C-reactive protein and related predictors in soft tissue sarcoma (Review)

TOMOKI NAKAMURA, KUNIHIRO ASANUMA, TOMOHITO HAGI and AKIHIRO SUDO

Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Tsu, Mie 514-8507, Japan

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Abstract. C-reactive protein (CRP) is a useful predictor of poor survival in patients with several types of cancer because inflammation is strongly associated with cancer progression. The production of CRP in hepatocytes appears to be primarily induced at the transcriptional level following the elevation of circulating interleukin-6 (IL-6), which is produced by various cell types, including cancer cells and cancer-associated fibroblasts. Serum CRP levels are associated with serum IL-6 levels in patients with soft tissue sarcoma (STS). Additionally, patients with elevated CRP levels had worse oncological outcomes than those with normal CRP levels. It has been attempted to combine CRP levels with other inflammatory or immune markers, and the utility of this has been demonstrated. Therefore, a novel treatment strategy should be developed for patients with STS with elevated CRP levels. The present review aimed to clarify the role of CRP levels and related tools in predicting clinical outcomes in patients with STS.

Contents

Correspondence to: Dr Tomoki Nakamura, Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
E-mail: tomoki66@clin.medic.mie-u.ac.jp

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1. Introduction

Soft tissue sarcoma (STS) is a rare and heterogeneous tumour with an incidence of STS is fewer than 6 cases per 100,000 people (1,2). The prognostic factors for STS are well-known and include tumor size, grade, and age (3-5). The standard treatment is surgical tumor resection with a wide margin (6). This implies the removal of the tumor in a single specimen with a rim of normal tissue around it. Perioperative radiotherapy or chemotherapy may be considered for patients with high-grade STS (6). Radiotherapy should be delivered at a total dose of 50 Gy in 1.8-2 Gy fractions in the preoperative setting. In the postoperative setting, doses of up to 66 Gy are administered, depending on clinical presentation, such as age, tumor site, and surgical margins (6). High-grade, large, and deep-seated STS is considered high-risk, and perioperative chemotherapy using doxorubicin and ifosfamide could be a treatment option for of STS (7). However, even after radical treatment of primary STS, as many as 50% of these patients experience local recurrence or distant metastasis (8,9). Patients receiving systemic chemotherapy for widely metastatic or locally advanced diseases are unsuitable for surgery or radiotherapy. Doxorubicin-based chemotherapy is commonly used as first-line chemotherapy (9,10). Pazopanib, trabectedin, and eribulin have been administered since 2012. However, the outcome for metastatic patients remains poor, with a median reported overall survival of 14-20 months (9). Therefore, easy, well-known, and low-cost markers may help to identify a high risk of tumor relapse. Most physicians are familiar with C-reactive protein (CRP) as an inflammatory marker. CRP level is a useful predictor of poor survival in patients with several types of cancer. Herein, we aimed to clarify the role of CRP level in predicting clinical outcomes in patients with STS.

2. Relationship between interleukin (IL)-6, CRP and STS

Virchow observed the infiltration of leucocytes in malignant tissues and proposed the site of chronic inflammation as the origin of cancer in 1863 (11). For the first time, they proposed a relationship between inflammation and carcinogenesis. Some tumors develop at the site of chronic inflammation, and some induce an inflammatory microenvironment in the tumor (12). The inflammatory component is present in the microenvironment of tumor cells, which contain white blood cells, macrophages with cytokines, and chemokines as principal

