DOI: 10.14744/ejmi.2024.76627
EJMI 2024;8(4):226–232

Research Article

Prognostic Importance of Cyclooxygenase-2 Expression and Its Relationship with Histology in Non-Hodgkin's Lymphomas

Mehmet Gökhan Gönenli,[1] Yavuz Burak Tor,[2] Burçin Sağlam,[1] Bahar Tekin Çetin,[1] Faysal Dane[3]

[1]Department of Internal Medicine, Koc University, Faculty of Medicine, Istanbul, Türkiye
[2]Department of Internal Medicine, Memorial Bahcelievler Hospital, Istanbul, Türkiye
[3]Department of Medical Oncology, Acibadem Altunizade Hospital, Istanbul, Türkiye

Abstract

Objectives: The presence and prognostic relevance of cyclooxygenase-2 (COX-2) expression have been explored in various neoplasms, but its role in non-Hodgkin's lymphomas (NHLs) is poorly understood. This study aims to reveal the clinicopathologic and prognostic importance of COX-2 expression in NHLs.

Methods: Diagnostic tissue samples from 66 NHL patients were immunohistochemically stained to assess COX-2 expression, with a final cohort of 64 patients. Clinicopathological parameters were compared between COX-2 positive and negative groups.

Results: From a histological perspective, the indolent group comprised 21 patients (32.8%), while the aggressive group included 43 patients (67.2%). The samples of 26 patients (40.6%) were COX-2 positive and 38 (59.4%) were COX-2 negative. A significant relationship was observed between IHS scores and lymphoma aggressiveness (p=0.044), indicating a connection between COX-2 overexpression and aggressive histology. Response to treatment rate was 89.5% in COX-2 negative group and 73.1% in COX-2 positive group (p=0.088). The overall survival (OS) was 31.81 months for the COX-2 positive group and 34.87 months for the COX-2 negative group, with no statistically significant difference (p=0.581).

Conclusion: COX-2 overexpression is significantly associated with aggressive histology in NHLs. However, its impact on OS and treatment response needs further investigation with larger sample size.

Keywords: Cyclooxygenase-2, expression, non-Hodgkin lymphoma, prognosis

Cite This Article: *Gönenli MG, Tor YB, Sağlam B, Tekin Çetin B, Dane F. Prognostic Importance of Cyclooxygenase-2 Expression and Its Relationship with Histology in Non-Hodgkin's Lymphomas. EJMI 2024;8(4):226–232.*

Non-Hodgkin's lymphomas (NHLs) constitute a diverse group of lymphoproliferative disorders. Over the past two decades, the incidence of newly diagnosed NHL has been 2.7-2.8% of all cancers. Despite stable incidence rates, a significant increase in newly diagnosed cases of NHL has been observed, which appears to parallel the overall escalation in malignant diagnoses.[1,2] According to global data, more than half a million people were diagnosed with NHL in 2020, making it the 13th most common cancer type among newly diagnosed cancers.[2] Despite all the clinical, morphological, and molecular parameters used to classify this group of lymphoproliferative disorders, the prognosis can be remarkably different from patient to patient.

Address for correspondence: Yavuz Burak Tor, MD. Department of Internal Medicine, Memorial Bahcelievler Hospital, Istanbul, Türkiye
Phone: +90 530 580 05 92 **E-mail:** yavuzburaktor@gmail.com

Submitted Date: August 07, 2024 **Revision Date:** December 08, 2024 **Accepted Date:** December 17, 2024 **Available Online Date:** November 16, 2025

Cyclooxygenase (COX) is responsible for converting arachidonic acid into prostaglandins. This enzyme exists in three different isoforms: COX-1, COX-2, and COX-3, with COX-1 being the ubiquitous form responsible for maintaining homeostatic functions.[3] COX-3 is a novel isoform produced by the COX-1 gene.[4] COX-2 is the inducible isoform responsible for inflammation and has an important role in carcinogenesis. COX-2 has binding sites for nuclear factor-κβ, several cytokines including interleukin (IL)-6, and numerous mediators. When released into the tumor microenvironment, it causes apoptosis resistance, tumor growth, angiogenesis, and metastasis via upregulation of Bcl-2, epidermal growth factor receptor, vascular endothelial growth factor, and metalloproteinases, respectively.[5] These illustrate only a fraction of the established functions of COX-2 in carcinogenesis. The overexpression of COX-2 and its relationship with cancer prognosis has therefore attracted the attention of researchers for decades. COX-2 has been shown to be expressed in many different types of solid tumours, including gastrointestinal, breast, head and neck, gynaecological, lung, urinary tract and papillary thyroid cancers.[6-14]

The impact of COX-2 expression has been investigated in several haematological cancers, including multiple myeloma and lymphoma. Numerous reports indicate a correlation between COX-2 expression and unfavourable prognosis, as well as shorter progression-free intervals in multiple myeloma.[15-17] Similarly, there is evidence linking the absence of COX-2 with better therapeutic response rates, its presence with reduced overall survival, and its inhibition with increased apoptosis in lymphoma.[18-20] While a large number of studies have linked COX-2 expression to increased metastatic activity and poor prognosis in several cancer types, both in the laboratory and in vivo, comprehensive data on its expression in NHL are still scarce.

