Original Article / Özgün Araştırma

Meandros Med Dent J
doi:10.4274/meandros.galenos.2023.74317
Meandros Med Dent J 2023;24(2):168-174

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# The Importance of Serum Procalcitonin and C-reactive Protein Levels in Patients with Lymphoma

## Lenfomalı Hastalarda Serum Prokalsitonin ve C-reaktif Protein Düzeylerinin Önemi

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## Abstract

**Objective:** Increased inflammatory cells in the tumor microenvironment are important in the formation and progression of lymphomas. C-reactive protein (CRP) and procalcitonin (PCT) are biomarkers that can be used to detect infection and inflammation. We investigated the clinical significance of CRP and PCT levels in lymphoma cases.

**Materials and Methods:** We evaluated 82 Hodgkin and 120 diffuse large B-cell lymphoma (DLBCL) cases. Pre- and post-treatment PCT and CRP values were compared. The relationship between pre-treatment CRP and PCT levels and response to chemotherapy treatment, disease stage, performance score, extranodal involvement, presence of bulky mass, and bone marrow involvement was determined.

**Results:** In the Hodgkin lymphoma group, the CRP level was increased in 40 (48.8%) patients and the PCT level was increased in 16 (19.5%) patients. The CRP level was high in 36 (30%) cases and the PCT level was high in 34 (18.3%) cases in the DLBCL group. CRP and PCT levels were significantly lower after chemotherapy treatment in all of our cases compared to pretreatment ($p<0.001$, $p<0.001$, respectively).

**Conclusion:** The decrease in CRP and PCT levels after chemotherapy treatment in our Hodgkin and DLBCL cases compared with pretreatment supports the role of inflammation in the pathogenesis. In addition, these parameters may contribute to the determination of prognosis.

**Keywords:** Procalcitonin, C-reactive protein, Hodgkin lymphoma, diffuse large B-cell lymphoma, prognosis

## Öz

**Amaç:** Fazla enflamatuvar hücrenin bulunduğu tümör mikro çevresi, lenfomaların oluşumunda ve ilerlemesinde önemlidir. C-reaktif protein (CRP) ve prokalsitonin (PCT), enfeksiyon ve enflamasyonu tespit etmek için kullanılabilen biyobelirteçlerdir. Biz lenfoma olgularında CRP ve PCT düzeylerinin klinik önemini araştırdık.

**Gereç ve Yöntemler:** Seksen iki Hodgkin ve 120 diffüz büyük B-hücreli lenfoma olgusunu değerlendirdik. Tedavi öncesi ve sonrası PCT ve CRP değerleri karşılaştırıldı. Tedavi öncesi CRP ve PCT düzeyleri ile kemoterapi tedavisine yanıt, hastalık evresi, performans skoru, ekstranodal tutulum, hacimli kitle varlığı ve kemik iliği tutulumu arasındaki ilişki belirlendi.

**Bulgular:** Hodgkin lenfoma grubunda 40 (%48,8) hastada CRP düzeyi, 16 (%19,5) hastada PCT düzeyi yüksek idi. Diffüz büyük B-hücreli lenfoma grubunda CRP düzeyi 36 (%30) olguda, PCT düzeyi 34 (%18,3) olguda yüksekti. CRP ve PCT düzeyleri kemoterapi tedavisi sonrası tüm olgularımızda tedavi öncesine göre anlamlı olarak düşüktü (sırasıyla $p<0,001$, $p<0,001$).

**Sonuç:** Hogkin ve diffüz büyük B-hücreli lenfoma olgularımızda kemoterapi tedavisi sonrası CRP ve PCT düzeylerinin tedavi öncesine göre azalması inflamasyonun patogenezdeki rolünü desteklemektedir. Ayrıca bu parametreler prognozun belirlenmesinde de katkı sağlayabilir.

