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Original article

Evaluation of C-reactive protein and its prognostic relationship in patients with Hodgkin's Lymphoma

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ABSTRACT

Objectives: To assess the prognostic value of C-Reactive Protein (CRP), at diagnosis and during follow-up, of patients with Hodgkin's Lymphoma treated at the Hematology Service of the Santa Casa de São Paulo Hospital, and to correlate serum CRP levels with disease stage and treatment response.

Methods: A retrospective study involving review of 71 medical records of patients diagnosed with Hodgkin's Lymphoma between February 2012 and January 2016 was performed. Three patients were subsequently excluded, giving a total of 68 patients for analysis. A level of CRP > 1 mg/dl was considered elevated.

Results: Patients were predominantly male (61.8 %) and mean age was 34 years. Fifty-three (78 %) patients had advanced stage and (76.5 %) had B symptoms. Elevated baseline CRP was associated with greater likelihood of B symptoms (p = 0.02) and of advanced stage (p = 0.015). Patients with Low CRP level after 5th and 6th cycles of chemotherapy was associated with complete response (p = 0.04 and p = 0.03, respectively). Treatment-refractory patients had greater risk of death (p = 0.002).

Conclusion: CRP is clinically important for follow-up of patients with Hodgkin's Lymphoma, where high levels were associated with advanced disease and/or presence of B symptoms. CRP level was considered a predictor of treatment response. Persistence of high CRP values during treatment was associated with refractoriness.

Introduction

Hodgkin's Lymphoma (HL) is a rare malignancy involving the lymphatic system (lymph nodes, liver, spleen and bone marrow). The condition accounts for 10 % of all lymphomas and around 0.6 % of all cancer diagnosed worldwide annually. Around 8500 new cases, and roughly 1120 deaths, are attributable to HL in the United States annually.[1]

The association between inflammation and cancer has long been reported and a host of inflammatory parameters have been linked with the development of cancer and with disease progression. Numerous studies have shown that high C-Reactive Protein (CRP) levels are associated with worse

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prognosis for various solid tumors, such as esophageal cancer, colorectal cancer, renal cell carcinoma, hepatocellular carcinoma and lung cancer.[2]

Acute-phase reactants (APR) are defined at proteins whose concentrations increase by at least 25 % during inflammatory states. In spite of the name, acute-phase response accompanies both acute and chronic inflammatory states and is associated with a wide array of disorders, including infection, trauma, infarction, autoimmune diseases and neoplasms.[3]

C-Reactive Protein was first described in 1930 by Tillett and Francis, who noted its ability to precipitate the C-polysaccharide of the pneumococcal cell wall. Since its discovery, CRP has become widely used as a non-specific, yet sensitive marker of inflammation. It is synthesized by hepatocytes and induced by pro-inflammatory cytokines, mainly IL-6 and, to a lesser extent, IL-1 and tumor necrosis factor alpha (TNF-α).[4] In lymphomas, elevated CRP levels reflect increase in inflammatory cytokines, particularly Interleukin-6 (IL-6), which are associated with malignant processes. IL6 induces the production of CRP by the liver. In HL patients, this cytokine is produced by the cells of the lymphoma.[5] CRP production rises within 4–6 h after onset of the inflammatory process, doubling every 8 h and peaking at approximately 36–50 h thereafter. Levels remain high during inflammation and rapidly return to normal upon resolution of the inflammation. The rapid kinetics of the metabolism of CRP, which closely resemble the inflammatory course, serves as an acute measure of disease activity. CRP is superior to other acute-phase reactants, whose elevation phase is much slower.[5,6]

In a previous study at the Irmandade da Santa Casa de Misericórdia de São Paulo (SCMSP) by our group, a relationship was identified between CRP level and prognosis in patients with HL that were poor responders. CRP is a simple, inexpensive and easy-to-perform exam and thus lends itself for routine use. Although CRP is no substitute for more specific and sensitive tests, it can aid interpretation of CT when functional imaging is not available. The importance of the theme prompted further exploration, following on from the previous study. The aim of the present study was to determine CRP at initial stage and associate response and recurrence in patients with HL.

The objectives were to demonstrate the prognostic value of C-Reactive Protein, through the relationship of CRP level with disease stage or presence of B symptoms, and to assess the association between CRP values and treatment response of patients with HL.

