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# The importance of serum calprotectin level in patients with lymphoma

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**Abstract:**

**BACKGROUND:** Calprotectin is a protein found in the cytoplasm of neutrophils and monocytes and its serum level increases in inflammatory conditions and some cancer cases. It was aimed to determine the diagnostic and prognostic importance of serum calprotectin levels in patients with lymphoma in this study.

**MATERIALS AND METHODS:** In this study, 32 newly diagnosed or relapsed Hodgkin lymphoma (HL), 31 diffuse large B-cell lymphoma (DLBCL), and 26 healthy cases followed in the Hematology clinic of Atatürk University Medical Faculty Hospital were evaluated prospectively. Serum calprotectin levels of lymphoma cases and control groups were compared. In addition, the relationship between serum calprotectin level and bulky mass, B symptoms, Ann Arbor stage, extranodal involvement, and response to chemotherapy was investigated in lymphoma groups.

**RESULTS:** Serum calprotectin level was higher in the HL than that in the DLBCL and control groups ($P = 0.01$, $P = 0.001$, respectively). There was a correlation between serum calprotectin level and bulky mass, B symptoms, and Ann Arbor stage ($P = 0.03$, $P = 0.02$, and $P = 0.001$, respectively) in the HL group. Serum calprotectin level and international prognostic score were associated in the DLBCL group ($P = 0.001$).

**CONCLUSION:** Serum calprotectin level can be used as an additional diagnostic biomarker in HL. In addition, it is associated with some prognostic biomarkers in lymphoma cases.

**Keywords:**

Biomarkers, calprotectin, diffuse large B-cell lymphoma, Hodgkin lymphoma, prognosis

## Introduction

Lymphomas are a heterogeneous group of diseases originating from malignant lymphocytes and are the most common hematological cancers in the adult age group. Inflammatory cells are the main component in the tumor microenvironment, and these, together with pro-inflammatory cytokines, are associated with tumor initiation, growth, and metastasis. The mechanism of increased systemic inflammation in malignancies is not fully known. Inflammation plays an important role in the pathogenesis of diffuse large B-cell lymphoma (DLBCL).[1-4] The role of inflammation in the pathogenesis of Hodgkin lymphoma (HL) is better known than that in DLBCL. HL is characterized by a small number of Hodgkin and Reed–Sternberg (HRS) cells originating from the germinal center B cell in an inflammatory environment composed of T lymphocytes, B lymphocytes, plasma cells, eosinophils, neutrophils, and mast cells.[5] Some cytokines such as interleukin-5 (IL-5), CCL5, and CCL22 secreted by HRS cells act as chemokines for these inflammatory cells. HRS cells are located in the central region of this microenvironment formed by inflammatory cells. Therefore, malignant HRS cells are protected from the natural killer and cytotoxic T lymphocyte attacks.[6]

An excisional lymph node biopsy, which is an invasive procedure, is required for the

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diagnosis of lymphoma.[7] However, the biopsy procedure has complications such as bleeding and infection. In addition, the biopsy is an expensive procedure and the examination takes a long time to complete. Therefore, new noninvasive diagnostic biomarkers are needed in the diagnosis of lymphoma. The role of parameters such as C-reactive protein (CRP) and sedimentation values, which are biomarkers of inflammation that play an important role in the pathogenesis of both HL and DLBCL, was investigated. Various scoring systems are used to determine the prognosis in patients with lymphoma. Sedimentation value is one of the factors that determine whether early-stage HL cases are in the good or bad risk group. Laboratory parameters such as albumin, hemoglobin, leukocyte, and lymphocyte counts are important for prognosis in advanced-stage HL cases.[8] The International prognostic index (IPI) is used to determine the prognosis in DLBCL cases and there is no inflammatory biomarker in this scoring system.[9] However, the prognosis differs in cases with the same prognostic risk group in both HL and DLBCL cases. This leads to the search for new prognostic biomarkers.[10]

Calprotectin (S100A8/S100A9) is a heterodimer in the S100 group of calcium-binding proteins. It is also known as the S100A8/S100A9 complex, macrophage inhibitory factor-associated protein, MRP8/14, and calgranulin A/B proteins.[11] Calprotectin, first described by Fagerhol *et al*. in 1979, constitutes 40%–60% of the cytosolic proteins of neutrophils.[12,13] Since calprotectin is also secreted by stimulated monocytes and macrophages in the inflammatory state, its level increases in plasma, urine, or feces and is therefore considered an acute-phase reactant.[13-15] Calprotectin level is also increased in some cancers such as colon, ovarian, laryngeal, and lung cancers and lymphoma.[16-20] It is known that inflammation plays a role in the pathogenesis of lymphoma. Therefore, this study aimed to evaluate the diagnostic and prognostic importance of serum calprotectin level, an inflammatory biomarker, in lymphoma patients.