**Anahtar Kelimeler:** Prokalsitonin, C-reaktif protein, Hodgkin lenfoma, diffüz büyük B-hücreli lenfoma, prognoz

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**Received/Geliş Tarihi:** 10.03.2023
**Accepted/Kabul Tarihi:** 11.06.2023

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## Introduction

Chronic inflammation causes genetic instability and oncogenic mutations, creates the appropriate microenvironment for tumor development (1,2). Inflammation plays an important role in the pathogenesis of breast, lung, and liver cancer, multiple myeloma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) (3-5). In classic HL, Hodgkin/reed Steinberg (HRS) cells constitute approximately 1% of the tumor tissue (6). Lymphocytes, eosinophils, neutrophils, and plasma cells form an inflammatory microenvironment around HRS cells (7). These inflammatory cells contribute to the survival and proliferation of HRS cells through the cytokines they secrete and also allow them to escape from the body's immune system (6,7). The JAK-STAT pathway activated by interleukin (IL) 2, IL-6, IL-10 secreted from inflammatory cells contributes to the pathogenesis of the disease in diffuse large B-cell lymphoma (DLBCL) (8).

C-reactive protein (CRP) and procalcitonin (PCT) are acute-phase reactants (9,10). CRP increases in cases of bacterial and viral infections, collagen tissue diseases, burns and cancer. IL-6 secreted by HRS cells also stimulates CRP synthesis in HL cases. PCT used to distinguish bacterial infections from non-bacterial infections (10). PCT level increases extensive metastatic solid cancers, thyroid cancers, and neuroendocrine tumors (11).

Although there are many different factors that play a role in the pathogenesis of HL and DLBCL, inflammation is important in the pathogenesis. Inflammatory biomarkers are important in both the diagnosis and prognosis of HL (12). In DLBCL cases, CRP contributes to the determination of prognosis both alone and in combination with the international prognostic index score.

Inflammation is a factor that negatively affects cancer development and prognosis, and CRP and PCT are inflammatory biomarkers. Therefore, we investigated CRP and PCT levels and their clinical significance in HL and DLBCL.

## Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Atatürk University (decision no: 33, date: 25.11.2021). The requirement for informed consent was waived because the data used in the study were anonymous and the study was designed as a retrospective file review. We analyzed the files of 339 patients with HL and DLBCL. Two hundred-two cases who were given adriamycin, bleomycin, vinblastine, dacarbazine treatment for HL and rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone treatment for DLBCL treatment were included in the study. The lymphoma diagnosis and subgroup determination of the cases were made according to the World Health Organization 2016 criteria. Patients with fever, signs of active infection, and a history of inflammatory disease were not included in this study.

Age, gender, Ann Arbor stage, extranodal involvement, bone marrow infiltration, Eastern Cooperative Oncology Group (ECOG) performance score, presence of bulky mass, lactate dehydrogenase (LDH), beta 2 (β2) microglobulin, CRP, and PCT values at the time of admission were recorded. CRP and PCT values of the cases were also recorded after the first course of chemotherapy (15-30 days), and these values were accepted as post-treatment. Bone marrow biopsy was not performed in HL cases with bone marrow involvement in positron emission tomography/computerized tomography (PET-CT) and were considered stage 4. Bone marrow involvement was evaluated by bone marrow biopsy in all other cases. The response of the cases to chemotherapy was evaluated by PET-CT. Deauville criteria were used for PET-CT response evaluation of patients with HL. Response to treatment was classified as complete remission, partial remission, stable disease, and progressive disease.

### Statistical Analysis

Statistical analyzes were performed using the SPSS (Statistical Package for the Social Sciences) 20 program. The distribution normality of the data was analyzed with the Kolmogorov-Smirnov test. Comparisons between the two groups were made with the independent t-test if the data were normally distributed, otherwise with the Mann-Whitney U test. One-Way analysis of variance was used for comparisons between groups of more than two normally distributed quantitative variables. Comparisons of more than two groups without normal distribution were made with Kruskal-Wallis and Dunn-Bonferroni tests. For correlation analysis, Pearson correlation analysis was used if the data were normally distributed, and Spearman Rank correlation analysis was used if the data were not normally distributed. Survival analyzes were performed with the Kaplan-Meier test. $P<0.05$ value was considered statistically significant.