Methods

A retrospective study involving an analysis of data from medical records of patients with HL treated at the Hematology Outpatient Clinic of Santa Casa de São Paulo Hospital (SCMSP) between February 2012 and January 2016 was performed. Patients aged with incomplete medical records or without response data for first line of treatment at time of analysis were excluded. This study was approved by the Research Ethics Committee CEP-CONEP.

The variables analyzed were: gender, age, Ann Arbor stage (I to IV), bulky mass, localized or advanced stage, favorable or unfavorable disease, IPS (International Prognostic Score), treatment type (chemotherapy and/or radiotherapy), assessment of interim response and final response at end of treatment, relapses, death, and values for LDH values, CRP and Beta-2 microglobulin at baseline and after each cycle of chemotherapy and end of treatment.

Response to treatment was assessed using the Cheson[7] criteria. All patients underwent PET-CT scans at the end of treatment. CRP values were determined by the central laboratory of the SCMSP as part of the initial assessment of the patient and throughout treatment. A CRP level > 1 mg/dl was considered elevated. The CRP exam was performed using the particle enhanced immunoturbidimetric assay technique. The lab exams and immunohistochemistry assays were carried out by the SCMSP using the same method.

Progression-free survival (PFS) and overall survival (OS) were also analyzed used Kaplan Meyer curves, the Log-rank test and Cox Regression using the Backward method. Statistical analyses were performed using the statistical software package SPSS version 21, adopting a level of significance of 0.05. The relationships between patient characteristics and clinical factors were explored using chi-squared and Fisher exact tests, depending on the specifics of the data. Fisher's test was used in the case of pairs with calculated expected values <5 in contingency tables. The Chi-square test was used in all other cases.

Results

Seventy-one patients with HL were initially selected for the study. Three patients were subsequently excluded due to missing data in records, giving a final total of 68 patients for inclusion in the study. The sample was predominantly male, comprising 42 (61.8 %) men and 26 (38.2 %) women, while median age was 34 years (15 to 68 years).

The median follow-up time of the cohort was 26.9 months (min. 5.5, max. 49.1 and SD 11.1 months). Regarding clinical stage, none of the patients were stage I, 26 (38.2 %) were II, 18 (26.5 %) III and 24 (35.3 %) at stage IV. Of the cases, 52 (76.5 %) had presence of B symptoms, 15 (22.1 %) absence of B symptoms, 1 (1.5 %) case had no data available in medical record, and 11 (16.9 %) had bulky mass at diagnosis (Table 1).

In the cohort, 15 (22 %) had localized and 53 (78 %) advanced stage disease, where 8 (11.7 %) with IIXB stage were considered advanced, together with stages III and IV. Patients with localized stage were classified as early-stage favorable or unfavorable using German Hodgkin Study Group (GHSG) criteria, where 4 (25 %) had favorable and 12 (75 %) unfavorable prognosis. Patients with advanced stage were classified for IPS, where 27 (39.7 %) had IPS 0–2, while 26 (38.2 %) had IPS≥3.

Regarding chemotherapy treatment, 56 (82.4 %) performed the ABVD protocol, 1 (1.5 %) BVD, 9 (13.2 %) BEACOPPe, 1 (1.5 %) started on ABVD treatment with subsequent switch to BEACOPP, and 1 (1.5 %) received DHAP. The patient administered DHAP was advanced stage with high IPS indicating use of more aggressive therapy, but had hepatotoxicity on

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Table 1 – General characteristics of patients with HL (ISMCSP, 2012 to 2016).

Variables		Number	%
Gender	Male	42	61.8 %
	Female	26	38.2 %
Stage	I	0	0.0 %
	II	26	38.2 %
	III	18	26.5 %
	IV	24	35.3 %
B symptoms[1]	No	15	22.1 %
	Yes	52	76.5 %
Bulky mass	Absent	57	83.1 %
	Present	11	16.9 %

diagnosis precluding the use of BEACOPPe. The majority of patients 47 (71.2 %) underwent six cycles of chemotherapy, 3 (4.5 %) had three cycles, 8 (12.1 %) four cycles, 3 (4.5 %) five cycles, while 5 patients (7.6 %) had 8 cycles.