This study was conducted to assess the prognostic implications of COX-2 expression in NHL patients using immunohistochemical analysis. Its association with clinical and pathological parameters and prognostic indicators was also investigated.

Methods

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki at all stages and was approved by the ethics committee of the university where the research was carried out. Written informed consent was obtained from all participants in the study.

Patients over 18 years of age who were diagnosed with NHL and followed up in the haematology and medical oncology polyclinics of Marmara University Medical Faculty Hospital between 2002 and 2008 were retrospectively screened. A total of 214 NHL patients who met the study criteria were included in the preliminary assessment. Patients diagnosed in the last six months, patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma, and patients who died of another cause after being diagnosed with lymphoma were not included in the study.

Patient Groups

Patients were staged according to the Ann Arbor staging system. Histological evaluation was performed according to the World Health Organization classifications.[21] Biopsy specimens were divided into three subclasses based on the aggressiveness of the lymphoma subtype:

The indolent group with slow progression includes follicular lymphoma, extranodal marginal zone B-cell lymphoma, peripheral T-cell lymphoma and lymphoplasmacytic lymphoma. The aggressive group includes diffuse large B-cell lymphoma and mantle cell lymphoma. The highly aggressive group includes Burkitt's lymphoma and precursor lymphoblastic lymphoma.

For statistical analysis, aggressive and very aggressive lymphomas were considered as a single group, the aggressive group. For all study participants, International Prognostic Index (IPI) scores were derived using Eastern Cooperative Oncology Group (ECOG) performance status and serum lactate dehydrogenase (LDH) measurements obtained at the first outpatient visit. An age-adjusted IPI score was used for patients aged 60 years or younger. An IPI score of 0-1 defines low risk, 2 defines low intermediate risk, 3 defines high intermediate risk, and 4-5 defines high risk.[22]

Histological Examination

Immunohistochemical reactivity was quantified using the modified Histoscore (H-score) method, which combines a semiquantitative analysis that includes the intensity of staining scored on a scale; (İ)0 for no staining, (İİ)1 for weak, (İİİ)2 for moderate (using adjacent normal mucosa as a reference for moderate), and (İİİİİ)3 for strong staining. The percentage of stained cells was determined for each group.[23] The final H-score was calculated using the equation: 3 times the percentage of strongly stained nuclei, plus 2 times the percentage of moderately stained nuclei, plus the percentage of weakly stained nuclei. The score can range from 0 to 300. A score of less than 50 indicates COX-2 negative status, whereas a score of 50 or more indicates COX-2 positive status.

Statistical Analysis

The relationship between COX-2 expression and patients' demographic, clinical, radiological, and histological data was evaluated, including age, gender, performance status, IPI scores, disease stage, B symptoms, extranodal involvement, organomegaly, lymphadenopathy, cytopenias, and levels of lactate dehydrogenase (LDH) and beta-2 microglobulin levels, as well as treatment response and recurrence.In addition, the potential correlation between IHS scores (H-score) and histological subtypes (indolent versus aggressive) was investigated. The difference in overall survival between the COX-2 positive and negative groups was also assessed. Finally, to assess the reliability and consistency of the study data, the statistical significance of certain parameters known to influence overall survival (such as IPI, ECOG performance score, and B2M) was analyzed in relation to the overall survival data of the patients.

SPSS ver. 22.0 was used for statistical analysis (IBM Corp., Armonk, NY). Descriptive statistics were expressed as mean±standard deviation (SD), with minimum and maximum values given where appropriate. Categorical variables were expressed as frequencies (n) and percentages (%). Associations between clinical factors and COX-2 staining were assessed by chi-squared test. The effect of factors on survival was determined by Kaplan-Meier analysis using log-rank test values. Univariate analysis of the parameters was performed. Results are presented as mean±SD with 95% confidence interval and $p<0.05$ significance level.