## Results

Eighty-two (40.6%) of our cases were HL and 120 (59.4%) were DLBCL. The mean age of HL cases was 40.68±15.26 years; 38 (46.3%) were female and 44 (53.7%) were male. In the DLBCL group, the mean age was 51.95±11.95; 44 (36.7%) were female and 76 (63.3%) were male. Laboratory findings and clinical features of our cases were shown in Table 1.

There was no significant correlation between LDH value and pre-treatment PCT and CRP values in the HL (r=0.09, p=0.57; r=0.08, p=0.52, respectively) and DLBCL groups (r=0.198, p=0.21; r=0.04, p=0.75; respectively). There was no significant correlation between pre-treatment CRP and β2 microglobulin values in the HL group (r=0.238, p=0.23), but a significant correlation was found between pre-treatment PCT and β2 microglobulin values (r=0.63, p=0.015). Pretreatment PCT and CRP values and β2 microglobulin

levels were not significantly correlated in the DLBCL group (r=0.14, p=0.51; r=0.03, p=0.89; respectively).

CRP values were high in 40 (48.8%) of the HL patients and 36 (30%) of the DLBCL patients, and PCT values in 16 (19.5%) of the HL group and 34 (18.3%) of the DLBCL group. Pre-treatment CRP and PCT values were significantly higher than post-treatment CRP and PCT values in HL and DLBCL groups (Table 2). The relationship between the response status of lymphoma cases to chemotherapy treatment and pre-treatment CRP and PCT levels was shown in Table 3. The association with pre-treatment CRP and PCT levels and ECOG score, extranodal involvement status, presence of bulky mass, bone marrow infiltration, and Ann Arbor stages of our HL and DLBCL cases were shown in Tables 4 and 5.

The mean follow-up period of the cases was 24±11 months. Six cases in the HL group and 12 cases in the DLBCL group died due to disease-related reasons. The mean survival time of patients with high and normal CRP values in the HL group was 15±2.1 months and 19±3.1 months, respectively (p=0.04). The survival time of patients with high and normal PCT levels in the HL group was 14±1.8 months and 18±2.4 months, respectively (p=0.03). In the DLBCL group, the survival time of patients with high CRP value (12±2.1 months). In the DLBCL group, the survival time was shorter in patients with high CRP (12±2.1 months) value than in

**Table 1. Laboratory findings and clinical features of HL and DLBCL cases**

| | Group | | |
|---|---|---|---|
| **Parameters** | **HL** | **DLBCL** | **All patients** |
| Lactate dehydrogenase (135-225 U/L) | 293±156.73 | 445.39±168.74 | 500.91±1303 |
| β2 microglobulin (0.8-2.4 mq/L) | 2.49±1.33 | 3.34±2 | 2.97±1.8 |
| Sedimentation (0-20 mm/h) | 19±6.2 | 14±5.1 | 15±4.8 |
| **ECOG performance score** | **HL n (%)** | **DLBCL n (%)** | **All patients n (%)** |
| ECOG 1 | 8 (9.8%) | 22 (18.3%) | 30 (14.9%) |
| ECOG 2 | 60 (73.2%) | 66 (55%) | 126 (62.4%) |
| ECOG 3 | 14 (17%) | 22 (18.3%) | 36 (17.8%) |
| ECOG 4 | 0 (0%) | 10 (8.3%) | 10 (5%) |
| **Ann Arbor stage** | **HL** | **DLBCL** | **All patients** |
| Stage 1 | 4 (4.9%) | 10 (8.3%) | 14 (6.9%) |
| Stage 2 | 24 (29.3%) | 48 (40%) | 72 (35.6%) |
| Stage 3 | 36 (44%) | 44 (36.7%) | 80 (39.6%) |
| Stage 4 | 18 (22%) | 18 (15%) | 36 (17.8%) |
| Bulky mass (present) | 12 (14.6%) | 18 (15%) | 30 (14.9%) |
| Extranodal involvement (present) | 20 (2.4%) | 18 (15%) | 38 (18.8%) |
| Bone marrow infiltration (present) | 18 (22%) | 18 (15%) | 36 (17.8%) |