## Materials and Methods

### Ethics statement

This study was designed in accordance with the Declaration of Helsinki in 2000. Ethical approval was obtained from the Ethics Committee of Atatürk University Faculty of Medicine for this study (Approval number: B.30.2.ATA.0.01.00/244). In addition, informed consent was obtained from the participants.

### Study design and patients

The current study included 32 newly diagnosed/relapsed HL, 31 newly diagnosed/relapsed DLBCL cases followed in the Hematology Department of Atatürk University Medical Faculty Hospital, and 26 healthy control cases. The lymphoma diagnosis and subtype determination of the cases were made according to the lymphoma classification revised by the World Health Organization in 2016. Cases with a history of inflammatory disease and active infection were not included in this study. In addition, only DLBCL cases from the non-HL group were included in this study to ensure homogeneity within the group. The HL and DLBCL groups were evaluated prospectively.

### Study procedure

Hemogram parameters, lactate dehydrogenase (LDH), beta 2 microglobulin, CRP, Eastern Cooperative Oncology Group (ECOG) performance score, and Ann Arbor stages performed with positron emission tomography/computed tomography (PET/CT) of the cases were recorded. HL cases were accepted as early stage if stages 1 and 2 and advanced stage if stages 3 and 4. The International Prognostic Score (IPS) of the European Organization for Research and Treatment of Cancer has been calculated for patients with advanced HL. Revised IPI scores (rIPI) of DLBCL cases were determined. The cases were divided into three groups as low, low-intermediate, and high risk according to their rIPI scores. A bone marrow biopsy was performed in all cases except HL cases with bone marrow involvement on PET/CT to evaluate bone marrow involvement.

Adriamycin, bleomycin, vinblastine, and deticine combination therapy was applied to HL cases. DLBCL cases were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and methylprednisolone combination chemotherapy protocol. In all cases, intermediate response evaluation with PET/CT after 2 cycles of chemotherapy treatment and posttreatment response status after the planned treatment were evaluated.

### Analysis of serum calprotectin level

Approximately 10 cc of blood was taken from newly diagnosed lymphoma cases at the time of diagnosis and from relapsed cases at the time of relapse diagnosis. The collected blood samples were centrifuged at 3000 rpm for 4–5 min and the separated serum portions were frozen at − 80°C and stored until analysis. After the serum samples were thawed under suitable conditions to determine the serum calprotectin level, they were analyzed in the Medical Biochemistry Laboratory of Atatürk University Health Research and Application Center. Serum calprotectin levels were analyzed with calprotectin (calpro) human Elisa kit/96 test/cloud clone (USCNK) according to the standard protocol recommended by the manufacturer.

### Statistical analysis

Statistical analysis was performed using the Number Cruncher Statistical System 2007 (Kaysville, Utah, USA)

program. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum values) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was evaluated with the Shapiro–Wilk test. Mann–Whitney *U*-test was used for comparisons between two groups of quantitative variables that did not show normal distribution. One-way analysis of variance and binary evaluations with Bonferroni correction were used for comparisons between groups of more than two normally distributed quantitative variables. Kruskal–Wallis and Dunn–Bonferroni tests were used for comparisons between groups of more than two quantitative variables that did not show normal distribution. Fisher–Freeman–Halton exact test was used to compare qualitative data. Pearson's correlation analysis and Spearman's correlation analysis were used to evaluate the relationships between quantitative variables. Kaplan–Meier survival analysis and the log rank test were used to evaluate survival. The effects of risk factors on cumulative survival were investigated by Cox regression analysis. Statistical significance was accepted as $P < 0.05$.

## Results

Of the cases examined in our study, 36% ($n = 32$) were in the HL, 34.8% ($n = 31$) in DLBCL, and 29.2% ($n = 26$) were in the control group. The age and gender distribution of the cases are shown in Table 1, and there was no significant difference in age and gender between the groups.