Results

In 148 of the 214 patients, biopsy blocks could not be obtained or were insufficient for analysis. After these 148 patients were excluded, the study continued with 66 patients. The median age was 55 years (21-89) and 38 patients (57.6%) were male. The median follow-up was 30 months. Histological examination revealed localised lymphoma involvement in the biopsy specimens of two cases, which could lead to a false H-score. These patients were therefore excluded from the study and the study continued with 64 patients.

Histological examination revealed that 32.8% of the subjects (21 individuals) were classified as having indolent lymphoma, while the remaining 67.2% (43 individuals) were classified as having aggressive lymphoma. In terms of disease stage, 34.4% of participants (22 individuals) were diagnosed with stage I or II disease, while 65.6% (42 individuals) were diagnosed with stage III or IV disease. According to the International Prognostic Index, 35.9% of patients (23 individuals) were classified as low risk, 56.3% (36 individuals) as low-to-high intermediate risk and 7.8% (5 individuals) as high risk.

COX-2 positivity was detected in the samples from 40.6% of patients (n=26), while it was absent in 59.4% (n=38). In patients with indolent lymphoma, the rate of COX-2 expression was 38.10% (8 out of 21 patients), while in patients with aggressive and highly aggressive histology, it reached 41.86% (18 out of 43 patients). However, the discrepancy in COX-2 expression levels between the indolent and more aggressive groups was not statistically significant, with a p-value of 0.986. Among the 53 patients who achieved remission, COX-2 was expressed in 19 cases (35.9%) and not expressed in 34 cases (64.1%). In contrast, COX-2 was positively expressed in seven of the 11 patients (63.63%) who experienced disease progression. When comparing the relationship between chemotherapy response and COX-2 expression, the stable-progressive disease rate was 26.9% (7/26) in COX-2 positive patients and 10.5% (4/38) in COX-2 negative patients (p=0.088) (Table 1).

No significant association was observed between COX-2 expression and variables such as liver function tests, age, gender, performance status, stage of disease, extranodal involvement, hepatomegaly, splenomegaly, lymphadenopathy, presence of anaemia, leukopenia, thrombocytopenia, lactate dehydrogenase (LDH) levels and beta-2 microglobulin ($p>0.05$). Although there was no significant difference in COX-2 expression rates between different histologies, there was a meaningful association between immunohistochemical staining (IHS) scores and histology (indolent versus aggressive and very aggressive) with a p-value of 0.044.

Patients with COX-2 expression (n=26) had a mean overall survival of 31.81 months, which was slightly shorter than patients without COX-2 expression (n=38), who had a mean overall survival of 34.87 months (p=0.581) (Fig. 1). Kaplan-Meier survival analysis and log-rank test were used to evaluate the impact of different prognostic factors on survival. The performance score (PS) was significantly associated with overall survival (p=0.005), and the International Prognostic Index (IPI) also showed a significant association (p=0.041). A borderline association was observed for beta-2 microglobulin (B2MG) with a p-value of 0.077.

Discussion

Current research demonstrates the influence of COX-2 induction at all stages of carcinogenesis. COX-2 is associated with tumour progression, impaired apoptosis and metasta-

Table 1. Evaluation of demographic, clinical, and laboratory parameters and comparison between the groups

Parameters	COX-2 negative (n=38)	COX-2 positive (n=26)	Total (n=64)	p
Age				
<60	22	18	40	0.358
≥60	16	8	24	
Gender				
Male	21	16	37	0.618
Female	17	10	27	
Performance Score				
0-1	30	18	48	0.378
2-3-4	8	8	16	
Histology				
Indolent	13	8	21	0.986
Aggressive	25	18	43	
B symptoms				
Absent	17	8	25	0.261
Present	21	18	39	
Extranodal involvement				
Absent	21	16	37	0.618
Present	17	10	27	
Hepatomegaly				
Absent	33	22	55	0.801
Present	5	4	9	
Splenomegaly				
Absent	29	22	51	0.418
Present	9	4	13	
Lymphadenopathy				
Absent	11	3	14	0.098
Present	27	23	50	
Anemia*				
Absent	23	13	36	0.404
Present	15	13	28	
Lactate dehydrogenase				
Normal (<250 IU/L)	18	9	27	0.310
High (≥250 IU/L)	20	17	37	
Beta-2 Microglobulin				
Normal (<2.4 mg/L)	20	9	29	0.155
High (≥2.4 mg/L)	18	17	35	
Stage				
I-II	14	8	22	0.615
III-IV	24	18	42	
IPI Score				
0-1	13	10	23	0.560
2-3	23	13	36	
4-5	2	3	5	
Response to treatment				
Absent (SD-PD)	4	7	11	0.088
Present (CR–PD)	34	19	53	
Recurrence				
Absent	21	12	33	0.394
Present	13	7	20	
Progressive disease	4	7	11	