mediators of inflammation. The inflammatory microenvironment plays a critical role in tumor progression (13,14). Lymphocytes are the most important type of peripheral blood cells involved in cancer cells proliferation, migration, and invasion (15,16). Inflammatory cytokines and chemokines, such as IL-6 and tumor necrosis factor (TNF), which are produced by tumor cells or tumor-associated leucocytes and platelets, may contribute directly to tumor progression (13,14). Because of chronic inflammation at tumor sites, IL-6 is produced by various cell types, including cancer cells and cancer-associated fibroblasts (17). IL-6 also induces CRP production in hepatocytes (Fig. 1) (18). Nakamura *et al* (19) found a relationship between IL-6 and IL-6 receptor (IL-6R) expression in tumor tissues and survival in 86 patients with STSs. Patients exhibiting high expression of both IL-6 and IL-6R in tumors have poor survival. In contrast, patients with low tumor expression of both IL-6 and IL-6R had better survival. They also demonstrated the relationship between serum IL-6 and CRP levels and the expression of IL-6 in tissues. Fu *et al* (20) reported that positive expression of IL-6 and IL-6R in renal cell cancer was significantly associated with poor survival in multivariate analysis. The circumstances around the tumor may reflect systemic inflammatory conditions. Hagi *et al* (21) found that serum IL-6 levels could be useful for differentiating benign soft tissue tumors from STS in 99 patients. Serum IL-6 levels (median: 9.04 pg/ml) in 59 patients with STS were statistically higher than those (3.31 pg/ml) in 40 patients with benign soft tissue tumors. CRP, hemoglobin levels, and tumor grade were strongly correlated with serum IL-6 levels. In the multivariate analysis, they also found that serum IL-6 levels were associated with tumor-related death in 59 patients. Rutkowski *et al* (22) showed that increased serum levels of IL-6 were observed in 61% of STS patients. Serum IL-6 levels are correlated with tumor size and grade (22). The production of CRP in hepatocytes is primarily induced at the transcriptional level following the elevation of circulating IL-6. In renal and esophageal cancers, the immunohistochemical expression of CRP in tumor samples was a prognostic indicator. Cancer cells may increase the production of inflammatory proteins, which may explain their high CRP levels (23,24). However, there are no reports of STS cells.

3. Diagnostic value of serum CRP levels in STS

Clinically, more extensive, or deeper tumors are likely to be STS (3-5). Magnetic resonance imaging (MRI) is important for evaluating soft tissue masses (25,26). Although some lesions can be readily identified based on their imaging characteristics, many soft tissue tumors remain indeterminate and require biopsy for histological diagnosis (27). Identifying additional differential diagnostic markers that are accurate and readily available can facilitate the clinical management of patients with soft tissue tumors. Studies on the association between serum CRP levels and soft-tissue tumor diagnosis, including ours, have been reported in Japanese patients. Nakamura *et al* (28) measured high-sensitivity CRP (Hs-CRP) levels. Serum samples were collected from 14 healthy subjects, 35 patients with benign soft-tissue tumors, and 60 patients with STS. Blood samples were obtained before treatment from 35 patients with benign soft tissue tumors and 60 patients with STS. The Hs-CRP levels in patients with STS were significantly higher than those observed in patients with benign soft tissue tumors and healthy subjects. In the receiver operating characteristic (ROC) analysis, a value of 0.95 μg/ml was found to be an appropriate threshold for identifying patients at risk for diagnosis of STS. The area under the curve is 0.747. Serum hs-CRP levels exhibited a sensitivity and specificity of 50 and 94.3%, respectively, for identifying STS. Ariizumi *et al* (29) analyzed the hematological and chemical abnormalities in 158 benign soft tissue tumors and 201 STSs. The median CRP levels in benign tumors were 0.16 mg/dl, while 1.06 mg/dl in STSs ($P<0.001$). Significant increases in granulocyte count, erythrocyte sedimentation rate (ESR), and γ-glutamyl transpeptidase levels were also found in patients with STSs. Multiple logistic regression analysis showed that tumor size and ESR were independent variables (29). Fujibuchi *et al* (30) analyzed hematological and chemical abnormalities in 457 benign soft tissue tumors, 40 intermediate tumors, such as desmoid tumors, and 91 STSs. The CRP levels were 0.05 mg/dl in benign tumors, 0.07 mg/dl in intermediate tumors, and 0.19 mg/dl in STS, respectively. Multivariable analysis revealed that large tumor size, high white blood cell count, low hemoglobin count, elevated CRP levels, and high lactate dehydrogenase levels were significant predictive factors for STS. Universally, the normal levels of CRP as routine blood at hospitals vary from 0.2 to 1 mg/dl. Although those studies found higher levels of CRP in patients with STS than in those with benign tumors, the median CRP levels in patients with STS were around normal levels. Therefore, the diagnostic value of CRP for identifying patients at risk of STS in real-world practice may be low, although elevated CRP levels may be strongly supportive for identifying STS (Fig. 2).