The clinical findings of the HL and DLBCL groups are shown in Table 2. In the HL group, β2 microglobulin was 3.23 ± 1.82 μg/mL, LDH was 333.47 ± 224.29 U/L, and CRP was 29.43 ± 34.76 mg/L. The level of β2 microglobulin was 4.08 ± 2.45, LDH was 408.97 ± 431.09 U/L, and CRP was 46.49 ± 60.66 mg/L in the DLBCL group.

In the HL group, 13 (86.7%) cases were in the early-stage favorable prognostic group and 2 (13.3%) cases were in the early-stage, unfavorable prognostic group. The IPS score distribution of 17 patients with the advanced stage was low risk in 4 (23.5%) patients, intermediate risk in 6 (35.3%) patients, and high risk in 7 (41.2%) patients. The rIPI score of the DLBCL group was low risk in 5 (16.1%) cases, low-intermediate risk in 9 (29%) cases, and high risk in 17 (54.8%) cases.

Serum calprotectin level was 70.75 ± 12.31 pg/mL in HL cases, 61.71 ± 13.72 pg/mL in DLBCL cases, and 54.54 ± 8.44 in the control group [Figure 1]. There was a statistically significant difference between the calprotectin levels of the groups ($P = 0.001$). In the comparisons between the two groups, the serum calprotectin level in the HL group was found to be statistically significantly higher than that in the DLBCL and control groups ($P = 0.010$ and $P = 0.001$, respectively). No statistically significant difference was found between the DLBCL group and the control group ($P = 0.077$).

In HL group, there was a moderate positive correlation between serum calprotectin and LDH levels ($r = 0.532$; $P = 0.002$). There was a weak positive correlation between calprotectin and CRP and B2 microglobulin levels ($r = 0.395$; $P = 0.025$ and $r = 0.384$; $P = 0.030$; respectively). There was no significant correlation between calprotectin level and leukocyte count, lymphocyte level, and sedimentation value ($r = 0.254$, $P = 0.161$; $r = 0.05$, $P = 0.787$; $r = 0.088$, $P = 0.631$, respectively).

A significant correlation was found between serum calprotectin level, bulky mass, B symptoms, and Ann Arbor stage in HL cases [Table 3]. No significant

**Table 1: Age and gender distribution of the cases**

| Parameters | HL | DLBCL | Control group | *P* |
|---|---|---|---|---|
| Gender, *n* (%) | | | | |
| Female | 11 (34.4) | 13 (41.9) | 13 (50) | 0.505 |
| Male | 21 (65.5) | 18 (58.1) | 13 (50) | |
| Age (mean±SD) | 45.97±13.75 | 53.35±13.16 | 49.31±10.61 | 0.104 |

HL=Hodgkin lymphoma, SD=Standard deviation, DLBCL=Diffuse large B-cell lymphoma

**Table 2: Clinical findings of Hodgkin lymphoma and diffuse large B-cell lymphoma cases**

| Parameters | HL, *n* (%) | DLBCL, *n* (%) |
|---|---|---|
| Bulky mass | | |
| Absent | 26 (81.3) | 25 (80.6) |
| Present | 6 (18.8) | 6 (19.4) |
| Bone marrow infiltration | | |
| Absent | 28 (87.5) | 23 (74.2) |
| Present | 4 (12.5) | 8 (25.8) |
| Extranodal involvement | | |
| Absent | 20 (62.5) | 11 (35.5) |
| Present | 12 (37.5) | 20 (64.5) |
| B symptoms | | |
| Absent | 19 (59.4) | 18 (58.1) |
| Present | 13 (40.6) | 13 (41.9) |
| ECOG score | | |
| ECOG 1 | 16 (50) | 11 (35.5) |
| ECOG 2 | 7 (21.9) | 17 (54.8) |
| ECOG 3 | 9 (28.1) | 3 (9.7) |
| ECOG 4 | 0 | 0 |
| Ann Arbor stage | | |
| Stage 1 | 2 (6.2) | 3 (9.7) |
| Stage 2 | 13 (40.6) | 7 (22.6) |
| Stage 3 | 11 (34.4) | 8 (25.8) |
| Stage 4 | 6 (18.8) | 13 (42) |

ECOG=Eastern cooperative oncology group, HL=Hodgkin lymphoma, DLBCL=Diffuse large B-cell lymphoma

correlation was found between other parameters and serum calprotectin levels [Table 3].

