.
[35] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250(2):187–96. Aug.
[36] Nakamura K, Nakamura T, Iino T, et al. Expression of interleukin-6 and the interleukin-6 receptor predicts the clinical outcomes of patients with soft tissue sarcomas. Cancers 2020;12(3):585. Mar 3.
[37] Ruka W, Rutkowski P, Kaminska J, Rysinska A, Steffen J. Alterations of routine blood tests in adult patients with soft tissue sarcomas: relationships to cytokine serum levels and prognostic significance. Ann Oncol 2001;12(10):1423–32. Oct.
[38] Nakamura T, Matsumine A, Matsubara T, Asanuma K, Uchida A, Sudo A. The combined use of the neutrophil-lymphocyte ratio and C-reactive protein level as prognostic predictors in adult patients with soft tissue sarcoma. J Surg Oncol 2013;108(7):481–5. Dec.
[39] Szkandera J, Absenger G, Liegl-Atzwanger B, et al. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer Apr 30 2013;108(8):1677–83.
[40] Choi ES, Kim HS, Han I. Elevated preoperative systemic inflammatory markers predict poor outcome in localized soft tissue sarcoma. Ann Surg Oncol 2014;21(3):778–85. Mar.
[41] Que Y, Qiu H, Li Y, et al. Preoperative platelet-lymphocyte ratio is superior to neutrophil-lymphocyte ratio as a prognostic factor for soft-tissue sarcoma. BMC Cancer Oct 2 2015;15:648.
[42] Liu G, Ke LC, Sun SR. Prognostic value of pretreatment neutrophil-to-lymphocyte ratio in patients with soft tissue sarcoma: a meta-analysis. Sep Medicine (Baltimore) 2018;97(36):e12176.
[43] Viñal D, Martinez D, Garcia-Cuesta JA, et al. Prognostic value of neutrophil-to-lymphocyte ratio and other inflammatory markers in patients with high-risk soft tissue sarcomas. Clin Transl Oncol Oct 2020;22(10):1849–56.
[44] Griffiths TT, Arango MWF, Smith IM, Wade RG. The baseline neutrophil lymphocyte ratio predicts survival in soft-tissue sarcoma: a 17-year cohort study. J Plast Reconstr Aesthetic Surg 2022;75(4):1372–9. Apr.
[45] Fisher DT, Appenheimer MM, Evans SS. The two faces of IL-6 in the tumor microenvironment. Semin Immunol 2014;26(1):38–47. Feb.
[46] Guthrie GJ, Roxburgh CS, Horgan PG, McMillan DC. Does interleukin-6 link explain the link between tumour necrosis, local and systemic inflammatory responses and outcome in patients with colorectal cancer? Cancer Treat Rev 2013;39(1):89–96. Feb.
[47] Lippitz BE, Harris RA. Cytokine patterns in cancer patients: a review of the correlation between interleukin 6 and prognosis. OncoImmunology May 2016;5(5):e1093722.
[48] Plas M, Rutgers A, van der Wal-Huisman H, et al. The association between the inflammatory response to surgery and postoperative complications in older patients with cancer; a prospective prognostic factor study. *J Geriatr Oncol*. 2020;11(5):873–9. Jun.
[49] Trepanier M, Minnella EM, Paradis T, et al. Improved disease-free survival after prehabilitation for colorectal cancer surgery. Ann Surg 2019;270(3):493–501. Sep.
[50] Heger P, Probst P, Wiskemann J, Steindorf K, Diener MK, Mihaljevic AL. A systematic review and meta-analysis of physical exercise prehabilitation in major abdominal surgery (PROSPERO 2017 CRD42017080366). J Gastrointest Surg 2020;24(6):1375–85. Jun.
[51] Shen J, Dai S, Li Z, et al. Effect of enteral immunonutrition in patients undergoing surgery for gastrointestinal cancer: an updated systematic review and meta-analysis. Front Nutr 2022;9:941975.
[52] Wang AS, Armstrong EJ, Armstrong AW. Corticosteroids and wound healing: clinical considerations in the perioperative period. Am J Surg 2013;206(3):410–7. Sep.
[53] Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood*. Nov 15 2008;112(10):3959–64.
[54] Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with covid-19 pneumonia. N Engl J Med Jan 7 2021;384(1):20–30.
[55] Dijkgraaf EM, Santegoets SJ, Reyners AK, et al. A phase I trial combining carboplatin/doxorubicin with tocilizumab, an anti-IL-6R monoclonal antibody, and interferon-alpha2b in patients with recurrent epithelial ovarian cancer. Ann Oncol Oct 2015;26(10):2141–9.