HL: Hodgkin lymphoma, DLBCL: Diffuse large B cell lymphoma, ECOG: Eastern Cooperative Oncology Group

**Table 2. CRP and PCT values of our cases before and after treatment**

| Group | Parameters | Pre-treatment | Post-treatment | p-value |
|---|---|---|---|---|
| HL | CRP | 52.51±53.1 | 10.47±15.44 | <0.001 |
| | PCT | 3.23±3.15 | 0.48 ±1.95 | 0.002 |
| DLBCL | CRP | 39.12±49.3 | 10.79±14.01 | 0.045 |
| | PCT | 1.69±2.64 | 0.36 ±1.61 | 0.006 |
| All patients | CRP | 44.23±50.91 | 10.67±14.49 | <0.001 |
| | PCT | 2.16±2.87 | 0.4 ±1.7 | <0.001 |

HL: Hodgkin lymphoma, DLBCL: Diffuse large B cell lymphoma, CRP: C-reactive protein (normal range: 0-5 mg/L), PCT: Procalcitonin (normal range: 0-0.5 ng/mL)

**Table 3. The relationship between pre-treatment CRP and PCT levels and response to chemotherapy**

| Group | Chemotherapy response status | CRP (mg/L) | PCT (ng/mL) |
|---|---|---|---|
| HL | CR | 5.93±3.3 | 0.06±0.08 |
| | PR | 47.62±27.62 | 0.14±0.34 |
| | Stable disease | 93.34±26.36 | 0.32±0.35 |
| | Progressive disease | 124.35±54.45 | 1.89±3.99 |
| p-value | | <0.001 | 0.04 |
| Group | Chemotherapy response status | CRP (mg/L) | PCT (ng/mL) |
| DLBCL | CR | 7.57±8.87 | 0.04±0.04 |
| | PR | 33.72±31.2 | 0.33±0.38 |
| | Stable disease | 98.02±46.79 | 0.99±0.55 |
| | Progressive disease | 121.02±54.51 | 2.67±0.55 |
| p-value | | <0.001 | 0.04 |

HL: Hodgkin lymphoma, DLBCL: Diffuse large B cell lymphoma, CRP: C-reactive protein, PCT: Procalcitonin, CR: Complete remission, PR: Partial remission

**Table 4. The relationship between pre-treatment CRP level and ECOG score, extranodal involvement, bulky mass, bone marrow infiltration and Ann Anbor stage**

| Parameters | CRP | | |
|---|---|---|---|
| **ECOG performance score** | **HL** | **DLBCL** | **All patients** |
| ECOG 1 | 33.03±46.74 | 36.86±44.73 | 37.84±43.59 |
| ECOG 2 | 46.08±48.44 | 39.79±50.57 | 42.77±49.24 |
| ECOG 3 | 60.06±57.43 | 32.83±51.83 | 41.9±53.35 |
| ECOG 4 | | 40.17±54.35 | 40.17±54.35 |
| p-value | 0.71 | 0.98 | 0.97 |
| **Extranodal involvement** | **HL** | **DLBCL** | **All patients** |
| Present | 65.35±15.55 | 36.07±16.07 | 46.46±18.32 |
| Absent | 43.3±20 | 48.11±19.69 | 40.11±18.89 |
| p-value | 0.04 | 0.03 | 0.04 |
| **Bulky mass** | **HL** | **DLBCL** | **All patients** |
| Present | 48.25±10.16 | 44.74±11.72 | 43.74±10.91 |
| Absent | 35.77±8.95 | 23.6±15.5 | 27.95±10.06 |
| p-value | 0.04 | 0.04 | 0.03 |
| **Bone marrow infiltration** | **HL** | **DLBCL** | **All patients** |
| Present | 64.33±20.12 | 47.01±19.32 | 55.16±14.2 |
| Absent | 41.66±17.78 | 36.35±17.07 | 38.35±17.09 |
| p-value | 0.02 | 0.03 | 0.02 |
| **Ann Arbor stage** | **HL** | **DLBCL** | **All patients** |
| Stage 1 | 24.03±15.22 | 8.8±10.59 | 18.33±10.94 |
| Stage 2 | 38±13.97 | 33.6±9.75 | 33.21±12.24 |
| Stage 3 | 49±16.55 | 42.89±16.78 | 43.53±18.97 |
| Stage 4 | 67.59±17.9 | 47.01±9.32 | 57.3±13.36 |
| p-value | 0.01 | 0.04 | 0.03 |

