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Original Research Article

Association of C-reactive protein with grade of soft tissue sarcoma: a single centre study

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ABSTRACT

Background: Soft tissue sarcomas (STS) are a rare and heterogeneous group of malignant tumors originating from mesenchymal tissues. Tumor grade is a critical prognostic factor in STS, influencing treatment decisions and patient outcomes. Systemic inflammation, reflected by elevated levels of C-reactive protein (CRP), has been associated with tumor aggressiveness and poor prognosis in various cancers. However, the relationship between CRP levels and tumor grade in STS remains underexplored. To evaluate the association between pre-treatment serum CRP levels and histological tumor grade in patients diagnosed with soft tissue sarcoma.
Method: This cross-sectional study was conducted at Bangladesh Medical University (BMU) from December 2023 to December 2024. A total of 71 adult patients with histologically confirmed STS were included. Tumor grade was determined using the FNCLCC grading system, and serum CRP levels were measured prior to treatment. Statistical analyses were performed using SPSS version 27. A p value less than 0.05 was considered statistically significant.
Results: The mean age of participants was 43.65±14.84 years, with a male predominance (59.2%). High-grade STS cases showed significantly elevated CRP levels (mean: 84.14 mg/l) compared to low-grade tumors (mean: 10 mg/l). The association between CRP level and tumor grade was statistically significant ($p<0.001$). ROC analysis revealed excellent discriminative ability of CRP for high-grade STS (AUC=0.944), with an optimal cut-off at 10 mg/l (81% sensitivity, 77% specificity).
Conclusion: Elevated CRP levels are significantly associated with high-grade soft tissue sarcoma, suggesting CRP may serve as a useful, low-cost prognostic biomarker to aid in tumor grading and risk stratification.

Keywords: Soft tissue sarcoma, Tumor grade, C-reactive protein, Inflammation, Prognostic biomarker

INTRODUCTION

Soft tissue sarcomas (STS) are rare malignant tumors deriving from mesenchymal tissue and constitute a heterogeneous group of tumors. Soft tissue sarcomas arise predominantly from embryonic mesoderm but can also arise from ectoderm. Mesodermal cells give rise to the connective tissue throughout the body.[1] STS are comprised of malignant tumors which arise from tissues of mesodermal origin (e.g., fat, muscle, connective tissue, vessels) excluding bone and cartilage.[2] Therefore, soft tissue sarcomas can occur anywhere in the body. The majority of cases seem to arise de novo without an apparent causative factor. There is a slight male

predominance and approximately 10% of patients have detectable metastatic disease (frequently to the lungs) at the time of primary diagnosis. The most common anatomic sites for STS are the extremities (75%) followed by the trunk wall (10%), and retroperitoneum (10%).[3] STSs account for less than 1% of all malignant tumors4. The estimated incidence in Europe is 4-5/100,000 inhabitants.[4] In 2021, the estimated number of new cases in the United States were 13,460 (0.7% of all new cancer cases), with an estimated number of deaths of 5,350 (0.8% of all cancer deaths), based on data from American Cancer Society. At the time of presentation, 60% to 80% of patients have localized disease, whereas 15% to 20% have metastatic disease.[5] In recent years, there has been growing interest in the role of systemic inflammation in cancer biology. Systemic inflammation influences tumor progression, immune evasion, angiogenesis, and metastasis. Biomarkers of systemic inflammation, such as C-reactive protein (CRP), have emerged as valuable tools for understanding the interplay between tumor biology and the host immune response. CRP is an acute-phase reactant synthesized primarily in the liver under the influence of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). While CRP is traditionally used to monitor infections and inflammatory conditions, its role as a prognostic biomarker in cancer is increasingly evident.[6]

Elevated CRP levels have been linked to poor outcomes in various malignancies, including colorectal, breast, lung, and pancreatic cancers.[7] The association between elevated CRP levels and aggressive tumor behavior is thought to arise from chronic inflammation within the tumor microenvironment.[8] Chronic inflammation promotes a cascade of events, including enhanced tumor cell proliferation, resistance to apoptosis, and increased angiogenesis, all of which contribute to tumor progression. In addition, systemic inflammation, reflected by elevated CRP levels, may indicate an immune-suppressive environment that favors tumor survival and dissemination.[9] Several studies in other cancer types have demonstrated that elevated CRP levels are associated with advanced disease stages and worse survival outcomes. For example, in patients with colorectal cancer, high preoperative CRP levels have been correlated with poor differentiation and higher TNM stages.[10] Similarly, in breast cancer, elevated CRP levels have been associated with larger tumor sizes, nodal involvement, and lower overall survival rates.[11] These findings highlight the prognostic significance of CRP in various oncological settings and raise the possibility that CRP may serve a similar role in STS. From a clinical perspective, understanding the association between CRP levels and STS grade could have several implications. First, it could help identify patients at higher risk for aggressive disease who may benefit from more intensive monitoring and treatment. Second, CRP could serve as a marker to track disease progression or response to therapy, complementing imaging and histopathological evaluations.