4. Prognostic value of serum CRP in STS

Preoperative elevated CRP levels are strongly associated with oncological events and poor survival in many types of cancers, such as renal cell, colorectal, lung, gastrointestinal, prostate, and esophageal cancer (31-37). In 2012, Nakamura *et al* (38) reported the relationship between CRP and STS and first showed the predictive value of CRP for event-free survival (EFS) in a multivariate analysis. In total, 102 Japanese patients with primary STS were included in this study. Normal CRP levels at the hospital were < 0.3 mg/dl. Fourteen (32%) of the 44 patients with grade 3 STS, according to the French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system (39), had elevated CRP levels. Nakamura *et al* (40) investigated 332 UK patients with high-grade (FNCLCC grades 2 and 3) STS, and 45.8% of the patients had elevated CRP levels. The normal serum CRP level was < 10 mg/l. CRP elevation was associated with a larger tumor size and advanced clinical stage. In multivariate analysis, they first reported that pre-treatment CRP levels were a poor prognostic factor for disease-specific survival (DSS) and local control in patients with STS. In the last 10 years (38,40-47), the value of CRP for predicting clinical outcomes has been supported by several studies (Table I).

CRP elevation is an independent predictor of survival, EFS, and local recurrence-free survival in STS patients. The cut-off level varied from 0.14 to 1.0 mg/dl (10 mg/l). Many

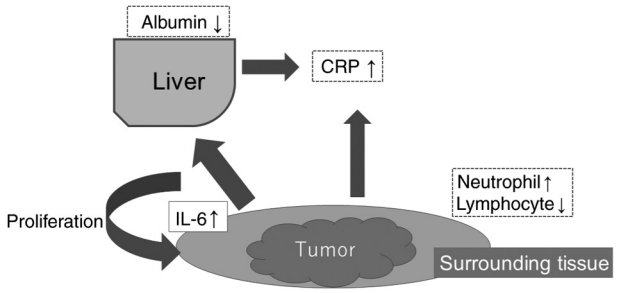

Figure 1. Inflammatory cytokine IL-6 contributes to the development of hypoalbuminemia and elevated CRP levels. Neutrophils release mediators to provide a stimulating microenvironment that allows for more aggressive tumor behavior around the tumor. Conversely, the absolute lymphocyte count is decreased in tumor-induced inflammation. CRP, C-reactive protein; IL-6, interleukin-6.

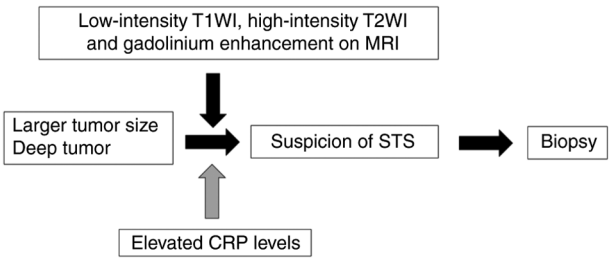

Figure 2. Process of evaluation and biopsy in STS. If elevated CRP levels (above standard levels of CRP) are observed in addition to clinical characteristics such as tumor size and depth, and MRI findings, biopsy should be considered to identify STS. CRP, C-reactive protein; STS, soft tissue sarcoma; T1WI, T1-weighted image; T2WI, T2-weighted image.

studies included all types of STS histology, but two studies included only one histology. Panotopoulos *et al* (43) analyzed 85 Austrian patients with liposarcoma (LPS). Patients with other sub-histologies (e.g. de-differentiated LPS) had more than triple the mean CRP level than patients with well-differentiated LPS (1.58 vs. 0.55 mg/dl, P=0.005). This study identified preoperative CRP (cut-off value=0.87 mg/dl) and alkaline phosphatase (ALP) levels as novel independent predictors of DSS in patients with LPS. Sambri *et al* (44) included 126 Italian patients with high-grade myxofibrosarcoma (MFS). In multivariate analysis, tumor size and grade, preoperative CRP values (cut-off value=0.5 mg/dl) and neutrophil-to-lymphocyte ratio (NLR, cut-off value=3.5) were confirmed to be independent factors for predicting DSS. Yanagisawa retrospectively compared the relationship between CRP levels and survival in patients with and without neoadjuvant radiotherapy (45). They measured CRP levels before upfront surgery and neoadjuvant radiotherapy in 49 Japanese patients with STS. Neoadjuvant radiotherapy is associated with increased CRP levels. However, there was no difference in overall survival (OS) between high (>0.5 mg/dl) and low CRP levels among 49 patients receiving neoadjuvant radiotherapy. In multivariate analysis, CRP was an independent predictor of OS in 49 patients who underwent upfront surgery, while CRP was not associated with survival in 49 patients receiving neoadjuvant radiotherapy. They hypothesized that neoadjuvant radiotherapy might impact the inflammatory microenvironment around tumor cells differently than upfront surgery and alter the interaction of inflammatory markers with the outcome (45,48,49). Although many studies have evaluated CRP levels before initial treatment, Sato *et al* (46) evaluated CRP levels before treatment with pazopanib in patients with advanced STS. They analyzed prospectively collected data from 141 Japanese patients with recurrent or metastatic non-round cell STS who began pazopanib treatment. Multivariate analysis indicated that pre-treatment NLR (cut off value=3.0), LPS histology, primary extremity site, Eastern Cooperative Oncology Group (ECOG) performance status and CRP levels (cut off value=0.3 mg/dl) were independent predictors of predicting OS. More than half of the patients (52%) had elevated CRP levels. Nakamura *et al* (47) also observed elevated CRP levels in 20 (42.6%) of 47 patients with metastasis at initial presentation, indicating that CRP was related to tumor aggressiveness and progression. In summary, CRP may be a useful maker for predicting oncological outcome in STS. However, as a limitation, the heterogeneity of histology and treatment were included in previous studies. Further studies should be necessary as prospective studies for evaluating the validation.