HL: Hodgkin lymphoma, DLBCL: Diffuse large B cell lymphoma, CRP: C-reactive protein, PCT: Procalcitonin, ECOG: Eastern Cooperative Oncology Group

Table 5. The relationship between pre-treatment PCT level and ECOG performance score, extranodal involvement, bulky mass, bone marrow infiltration, and Ann Arbor stage

| Parameters | PCT | | |
|---|---|---|---|
| **ECOG performance score** | **HL** | **DLBCL** | **All patients** |
| ECOG 1 | 0.02±0.01 | 0.24±0.4 | 0.18±0.35 |
| ECOG 2 | 0.46±1.7 | 0.1±0.18 | 0.27±1.18 |
| ECOG 3 | 0.04±0.02 | 0.07±0.07 | 0.06±0.06 |
| ECOG 4 | | 2.33±4.96 | 2.33±4.96 |
| p-value | 0.76 | 0.014 | 0.017 |
| **Extranodal involvement** | **HL** | **DLBCL** | **All patients** |
| Present | 0.97±0.03 | 0.94±0.61 | 0.99±0.64 |
| Absent | 0.03±0.01 | 0.15±0.04 | 0.03±0.04 |
| p-value | 0.04 | 0.02 | 0.04 |
| **Bulky mass** | **HL** | **DLBCL** | **All patients** |
| Present | 1.4±0.59 | 1.36±0.61 | 1.38±0.59 |
| Absent | 0.04±0.02 | 0.05±0.04 | 0.05±0.03 |
| p-value | 0.03 | 0.04 | 0.04 |
| **Bone marrow infiltration** | **HL** | **DLBCL** | **All patients** |
| Present | 1.39±0.06 | 1.36±0.01 | 1.37±0.02 |
| Absent | 0.21±0.44 | 0.08±0.07 | 0.14±0.3 |
| p-value | 0.03 | 0.04 | 0.04 |
| **Ann Arbor Stage** | **HL** | **DLBCL** | **All patients** |
| Stage 1 | 0.03±0.009 | 0.01±0.01 | 0.02±0.01 |
| Stage 2 | 0.7±0.08 | 0.7±0.02 | 0.4±0.29 |
| Stage 3 | 1.21±0.44 | 1.36±0.07 | 1.14±0.3 |
| Stage 4 | 2.66±0.03 | 2.36±0.05 | 2.63±0.08 |
| p-value | 0.03 | 0.04 | 0.04 |

HL: Hodgkin lymphoma, DLBCL: Diffuse large B cell lymphoma, CRP: C-reactive protein, PCT: Procalcitonin, ECOG: Eastern Cooperative Oncology Group

patients with normal CRP (16±3.1 months) value, and in patients with high PCT level (13±1.8 months) compared to those with normal PCT (15±2.4 months) level (p=0.03, p=0.04, respectively).

## Discussion

There is systemic inflammation in cancer cases and it causes an increase in the level of IL-6. It triggers an increase in CRP levels. Legouffe et al. (13) reported that the CRP value was high in 42% of the NHL cases. Wieland et al found that the CRP value was high in 54% of the HL cases (14). In our study, 48.8% of HL cases and 30% of DLBCL cases had elevated CRP values, and these rates were lower than in the literature. This may be because we included only DLBCL cases from the NHL group in our study and excluded cases with signs of infection from our study.