This study aims to determine the relationship between CRP levels and tumor grade in STS, providing a comprehensive analysis of how systemic inflammation correlates with tumor biology in this rare and heterogeneous group of malignancies.

METHODS

This cross-sectional study was conducted at Bangladesh Medical University (BMU) from December 2023 to December 2024 in the Department of General Surgery & Surgical Oncology, BMU, Dhaka, Bangladesh. A purposive sampling method was used. All patients diagnosed with soft tissue sarcoma (STS) who fulfilled the inclusion and exclusion criteria were enrolled in the study. An ethical clearance was taken from Ethical Clearance Committee of BMU to conduct the study. An informed written consent was obtained from all the participants regarding the study procedure.

Inclusion criteria

Histologically diagnosed cases of soft tissue sarcoma irrespective of age and gender.

Exclusion criteria

Patients with STS treated with neoadjuvant therapy. Patients with recurrent STS. Patients presented with metastasis. Patients presented with sign of inflammation. A pre-formed questionnaire was used for data collection. Data was collected regarding the demographic characteristic of the study population like age, sex, body mass index (BMI) and socio-economic condition. Then Grade of soft tissue sarcoma was identified according to FNCLCC (French Federation of Cancer Centers) to grade malignancy based on differentiation, mitotic count, and necrosis, assigning points (0-3 each) for a total score (Grade 1-3) that predicts prognosis, with higher scores indicating more aggressive tumors, though grading varies by specific sarcoma type.

Tumor differentiation

How much the cancer cells look like normal cells (Well-differentiated: 1, Conventional: 2, Poorly differentiated/ Pleomorphic/Epithelioid: 3).

Mitotic count

Number of dividing cells (e.g., 0-9/10HPF: 1, 10-19/10HPF: 2, >20/10HPF: 3).

Tumor necrosis

Presence of dead tumor cells (No necrosis: 0, <50% necrosis: 1, >50% necrosis: 2)

Low grade STS

Histopathological score 2 and 3 considered as low-grade soft tissue sarcoma.

Intermediate grade STS

Histopathological score 4 and 5 considered as intermediate grade soft tissue sarcoma.

High grade STS

Histopathological score 6, 7 and 8 considered as high-grade soft tissue sarcoma.

Sites and histopathogical type of STS were also documented. The association of CRP and STS was analyzed Association between CRP and tumor grade and stage were also noted separately.

Statistical analyses were performed using SPSS version 27. Descriptive statistics were used to describe the variables in percentage, mean, and SD, as appropriate. The chi-square test was used to test the association between attributes. Receiver operating characteristic curve (ROC) was also plotted to determine the area under curve (AUC) to predict the sensitivity and specificity of CRP. A p value less than 0.05 was considered statistically significant.

RESULTS

A total number of 71 patients were included in the current study. The overall age range of the patients was between 18 and 80 years, with a mean of 43.65±14.84 years and median age 45 years. Male patients (59.15%) were predominant with a male female ratio of 1:1.4. Most frequent site among all patients was retroperitoneum and the thigh with same proportion (22.5%). The most common histopathological diagnosis was spindle cell sarcoma (16.9%). The second most common diagnosis was undifferentiated pleomorphic sarcoma (15.5%) and the third most common one was liposarcoma (12.7%). Majority of patients suffered from low grade STS (n=35). A total number of 71 patients were included in the current study. The overall age range of the patients was between 18 and 80 years, with a mean of 43.65±14.84 years and median age 45 years. Male patients (59.15%) were predominant with a male female ratio of 1:1.4. Most frequent site among all patients was retroperitoneum and the thigh with same proportion (22.5%). The most common histopathological diagnosis was spindle cell sarcoma (16.9%). The second most common diagnosis was undifferentiated pleomorphic sarcoma (15.5%) and the third most common one was liposarcoma (12.7%). Majority of patients suffered from low grade STS (n=35).