5. Prognostic tool using CRP for predicting survival in STS

Some studies have demonstrated the utility of a combination of CRP levels and other serum markers (Table II). The Glasgow prognostic score (GPS), modified GPS (mGPS), and high-sensitivity mGPS (HS-mGPS) have been shown to predict oncological outcomes in several types of cancers, including STS (50-52). A combination of CRP levels and hypoalbuminemia was applied to these scoring systems. Albumin is the most abundant circulatory protein, and serum albumin levels vary according to the degree of catabolism during normal homeostasis and in the presence of disease (53). Various causes of hypoalbuminemia have been described in patients with cancer. The most important cause is increased catabolism and following cachexia (54). Since 2015, GPS, mGPS, and HS-mGPS have been shown to provide additional prognostic information in patients with STS (55-62). Appropriate GPS may depend on the type of cancer. Recently, Spence *et al* (55) reported 493 STS patients using clinical databases from six collaborating hospitals in three countries. Multivariant Cox regression analysis demonstrated an elevated mGPS was significantly associated with reduced overall survival (HR 1.8 (95% CI 1.1 to 2.9); P=0.007). Therefore, mGPS may be an appropriate tool for predicting survival in STS. Further studies using GPS and HS-mGPS must be considered in multicenter or international institutions.

Other studies reported the utility of a combination of CRP level and absolute lymphocyte count (ALC) in patients with STS (63,64). Peripheral lymphocytes play a critical role in host cell-mediated cytotoxic immunity against tumors by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration. High lymphocytic infiltration into the tumor stroma has been reported to be associated with better survival and superior response to systemic therapy (65). The combination of CRP levels and ALC is considered a surrogate marker of immunity and inflammation in patients with cancer. The lymphocyte-CRP ratio (LCR), the reciprocal of CLR, has been reported as a poor prognostic marker in several types of

Table I. Relationship between threshold of CRP levels and oncological outcomes.

First author/s, year	No.	Histology	CRP levels, mg/dl	Worse outcome	(Refs.)
Nakamura *et al*, 2012	102	L-STS	>0.3	EFS	(38)
Nakamura *et al*, 2013	332	L-STS	>10	DSS, LRFR	(40)
Szkandera *et al*, 2013	304	L-STS	>6.9	CSS, DFS	(41)
Choi *et al*, 2014	162	L-STS	>0.2	DSS, LRFR	(42)
Panotopoulos *et al*, 2015	85	L- or M-LPS	0.87	DSS	(43)
Sambri *et al*, 2020	126	L-MFS	0.5	DSS	(44)
Yanagisawa *et al*, 2018	98	L-STS	0.5	OS	(45)
Sato *et al*, 2021	141	M-STS	0.3	OS	(46)
Nakamura *et al*, 2017	47	M-STS	0.2 or 0.3[a]	DSS	(47)

[a]This was a multi-center study. One institute defined the threshold of CRP as 0.2 mg/dl, while the others defined it as 0.3 mg/dl. CRP, C-reactive protein; CSS, cancer-specific survival; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival; L-, localized; LPS, liposarcoma; LRFR, local recurrence-free survival; M-, metastatic; MFS, myxofibrosarcoma; OS, overall survival; STS, soft tissue sarcoma.