Patients with CRP level >1.0 mg/dL at diagnosis were more likely to have B symptoms than patients with normal CRP level, where this association proved statistically significant ($p = 0.02$), i.e. patients with elevated CRP more frequently had B symptoms. This finding reiterated the association between CRP and inflammation.

The assessment of CRP levels at baseline and after chemotherapy cycles revealed that levels were significantly associated with disease stage. Patients at localized stages had median CRP of 3.10 mg/dL (0.5–80), while those at advanced stages had median CRP of 11.2 mg/dL (0.4–168.9), reaching statistical significance ($p = 0.015$), i.e. having advanced stage was associated with a 5-fold greater likelihood of having high CRP level (HR = 5.53 and IC = [1.18;25.93]) (Figure 1).

Baseline serum CRP was high in 56 (82.3 %) and normal in 6 (8.8 %) patients, while values were unavailable for 6 (8.8 %) patients. Median value of 7.7 mg/dL (0.4- 168.9). Baseline CRP level showed no significant association with response to treatment $p = 0.24$. Overall, 56 (90.3 %) out of 62 the patients had elevated baseline CRP, and 6 (9.7 %) patients were not assessed due to absence of initial CRP measurements.

The CRP assessment after the 1st cycle of chemotherapy showed a median value of 0.5 mg/dL (0.0–23.8). CRP levels declined in 91.1 % of the 46 patients who underwent the test. However, no statistically significant association was found between elevated CRP after the first cycle and response to treatment $p = 0.39$.

After the 4th cycle of chemotherapy, median CRP was 0.60 mg/dL (0.1–30.6). A decrease in CRP levels after the 4th cycle was not associated with treatment response ($p = 1.0$). Twelve (47.7 %) out of 42 patients had high CRP after the 4th cyc1e, and the 26 (38.2 %) patients not undergoing the exam were excluded from the analysis.

After the 5th cycle of chemotherapy, median CRP was 0.90 mg/dL (0.0–2.9) and there was a significant relationship with response to treatment ($p = 0.044$). Patients whose CRP decreased to below 1 had better treatment response rates compared to individuals whose CRP values remained high. Twelve (58.8 %) out of 34 patients had elevated CRP after cycle 5 and 34 (50 %) patients were excluded due to missing data.

After the 6th cycle of chemotherapy, median CRP was 0.70 mg/dL (0.10–18.10). A decline in CRP level after the 6th cycle was correlated with treatment response ($p = 0.003$), (Figure 2, Table. 2). Twelve out (60.6 %) of 33 patients had high CRP after cycle 6, while 35 (51.4 %) patients failed to undergo the exam and were excluded from the analysis.

Assessment of interim response was performed using PET-CT or CT scans in 17 (25 %) of the patients, where 8 (47 %) showed partial response (PR), 2 (11.7 %), clinical complete response (CCR), 1 (5.8 %) complete response unconfirmed (CRu), 2 (11.7 %) progressive disease (PD) and 4 (23.5 %) had stable disease (SD).

The small sample of patients 17 (25 %) who underwent interim imaging scans precluded any assessment of the statistical relationship between this type of response and refractoriness at end of treatment and/or with CRP values.

At the treatment endpoint, patients were assessed using PET-CT scan, with 53 (78 %) testing negative, 12 (17.6 %) positive, and 3 (4.4 %) awaiting the scan or still undergoing treatment. Most patients 53 (78 %) had CCR and 12 (17.6 %) were refractory. Refractoriness was later confirmed by biopsy.

The median follow-up time of the cohort was 26.9 months (min. 5.49, max. 49.11, mean 26.1 and SD 11.15 months). Overall survival (OS) in 36 months was 93.9 % and 24- month OS was 96.6 %, with 95 %CI (45.2–49.2) (Figure. 3). Three patients (4, 4 %) evolved to death during the follow-up period, due to the following causes: pulmonary embolism, sepsis due to pneumonia and secondary to the lymphoma according to medical records.