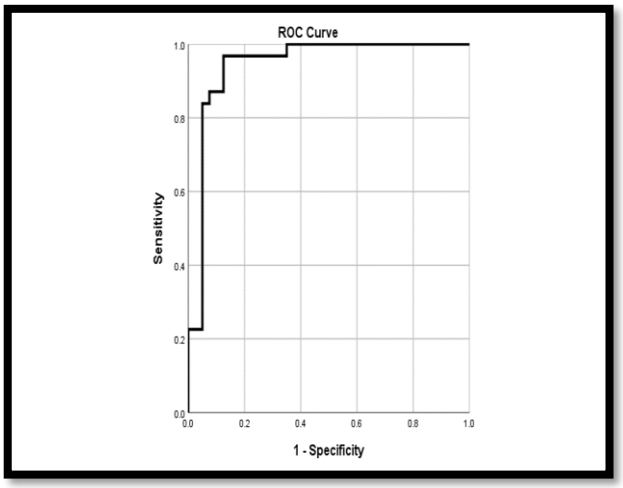

Figure 1: ROC curve analysis of the study population.

The distribution of serum CRP levels across different age groups shows no statistically significant association (χ^2=2.241, p=0.328). Although individuals aged 31–59 years had a higher proportion of elevated CRP (>10 mg/L) compared to younger (18–30 years) and older (60–80 years) participants, the differences were not significant. Among patients with low-grade soft tissue sarcoma (STS), the vast majority (35 out of 37; 94.6%) had a C-reactive protein (CRP) level below 10 mg/l, whereas only 5 cases (14.7%) showed elevated CRP (>10 mg/l). In contrast, among high-grade STS, only 2 cases (5.4%) had CRP below 10 mg/l, while a large proportion (29 cases; 85.3%) showed elevated CRP levels. The observed difference in CRP distribution between low- and high-grade tumors was highly statistically significant (χ^2=45.971; p<0.001). A statistically significant association was observed between tumor stage and CRP level (χ^2=22.607, p<0.001). Elevated CRP (>10 mg/l) was markedly more frequent among patients with Stage III disease (57.6%) compared to those with Stage II disease (42.4%), indicating that higher CRP levels are associated with advanced tumor stage.

Table 1: Characteristics of study population.

Characteristics	Frequency (%)
Sex	
Male	42 (59.15)
Female	29 (40.85)
Age (in years)	
18-39	28 (39.43)
40-59	31 (43.66)

Continued.

Characteristics		Frequency (%)
60-80		12 (16.91)
Mean age±SD in years)	43.65±14.84	
Grade of STS		
Low grade	35 (49.3%)	
Intermediate	5 (7.0%)	
High grade	31 (43.7%)	

Table 2: Histopathological diagnosis of the patients.

Histopathological diagnosis of STS	N (%)
Spindle cell sarcoma	12 (16.90)
Undifferentiated pleomorphic sarcoma	11 (15.50)
Liposarcoma	9 (12.70)
Fibromatosis	6 (8.50)
Well differentiated liposarcoma	6 (8.50)
Fibrosarcoma	5 (7.0)
Rhabdomyosarcoma	4 (5.60)
Malignant peripheral sheath tumor	3 (4.20)
GIST	2 (2.80)
Fibromyxoid sarcoma	2 (2.80)
Benign mesenchymal neoplasm	2 (2.80)
Malignant mixed tumor	1 (1.40)
Osteosarcoma	1 (1.40)
Myofibroblastic tumor	1 (1.40)
Dermatofibroma	1 (1.40)
Fibrous histocytoma	1 (1.40)
Leiomyosarcoma	1 (1.40)
Poorly differentiated sarcoma	1 (1.40)
Ganglioneuroma	1 (1.40)
Synovial biphasic sarcoma	1 (1.40)

Table 3: Sensitivity and specificity of CRP.

Attribute	Sensitivity	Specificity	Youden's Index & cut offs	AUC	P value	95% CI
CRP	81%	77%	10 mg/l	0.944	<0.001	0.88-1.00

Table-4 showing association between CRP and STS of the study population.