Table II. Predictive tools using CRP in STS.

First author/s, year	No.	Histology	Tool	Outcome	(Refs.)
Spence *et al*, 2022	493	L-STS	mGPS	OS	(55)
Nakamura *et al*, 2015	139	L-STS	Hs-mGPS	DSS, EFS	(56)
Tsuda *et al*, 2017	202	L-STS	Hs-mGPS	EFS	(57)
Jiang *et al*, 2017	165	L-STS	mGPS	PFS	(58)
Aggerholm-Pedersen *et al*, 2019	265	M-STS	GPS	DSS	(59)
Hou *et al*, 2020	454	L-STS	Hs-mGPS	OS	(60)
Mahyudin *et al*, 2020	80	L-STS	mGPS	OS	(61)
Nakamura *et al*, 2022	132	L-STS	LCR	EFS	(63)
Matsui *et al*, 2022	113	L-STS	CLR	OS	(64)
Nakamura *et al*, 2013	142	L- or M-STS	CRP and NLR	DSS	(69)

CLR, C-reactive protein-lymphocyte ratio; CRP, C-reactive protein; DSS, disease-free survival; EFS, event-free survival; GPS, Glasgow prognostic score; Hs-mGPS, high sensitivity Glasgow prognostic score; L-, localized; LCR, lymphocyte-C-reactive protein ratio; M-, metastatic; mGPS, modified Glasgow prognostic score; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; STS, soft tissue sarcoma.

cancer (66-68). In 2022, two studies were published in the field of STS using LCR or CLR (63,64). Matsui *et al* (64) reviewed 113 patients with retroperitoneal STS. Multivariate analysis showed that elevated CLR and de-differentiated LPS were associated with poor overall survival in all retroperitoneal STS cases (64). Interestingly, in de-differentiated LPS, patients with high preoperative CLR, whose postoperative CLR was normalized, demonstrated a favorable survival rate similar to those with low preoperative CLR. Nakamura *et al* (63) analyzed 132 patients with STS and found that LCR might be a prognostic factor for predicting oncological events. However, on Receiver operating characteristic analysis, there was no significant difference in predicting DSS in the area under the curve (AUC) between CRP level and LCR. However, the utility of LCR or CLR for predicting survival in STS were not validated in multicenter international studies. Finally, Nakamura *et al* (69) confirmed whether the combined use of CRP level and NLR before treatment predicted DSS in adult patients with STS. In addition to the role of lymphocytes in the tumor microenvironment (65), neutrophils release mediators to provide a stimulating microenvironment that allows for more aggressive tumor behavior by sustaining cell proliferation and facilitating genomic instability (70). Therefore, NLR has also been reported to be a prognostic factor for predicting survival in cancer patients, including STS (55,71,72). Especially, Spence *et al* (55) also analyzed 493 STS patients from six collaborating hospitals in three countries and showed an elevated NLR (>4) was significantly associated with reduced overall survival (HR 1.5 (95% CI 1.0 to 2.3); P=0.029) in multivariate analysis. Although there is no definitive ratio of

NLR for predicting survival, the subgroup of patients with a high NLR and elevated CRP level is at high risk of oncological events and may represent a study population for a new adjuvant therapy trial in the future.

6. Future perspective

The production of CRP is stimulated in hepatocytes by IL-6 (18). IL-6 first binds to IL-6R. The IL-6/IL-6R complex then associates with the signal-transducing membrane protein gp130, inducing its dimerization to initiate IL-6 signaling (17,73). They regulate the expression of signal transducer and activator of transcription 3 (STAT3), a prooncogenic transcription factor. STAT3 activation induces the expression of numerous effector genes involved in cell proliferation, differentiation, and survival. Thus, the blockade of IL-6/STAT3 signaling cascades may be a promising approach to improve clinical outcomes in cancers.

7. Conclusions

We reviewed the role of CRP in STS. CRP is a surrogate marker of the cancer-related inflammation. CRP and its combined use may be useful tools for predicting oncological outcomes. A new aggressive strategy is necessary to improve future outcomes in patients with elevated CRP levels.

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Availability of data and materials

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

Authors' contributions

TN conceived and designed the study. TN, TH and KA acquired data. TN, TH, KA and AS analyzed and interpreted the data. TN drafted the manuscript. TH created tables and figures. KA and AS edited and reviewed the manuscript. AS was responsible for funding acquisition. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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