In the evaluation of the intermediate response after two courses of chemotherapy, partial response was observed in 2 patients, progressive disease in 13 patients, stable disease in 11 patients, and complete response in 6 patients. The serum calprotectin values of these cases were 74.99 ± 8.69 pg/mL, 77.25 ± 4.45 pg/mL, 91 ± 0 pg/mL, and 67.9 ± 12.77 pg/mL, respectively, and there was no statistically significant difference ($P$ = 0.185). After the completion of the planned treatment, progressive disease was observed in 1 case, stable disease in 2 cases, and complete response in 29 cases. Due to the small number of cases in the progressive and stable disease groups, the relationship between posttreatment response status and serum calprotectin level could not be investigated.

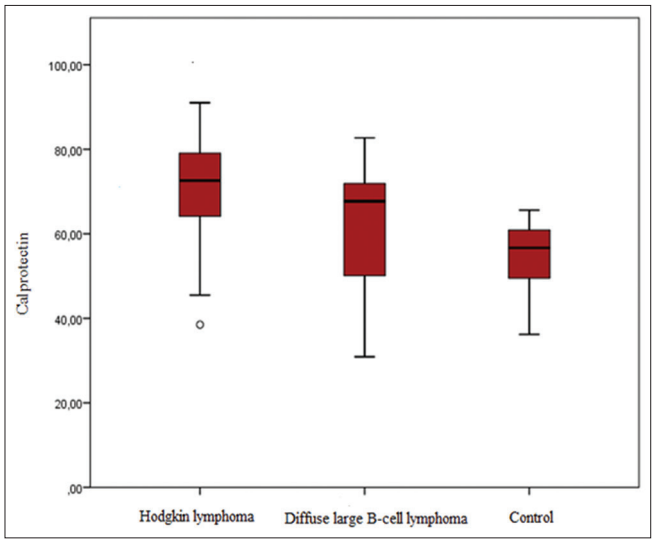


**Figure 1:** Serum calprotectin level in HL, DLBCL, and control groups. HL = Hodgkin lymphoma, DLBCL = Diffuse large B-cell lymphoma

**Table 3: The relationship between serum calprotectin level and clinical parameters in Hodgkin lymphoma cases**

| Parameters | Calprotectin level (pg/mL) | *P* |
|---|---|---|
| Bulky mass | | |
| Absent | 68.47±12.12 | 0.03 |
| Present | 80.65±7.79 | |
| B symptoms | | |
| Absent | 66.70±12.61 | 0.02 |
| Present | 76.68±9.43 | |
| Ann Arbor stage | | |
| Stage 1 | 50.42±16.85 | 0.001 |
| Stage 2 | 63.06±9.22 | |
| Stage 3 | 76.82±4.64 | |
| Stage 4 | 83.08±7.25 | |
| Extranodal involvement | | |
| Absent | 68.46±13.95 | 0.36 |
| Present | 74.58±8.09 | |
| ECOG score | | |
| ECOG 1 | 63.88±15.25 | 0.116 |
| ECOG 2 | 73.30±8.78 | |
| ECOG 3 | 80.67±8.10 | |
| ECOG 4 | | |
| IPS score (advanced stage cases) | | |
| Low + intermediate risk | 79.03±6.16 | 0.916 |
| High risk | 79.93±6.86 | |

ECOG=Eastern cooperative oncology group, IPS=International prognostic system

There was no significant correlation between serum calprotectin level and LDH, CRP, and B2 microglobulin levels in DLBCL cases ($r$ = 0.234, $P$ = 0.746; $r$ = 0.221, $P$ = 0.233; and $r$ = 0.224, $P$ = 0.226; respectively). A significant correlation was found between serum calprotectin level and only ECOG score and IPI score [Table 4].

In the evaluation of the intermediate response to treatment after two cycles of chemotherapy in the DLBCL group; partial response in 7 cases (calprotectin level = 70.53 ± 4.22 pg/mL), progressive disease in 2 cases (calprotectin level = 70.8 ± 1.41 pg/mL), stable disease in 4 cases (calprotectin level = 59.15 ± 19 pg/mL), and complete response in 18 cases (calprotectin level = 57.84 ± 14.25 pg/mL) were detected. No significant correlation was found between the intermediate response to treatment and serum calprotectin level ($P$ = 0.053). In the evaluation of response after treatment was completed, partial response was observed in 4 cases, progressive disease in 2 cases, stable disease in 2 cases, and complete response in 23 cases. Due to the low number of cases, the relationship between the response status and serum calprotectin level could not be investigated after the planned treatment was completed.