Variable	CRP <10 mg/l n (%)	CRP>10 mg/l n (%)	Chi-square value	P value
Age (in years)	10 (27.0)	5 (14.7)		
18-30			2.241	0.328
31-59	20 (54.1)	24 (70.6)		
60-80	7 (18.9)	5 (14.7)		
Tumor grade				
Low grade STS	35 (94.6)	5 (14.7)	45.971	<0.001
High grade STS	2(5.4)	29 (85.3)		
Tumor stage				
Stage II	35 (94.6)	14 (42.4)	22.607	<0.001
Stage III	2(5.4)	19 (57.6)		

DISCUSSION

This cross-sectional study was conducted with the primary objective of determining the association between CRP and grading of soft tissue sarcoma at BMU in Dhaka city on 71 patients diagnosed with soft tissue sarcoma. The overall age range of the patients was between 18 and 80 years, with a mean of 43.65±14.84 years and median age 45 years. In Bangladesh, there is a 72.4-year life expectancy, according to the Bangladesh Bureau of

Statistics.12 The total number of elderly patients aged ≥60 years was 11 in this study showing similarities with other studies.[12,13] The analysis showed that the most common sites of STS were the retroperitoneum (22.5%) and thigh (22.5%). This result represents the usual scenario of soft tissue sarcoma. A study in Australia showed the same result. It showed that thigh was the commonest site of soft tissue sarcoma with 44% proportion. The predominance of spindle cell sarcoma and undifferentiated pleomorphic sarcoma underscores the diversity within STS presentations.[13]

Moreover, the mean CRP value of 42.74 mg/l indicates a significant inflammatory response among the patients. The variation in CRP levels, with a range from 0.59 to 291.83 mg/l, reflects the heterogeneity in disease presentation and patient responses. It is well-documented that CRP, as an acute-phase reactant, responds to inflammation and tissue injury, thus serving as a potential biomarker for disease severity.[14] The critical finding of this study is the statistically significant association between CRP levels and the grading of STS. Patients with high-grade STS exhibited a markedly higher mean CRP value (84.14 mg/l) compared to their low-grade counterparts (10 mg/l). This substantial difference underscores the potential of CRP as a valuable prognostic marker in STS. The χ^2 test results (χ^2=42.163, p<0.001) highlight the robustness of this association. These results coincide with previous studies which demonstrated that serum CRP levels are significantly higher in malignant soft tissue tumors than in benign ones.

The ROC curve analysis further supported this relationship. The area under the curve (AUC=0.944, p<0.001) demonstrated excellent discriminative ability to differentiate high-grade from low-grade sarcomas. The optimal cut-off value of 10 mg/l yielded 81% sensitivity and 77% specificity for predicting high-grade tumors. This suggests that patients with CRP levels above 10 mg/l are considerably more likely to have aggressive sarcomas. CRP therefore has potential as a simple, inexpensive, and effective prognostic biomarker for tumor aggressiveness.[15]

This result coincides with previous studies on the association between serum CRP levels and grading of soft tissue tumor. The CRP levels in patients with STS were significantly higher than those observed in patients with benign soft tissue tumors and healthy subjects.[16] Another study among 457 benign soft tissue tumors also showed lower CRP values in benign and low-grade soft tissue sarcomas and higher CRP values in high grade soft tissue sarcomas.[17] Significantly higher level of CRP was observed in patients with high grade STS. For STS, grade III tumors were associated with a higher CRP level (p=0.05). The biological explanation for this relationship may lie in the interaction between tumor cells and the host immune system. High-grade sarcomas, which exhibit rapid proliferation and greater necrosis, trigger the release of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha. These cytokines stimulate hepatic CRP production. Elevated CRP therefore serves as a surrogate indicator of tumor behavior and micro environmental activity.[18,19] A significant association was also observed between CRP level and tumor stage. Elevated CRP was more common among patients with stage III disease (57.6%) than those with stage II disease (42.4%) (χ^2=22.607, p<0.001). This finding implies that CRP increases with tumor burden and depth of invasion. Advanced stage often indicates larger tumors and possible infiltration into surrounding structures, leading to greater inflammatory response. Thus, elevated CRP can be interpreted as an indirect measure of tumor advancement and systemic reaction.[20]

In contrast, no statistically significant association was found between CRP and patient age (χ^2=2.241, p=0.328). Elevated CRP levels were distributed similarly across all age groups, indicating that inflammation in sarcoma is primarily tumor-driven rather than age-related. While CRP may rise slightly with aging or chronic diseases in the general population, in sarcoma patients its elevation is largely due to tumor biology. This reinforces the concept that CRP is a disease-specific biomarker rather than a demographic one.[21]

The current study had some limitations. It was a single center study with a small sample size. Besides subtyping was not done in STS. Further large-scale multicenter study should be conducted in order to provide a better result.

CONCLUSION

The current study demonstrated that high level of CRP is associated with high grade soft tissue sarcoma. The observed relationships highlight the dual role of CRP as both a marker of systemic inflammation and a potential reflection of tumor biology. So CRP should be done in all patients with STS and association should also be sought for different subtypes of STS.

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