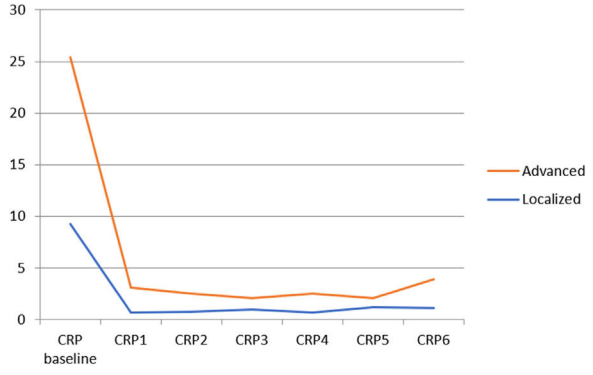

Figure 1 – Median C-reactive Protein (CRP; mg/dL) level at baseline and after each chemotherapy cycle according to clinical stage.

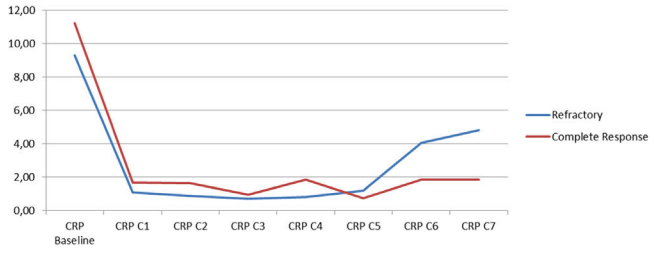

Figure 2 – Median C-reactive protein (CRP; mg/dL) level at baseline and after each chemotherapy cycle according to final response. CRP C5* p 0.044, CRP C6* p 0.003.

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Table 2 – CRP values at baseline and after chemotherapy, and correlation with final outcome (response to chemotherapy).

CRP*	Baseline	CRP after 2nd	CRP after 4th	CRP after 5th	CRP after 6th
n	62/68	50/68	42/68	34/68	33/68
Median	7.7	0.5	0.6	0.9	0.7
Minimum	0.4	0.1	0.1	0.0	0.1
Maximum	168.9	27.6	30.6	2.9	18.1
p-value	0.24	0.117	1.0	**0.044**	**0.003**

CRP*: C-Reactive Protein in mg/dL.

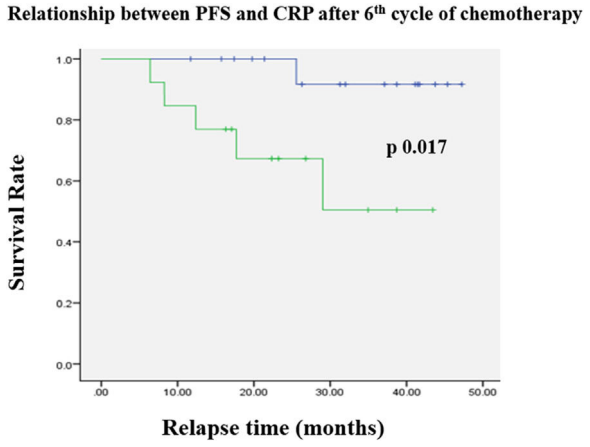

Figure 3 – Progression-free survival curve and CRP after 6th cycle of chemotherapy. Low CRP, blue line; High CRP, green line.

Table 3 – Laboratory test results and progression-free survival (PFS) of Hodgkin Lymphoma (HL) patients from ISCMSP.

Factors	No.	%	Univariate p-value	PFS
Low CRP				
Baseline *	6	9.6 %	0.94	83.3 %
After 4**	29	69 %	0.59	84.3 %
After 6***	20	62.5 %	**0.017**	91.7 %

Low CRP < 1.0 mg/ dL.

* of the 62 patients tested.
** of 42 tested.
*** of 32 tested.

Table 4 – Prognostic factors for PFS of HL patients.

FACTORS	No.	%	Univariate p-value	PFS
Staging				
Localized	15	22	0.88	85 %
Advanced	53	78		80 %
IPS				
0–2	27	39.7	0.056	95 %
Favorable	4	5.8	0.43	100 %

The mean likelihood of progression-free survival (PFS) was 79.4 %. In total, 14 patients (20.5 %) had disease progression or were treatment-refractory. The mean likelihood of 36-month PFS was 81 % and of 24-month PFS was 87.8 %. Patients with localized disease had a 36-month PFS of 85 %, and those with advanced stage 80 %, with no statistically significant difference ($p = 0.88$). Patients with early stage disease, and favorable and unfavorable prognosis for 36-month PFS was 100 % and 80 %, respectively.