The follow-up period of the cases was 10 ± 2.1 months, and 6 (9.5%) of 63 lymphoma patients died due to disease-related causes during the follow-up period. The serum calprotectin level of the living cases was 66.15 ± 12.95 pg/mL, which was lower than that of the cases that died. However, there was no statistically significant difference ($P$ = 0.59). Univariable and multivariable Cox proportional hazards regression analyses were performed to determine the factors affecting survival. It was determined that the serum calprotectin level did not differ significantly according to survival in univariable evaluations ($P > 0.05$).

## Discussion

The importance of inflammation in the development and progression of cancer is known.[21,22] It is thought that genetic mutations that cause cancer occur more easily in the inflammatory environment.[22] For this

**Table 4: The relationship between serum calprotectin levels and clinical parameters in diffuse large B-cell lymphoma cases**

| Parameters | Calprotectin level (pg/mL) | *P* |
|---|---|---|
| ECOG score | | |
| ECOG 1 | 52.94±15.94 | 0.018 |
| ECOG 2 | 61.08±12.93 | |
| ECOG 3 | 71.4±2.98 | |
| Bulky mass | | |
| Absent | 61.6±13.43 | 0.726 |
| Present | 62.18±16.26 | |
| Bone marrow involvement | | |
| Absent | 59.02±15 | 0.13 |
| Present | 69.45±2.79 | |
| Extranodal involvoment | | |
| Absent | 56.56±14.91 | 0.231 |
| Present | 64.55±12.51 | |
| B symptoms | | |
| Absent | 58.78±14.2 | 0.144 |
| Present | 65.78±12.42 | |
| Ann Arbor stage | | |
| Stage 1 | 48.87±8.05 | 0.06 |
| Stage 2 | 54.34±16.46 | |
| Stage 3 | 58.81±16.21 | |
| Stage 4 | 70.43±3.22 | |
| IPI score | | |
| Low | 47.84±11.93 | 0.001 |
| Low-intermediate | 59.54±15.76 | |
| High | 69.69±6.52 | |

ECOG=Eastern cooperative oncology group, IPI=International prognostic index

reason, the importance of inflammatory biomarkers in the diagnosis of cancer cases has been investigated in various studies. Since inflammation plays an important role in the pathogenesis of lymphoma, inflammatory biomarkers have been investigated in the diagnosis of both HL and DLBCL cases. Hamed Anber *et al*. examined 37 HL and 44 non-HL cases in terms of inflammatory biomarkers (IL-1 β, IL-6, IL-10, tumor necrosis factor-α, monocyte chemotactic protein-1, granulocyte colony-stimulating factor, and eotaxin) in the diagnosis of lymphoma.[18] They noted that in cases with lymphoma, inflammatory biomarkers were elevated before treatment and decreased significantly after treatment. Bontekoe *et al*. studied 96 lymphoma cases and reported that the CRP value in lymphoma cases was significantly higher than that in the control group.[19] In the current study, we investigated the diagnostic importance of serum calprotectin level, which is an inflammatory biomarker. It was found that serum calprotectin levels were higher in our HL patients compared to the control group. Therefore, this study concludes that serum calprotectin levels can be used as an additional biomarker in the diagnosis of HL. It was also found that there were elevated serum calprotectin levels in DLBCL cases compared to the control group, but this difference was not statistically significant. This may be due to the small number of DLBCL cases.

Inflammatory cytokines are associated with worse survival in lymphoma cases.[20,23,24] Inflammatory biomarkers such as CRP, neutrophil/lymphocyte, and lymphocytes/monocyte ratios were associated with worse prognoses in DLBCL cases.[3,4,25] In this study, a significant relationship was found between the IPI risk score used to determine the prognosis of DLBCL patients and the serum calprotectin level. Hamed Anber *et al*. reported that the elevated serum inflammatory biomarkers were associated with severe disease.[18] In mixed-lineage leukemia-positive infant B-cell acute lymphoblastic leukemia cases, elevated calprotectin levels were associated with resistance to glucocorticoid therapy.[26] In another study, the elevated calprotectin level in acute myeloid leukemia cases was associated with resistance to venetoclax treatment.[27] Şumnu *et al.* did not find a significant relationship between the level of serum calprotectin level and the response to treatment in HL cases.[28] In the current study, there was no relationship between the intermediate response to treatment in HL and DLBCL cases and serum calprotectin levels.