Inflammation affects not only the development of cancer but also its spread. Weinstein et al. (15) evaluated solid tumor or hematologic malignancy cases and found a correlation between disease stage and CRP level. It has been reported that CRP value before treatment is associated with disease stage and IPI score in DLBCL cases (16). There were also studies reporting a relationship between disease stage and pre-treatment CRP value in HL cases (14,17). A relationship was found between CRP value and the presence of extranodal involvement in HL (18). In our study, a correlation was found between pre-treatment CRP and extranodal involvement, presence of bulky mass, bone marrow infiltration, and disease stage in HL and DLBCL.

Da Silveira da Rocha et al. (17) stated that after the first course of chemotherapy treatment in HL cases, the CRP value decreased to near normal levels. In our study, the post-treatment CRP value was significantly lower than the pre-treatment CRP value in HL and DLBCL. This result supports the role of inflammation in the pathogenesis of both HL and DLBCL. We think that the reason for the decrease in CRP value is the corticosteroid treatment

used in the chemotherapy protocol in DLBCL cases, and the decrease in HRS cells, which ensures the continuity of inflammatory cells in HL cases. Therefore, we think that the pre-treatment CRP value may be a biomarker to predict response to chemotherapy treatment.

It was reported high PCT levels in 30.6% of patients with hematological malignancies. In our study, PCT values were elevated in 19.5% of the HL group and 18.3% of the DLBCL group, and these rates were lower compared to the literature. This may be because cases with signs of infection were not included in our study.

Very few studies investigate the diagnostic and prognostic importance of PCT levels in solid organ cancers. Chaftari et al. (19) stated that PCT levels can be used as a biomarker to predict cancer in cases without fever. The significant decrease in the post-treatment PCT level compared to the pre-treatment PCT level in our study supports this hypothesis for HL and DLBCL cases. PCT level is elevated in patients with medullary thyroid cancer, and elevated PCT level is associated with short surveillance. Matzaraki et al. (11) stated that PCT level is high if primary tumors have liver metastases. Our study is the first in the literature to investigate the relationship between PCT level, disease severity, and treatment response in lymphoma cases. We found a significant correlation between pre-treatment PCT level and response to chemotherapy treatment, extranodal involvement, presence of bulky mass, and disease stage. This result supports that PCT level is a laboratory test that can be used to evaluate disease prognosis and response to treatment.

Kawaguchi et al. (20) detected that progression-free survival was significantly shorter in follicular lymphoma patients with a high CRP value (>5 mg/dL). In our study, we found that the survival time was shorter in patients with high CRP and PCT levels in both HL and DLBCL groups compared to patients with normal levels. This supports that increased inflammation at the time of diagnosis may be associated with worse response to treatment and worse prognosis.

## Conclusion

A better understanding of the pathogenesis of lymphoma disease will provide a better determination of prognostic factors. As etiopathogenesis is better understood, the parameters used in the prognostic scoring of lymphoma are updated. PCT and CRP are inexpensive biochemical tests that can be performed in almost every hospital. In our study, we found that CRP and PCT values can be used as additional biomarkers in predicting prognosis and response to chemotherapy in HL and DLBCL cases.

### Ethics

**Ethics Committee Approval:** Approval was granted by the Ethics Committee of Atatürk University (decision no: 33, date: 25.11.2021).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: G.S., Concept: S.S., G.S., F.E., Design: S.S., G.S., F.E., Data Collection or Processing: M.N.K., Z.A., Analysis or Interpretation: S.S., M.N.K., Z.A., Literature Search: S.S., M.N.K., Z.A., F.E., Writing: S.S., G.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