A difference in PFS was detected only after the 6th cycle of chemotherapy treatment according to the log rank value= 0.017, i.e. patients with high CRP level >1 had shorter time to relapse. 36-month PFS was 91.7 % for patients with CRP ⟨ 1 mg/dL versus 50.5% for CRP ⟩ 1 mg/dL (Table. 3 and Table. 4).

For OS estimates, no differences were found for CRP level, likely explained by the low number of deaths. Most patients were young, had long survival and required longer follow-up.

The univariate analysis of laboratory exams for initial assessment of patients revealed low baseline CRP ⟨ 1.0 mg/dL had OS of 100 %, i.e. none of the patients with normal CRP at diagnosis evolved to death. Patients exhibiting high baseline CRP ⟩ 1.0 mg/dL had a 36-month OS <92.5 %, although this relationship was not statistically significant ($p = 0.58$), (HR=23.4, and IC [could not be calculated]).

Univariate analysis revealed that laboratory tests showing a positive association with greater PFS had CRP.<1.0 mg/dL after the 6th cycle of chemotherapy ($p = 0.037$), (HR=76.2 IC [could not be calculated]). (Figure 3).

DISCUSSION

The study sample was representative, having similar epidemiological characteristics to those of the literature. The sample comprised a greater proportion of men and had two age peaks between 15 and 68 years, predominantly younger adults with median age of 33 years.

The literature confirms that people with lower income have more advances malignancies. This phenomenon is highly evident in colorectal and lung cancer. Studies of patients with HL treated in Brazil in the 1980s found that most had advanced disease.[8] In the present study, 15 (22 %) had localized disease and most patients 53 (78 %) were at advanced clinical stage. In general, one of the causes associated with advanced clinical stage in cancers in Brazil is the low socioeconomic level of the population, with consequent delayed diagnosis and start of treatment. Britto et al.,[9] in the study Brazilian Prospective Hodgkin's Lymphoma Registry, after assessing 624 patients with HL, found that most (58 %) had advanced disease and detected a statistical association with socioeconomic status (71×58 %, $p = 0.003$).

CRP is an acute-phase reactant that reflects tissue injury[10] and has a half-life of 19 h. Its secretion by hepatocytes

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appears to be controlled by IL-6. It is a stable downstream marker of inflammation, unlike pro-inflammatory cytokines, whose half-life is short (minutes).[11] In the present study, baseline CRP levels were associated with disease stage, i.e. localized HL stages were associated with lower CRP levels, whereas advanced stages had higher values. Median CRP in patients with advanced disease was 11.2 mg/dL (0.4–168.9) versus 3.1 mg/dL (0.5–80) in patients with localized disease, (p = 0.015) (HR=5.53 and IC= [1.18;25.93]). This relationship was also found by Haase et al.,[12] in which median CRP at stages I and II was 5.3 mg/l (0.5–230) compared with 15.5 mg/l (0.5–400) in stage III and IV patients (p<0.05).

The initial pilot study also revealed an association between CRP levels and disease stage, where HL localized stages had lower CRP values while advanced stages had higher values. Mean CRP in patients with advanced disease was 7.85 ± 7.7 mg/dL versus 1.21 ± 1.6 mg/dL in patients with localized disease (p = 0.0035).[13] Therefore, besides being an inflammatory marker, CRP can also be considered a prognostic factor in Hodgkin Lymphoma, where the presence of inflammation is associated with both increased CRP and advanced stages.

In the cohort, patients with B symptoms at time of diagnosis had a tendency to have high CRP levels. Among patients with B symptoms, 95.8 % had high CRP and 4.2 % normal levels, where this difference was statistically significant (p = 0.02). This relationship was also observed by Wieland et al.[14] in a study assessing CRP in 95 children with HL, in which median CRP in patients with B symptoms was 8.0 mg/dL compared to 1.3 mg/dL (p <0.001) in those without B symptoms, reiterating the correlation between CRP and B symptoms.

Analysis of the factors related to refractoriness in the present study showed that high CRP levels persisting after 5th and 6th cycles of chemotherapy were statistically associated with refractoriness to treatment. At the end of the 5th chemotherapy cycle, median CRP was 0.90 mg/dL (0,0–2.9). Patients whose CRP declined after the 5th chemotherapy cycle had a greater likelihood of positive treatment response (p = 0,044). Twelve (58.8 %) out of 34 patients had elevated CRP after cycle 5 and 34 (50 %) patients were excluded due to missing data.