The S100 family of proteins are calcium-binding proteins that form homodimeric or heterodimeric complexes with each other. Calprotectin is a heterodimeric complex of S100A8 and S100A9. While intracellular S100 proteins are effective in cell proliferation and differentiation through target proteins, extracellular S100 proteins may contribute to oncogenesis by activating JAK-STAT, NF-KB, and MAPK pathways.[29] For this reason, many studies investigating serum calprotectin levels in various cancer cases have been conducted.[30-32] Dysregulation of NF-KB and JAK-STAT signaling pathways is important in the pathogenesis of both HL and DLBCL. Therefore, we investigated the diagnostic importance of serum calprotectin levels in our HL and DLBCL cases.

There are conflicting results regarding the effects of serum calprotectin levels in cancer cases because calprotectin produced by immune cells has apoptotic properties. On the contrary, it has been reported that cancer cells secrete calprotectin, which is associated with metastasis and invasion. Calprotectin level in feces is approximately six times higher than that in serum. For this reason, fecal calprotectin levels were investigated in patients with gastrointestinal lymphoma and gastrointestinal tumors. Vincent *et al.* studied fecal calprotectin levels in 39 patients with upper gastrointestinal system cancer.[33] They found that the fecal calprotectin level was higher in patients with upper gastrointestinal tract cancer than that in the control group. Many studies have shown increased fecal calprotectin levels in colorectal cancer patients.[34-36] Lehmann *et al*. evaluated the level of calprotectin in the

stool of 80 patients with colorectal cancer preoperatively and 3 months postoperatively.[37] In 71.2% of the cases, calprotectin levels were high in the preoperative period and a statistically significant decrease was observed in the postoperative period. Calprotectin levels were higher in T3 and T4 stages cases than in T1 and T2 stages cases. In some studies, however, no correlation was found between the location and clinical stage of colorectal cancers and fecal calprotectin levels.[34,38] We determined that there was a significant positive correlation between serum calprotectin level, presence of bulky mass, and Ann Arbor stage in HL cases.

There are few studies investigating serum calprotectin levels in hematological patients. Krečak *et al.* investigated serum calprotectin levels in 43 chronic myeloproliferative diseases (CMPD) cases since inflammation plays a role in the pathogenesis of the Philadelphia-negative CMPD.[39] They reported that patients with an ECOG score of 2–4 had higher serum calprotectin levels. They also associated this condition with inflammation. We also found a significant correlation between serum calprotectin level and ECOG score in the DLBCL group.

Sumnu *et al.* studied serum calprotectin levels in 33 HL and 20 healthy subjects.[28] Calprotectin values of lymphoma patients before chemotherapy treatment were significantly higher than the control group, and this result was similar to our study result. However, they reported that calprotectin values after chemotherapy treatment were similar to the control group. We could not evaluate the calprotectin levels of the cases after chemotherapy treatment. Sumnu *et al*. stated that there was no significant correlation between pretreatment sedimentation and CRP values and calprotectin level; therefore, serum calprotectin level could be a sign of active disease independent of inflammation. In our study, while serum calprotectin level and sedimentation value were not significantly correlated, there was a significant correlation with CRP value. Therefore, more studies are needed to show the relationship between serum calprotectin levels and active disease in HL cases.

Studies have shown that neutrophil/lymphocyte, platelet/lymphocyte, and lymphocyte/monocyte ratios, which are inflammatory markers, have prognostic significance in newly diagnosed or relapsed DLBCL cases.[2-4] In our study, we found that calprotectin level was associated with prognostic markers such as LDH, beta 2 microglobulins, presence of bulky mass, presence of B symptom, and Ann Arbor stage in the HL group. In DLBCL cases, the serum calprotectin level was significantly associated with the IPI score used to determine the prognosis.

## Conclusion

As the pathogenesis of lymphoma disease is better understood, studies on both diagnostic and prognostic biomarkers are increasing. We conducted this study because inflammation is important in the pathogenesis of HL and DLBCL, and serum calprotectin level is an inflammatory biomarker. With our study results, we think that serum calprotectin level can be used as an additional diagnostic biomarker in HL cases. In addition, if our study results are supported by more studies, serum calprotectin levels may be a guide in terms of prognosis in HL and DLBCL cases.

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### Conflicts of interest

There are no conflicts of interest.

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