## References

1. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: How hot is the link?. Biochem Pharmacol 2006; 72: 1605-21.
2. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420: 860-7.
3. Li F, Tiede B, Massagué J. Kang Y. Beyond tumorigenesis: cancer stem cells in metastasis. Cell Res 2007; 17: 3-14.
4. Makgoeng SB, Bolanos RS, Jeon CY, Weiss RE, Arah OA, Breen EC, et al. Markers of Immune Activation and Inflammation, and Non-Hodgkin Lymphoma: A Meta-Analysis of Prospective Studies. JNCI Cancer Spectrum 2018; 2: pky082
5. Poppema S, Potters M, Emmens R, Visser L, van den Berg A. Immune reactions in classical Hodgkin's lymphoma. Semin Hematol 1999; 36: 253-9.
6. Steidl C, Connors JM, Gascoyne RD. Molecular pathogenesis Hodgkin's lymphoma: increasing evidence of the importance of the microenvironment. J Clin Oncol 2011; 29: 1812-26.
7. Schottenfeld D, Beebe-Dimmer J. Chronic Inflammation: A Common and Important Factor in the Pathogenesis of Neoplasia. CA Cancer J Clin 2006; 56: 69-83.
8. Gupta M, Han JJ, Stenson M, Maurer M, Wellik L, Hu G, et al. Elevated serum IL-10 levels in diffuse large B–cell lymphoma: A mechanism of aberrant JAK2 activation. Blood 2012; 119: 2844-53.
9. Yeh ET. CRP as a mediator of disease. Circulation 2004; 109: II11-4.
10. Li S, Rong H, Guo Q, Chen Y, Zhang G, Yang J. Serum procalcitonin levels distinguish gram-negative bacterial sepsis from gram-positive bacterial and fungal sepsis. J Res Med Sci 2016; 21: 39-46.
11. Matzaraki V, Alexandraki KI, Venetsanou K, Piperi C, Myrianthefs P, Malamos N, et al. Evaluation of serum procalcitonin and interleukin-6 levels of liver metastasis. Clin Biochem 2007; 40: 336-42.
12. Zielinski CC, Preis P, Aiginger P, Eibl MM. Acute-phase-proteins and parameters of humoral immunity in patients with advanced Hodgkin's disease. J Cancer Res Clin Oncol 1985; 110: 65-70.
13. Legouffe E, Rodriguez C, Picgt MC, Richard B, Klein B, Rossi JF, et al. C-reactive protein serum level is a valuable and simple prognostic marker in non-Hodgkin's lymphoma. Leuk Lymphoma 1998; 31: 351-7.
14. Wieland A, Kerbl R, Berghold A, Schwinger W, Mann G, Urban C. C-reactive protein (CRP) as tumor marker in pediatric and adolescent patients with Hodgkin disease. Med Pediatr Oncol 2003; 41: 21-5.

15. Weinstein PS, Skinner M, Sipe JD, Lokich JJ, Zamcheck N, Cohen AS. Acute-phase proteins or tumour markers: the role of SAA, SAP, CRP and CEA as indicators of metastasis in a broad spectrum of neoplastic diseases. Scand J Immunol 1984; 19: 193-8.

16. Cao Y, Shi YX, Chen JO, Tan YT, Cai YC, Luo HY, et al. Serum C-reactive protein as an important prognostic variable in patients with diffuse large B cell lymphoma. Tumour Biol 2012; 33: 1039-44.

17. Da Silveira da Rocha TM, Miranda Silva AL, Fortier SC, Chiattone CS. Evaluation correlates C-reactive protein with advanced stage Hodgkin's lymphoma and response to treatment in a tertiary university hospital in Brazil. Rev Bras Hematol Hemoter 2015; 37: 242-6.

18. Haase R, Vilser C, Mauz-Körholz C, Hasenclever D, Kluge R, Ruschke K, et al. Evaluation of the prognostic meaning of C-reactive protein (CRP) in children and adolescents with classical Hodgkin's lymphoma (HL). Klin Padiatr 2012; 224: 377-81.

19. Chaftari AM, Hachem R, Reitzel R, Jordan M, Jiang Y, Yousif A, et al. Role of Procalcitonin and Interleukin-6 in Predicting Cancer, and Its Progression Independent of Infection. PLoS One 2015; 10: 1-11.

20. Kawaguchi Y, Saito B, Nakata A, Matsui T, Sasaki Y, Shimada S, et al. Elevated C-reactive protein level is associated with poor prognosis in follicular lymphoma patients undergoing rituximab-containing chemotherapy. Int J Hematol 2020; 112: 341-8.