After the 6th cycle of chemotherapy, median CRP was 0.70 mg/dL (0.10–18.10). A decline in CRP level after the 6th cycle was correlated with treatment response (p = 0.003), (Figure 2) (Table. 2). Twelve out (60.6 %) of 33 patients had high CRP after cycle 6, while 35 (51.4 %) patients failed to undergo the exam and were excluded from the analysis.

Thus, CRP holds promise as a prognostic marker for stratifying patients with higher risk of poor treatment response or failure. This serves as an early indicator, in patients whose CRP levels do not fall during therapy, of the need for an earlier change in therapeutic approach.

In addition, a correlation was identified between a fall in CRP and a tendency toward better response to chemotherapy. There are, however, limitations for the use of CRP as a prognostic factor in HL. For instance, CRP is a non-specific acute-phase reactant and its elevation can be associated with infection, besides tumor activity, leading to misinterpretation of the test. Studies highlight the importance of clinical assessment and comparison with other prognostic factors, in determining whether elevated CRP test results can be attributed to infection or to persistence of the disease.[15]

Another confounding factor is that patients receiving cytotoxic treatment have slightly increased CRP levels, probably due to tumor degradation. In the present casuistic, it was not possible to associate high CRP with infectious processes or secondarily with tumor degradation, but the importance of correlating these events is clear.

The limitations of the test, which should not be assessed in isolation, should be acknowledged. CRP is an acute-phase protein and therefore the predictive value of a single measurement should not be considered alone, but based on a series of measurements.

The median follow-up time of the cohort was 26.9 months (min. 5.49, max. 49.11, mean 26.1 and SD 11.15 months). Overall survival (OS) in 36 months was 93.9 % and 24- month OS was 96.6 %, with 95 %CI (45.2–49.2) (Figure 3). Three patients (4,4 %) evolved to death during the follow-up period, due to the following causes: pulmonary embolism, sepsis due to pneumonia and secondary to the lymphoma according to medical records. These data are in line with the international literature showing that, given the current advances in treatment, around 90 % of all patients diagnosed with HL are long-term survivors.[16]

Mean probability of 36-month OS was 93.6 % in men and 95 % in women, and there was only one death in the female group and 2 in the male group, with no statistical difference (p = 0.92 HR 1.11 IC= 0.10–12.40]). These findings are similar to the results found by Li et al.,[17] in which no statistically significant differences in overall survival were found between men and women in general, nor for any of the lymphoma subtypes investigated. However, male gender is a known prognostic factor for IPS and is associated with a 7–8 % lower survival rate per year in patients with HL.[18]

The mean probability of 36-month PFS was 81 % overall, and proved higher (85 %) for more localized stage and lower (80 %) for advanced stage, albeit without statistical correlation (p = 0.88), HR 1.1 with 95 %CI (0.23–5.43). Most of the individuals (78 %) included in the study had advanced stage (III and IV) disease, while none of the patients had stage I. These factors indicate a possible selection bias, contributing to the lack of differences in PFS between disease stages.

Despite this lack of statistical significance, results were similar to those of a study in Latin America showing that, in low-to-middle income countries, over 60 % of patients with Hodgkin Lymphoma were diagnosed at advanced stages, while greater survival was seen in early stages.[19] Britto et al.[9] found 36-month PFS of 78 % and 64 % in patients with high and low socioeconomic status, respectively (p < 0.0001), corroborated by the present study findings.

Our results show that baseline CRP level was higher in patients with advanced disease and B symptoms. Level of CRP was associated with final response to treatment, showing that patients with persistent high serum CRP during treatment should be assessed carefully for potential poor response. Given this laboratory test is simple, routine and readily available in public services or geographically distant facilities with limited access to complementary imaging scans, CRP holds promise for widespread use in follow-up and monitoring treatment response.

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Conclusions

High CRP levels were associated with advanced disease and presence of B symptoms. CRP was considered a predictor of treatment response after the 5th and 6th cycle of chemotherapy, while persistent high CRP levels during treatment were associated with refractoriness.

Conflicts of interest

The authors declare no conflicts of interest.

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