* Anemia is defined as hemoglobin <12 g/dL for women and <13 g/dL for men; IPI: International prognostic index; CR: Complete remission; PR: Partial remission; SD: Stable disease; PD: Progressive disease

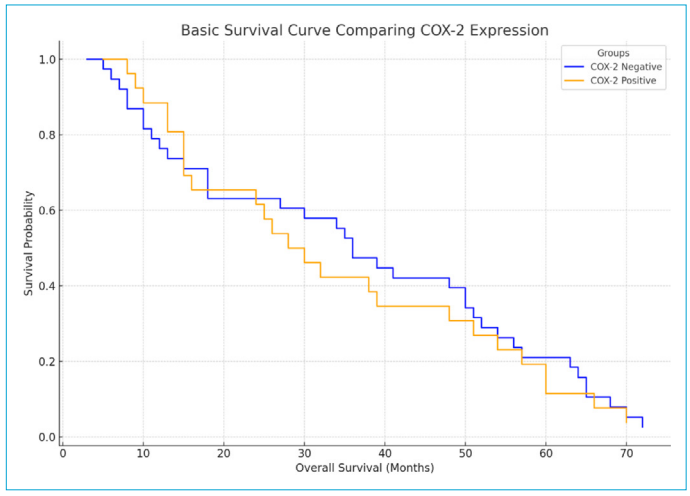

Figure 1. Kaplan-Meier analysis of overall survival in patients with positive versus negative COX-2 expression (p=0.581).

sis through the regulation of gene expression, growth factors, cytokines, mediators and enzymes, not only through prostaglandins.[5]

There is evidence that COX-2 expression in solid tumors correlates with increased tumor invasiveness, metastatic activity and poor prognosis.[11,12,24] However, several reports contradict this and show that COX-2 expression has no significant prognostic value or impact on overall survival.[9,25,26] Although the data show that COX-2 expression has a clear effect on cancer pathogenesis, there are conflicting results regarding its effect on prognosis, and similar results apply to haematological neoplasms. This discrepancy is not surprising given the complex pathogenesis of critical carcinogenic steps such as apoptosis resistance, cell proliferation, invasion and metastasis, where multiple genes, proteins, mediators and enzymes play a role in addition to COX-2.

Conversely, meta-analytic studies have shown that COX-2 inhibition by non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced incidence of breast and colon cancer and a reduction in the number and size of colon polyps.[27,28] In addition, some studies have demonstrated the benefit of COX-2 inhibition in multiple myeloma through the induction of myeloma cell apoptosis, and COX-2 inhibitors have been proposed as alternative therapies.[29,30] Results from a multicentre phase II trial showed improved response rates and progression-free and overall survival in patients with relapsed and refractory multiple myeloma treated with a combination of thalidomide and celecoxib. However, the combination was associated with unacceptable toxicity.[31]

A review of the literature shows a lack of consensus regarding the prognostic value of COX-2 in lymphoma. For example, a study of 52 lymphoma patients found no significant correlation between COX-2 positivity and overall survival;

however, COX-2 positive patients with more advanced disease stages had lower treatment response rates.[18] Conversely, another study of 177 cases of non-Hodgkin's lymphoma (NHL) reported a significant association between COX-2 positivity and aggressive histology.[32] In addition, a separate study of paediatric NHL patients found no significant association between COX-2 expression and variables such as histology or prognosis.[33]

Furthermore, a study of 50 patients with small lymphocytic lymphoma and 100 patients with diffuse large B-cell lymphoma showed a significant association between COX-2 expression and advanced disease stage, high-grade lymphoma and disease relapse. The results of this study also suggested that COX-2 may act as a negative prognostic factor, correlating with shorter overall and progression-free survival.[34] The inconsistent results of these studies highlight the need to consider the biological heterogeneity of lymphoma subtypes when interpreting the prognostic value of COX-2.

In line with this, our study showed that patients with COX-2 expression had a shorter mean overall survival compared to patients without COX-2 expression. However, this difference was not statistically significant (p=0.581), indicating that COX-2 positivity alone does not have a significant impact on overall survival in our cohort. These findings suggest that COX-2 expression, despite its potential biological significance, may not be a reliable independent prognostic indicator in this patient population.

This study showed a discrepancy between the COX-2 expression rates and the p-values associated with the IHS scores for histological aggressiveness. While the p-value for the difference in COX-2 expression rates between our patient groups was 0.986, indicating no statistically significant difference, the p-value for the relationship between IHS scores and histological aggressiveness was 0.044, indicating a statistically significant association. This means that although the rates of COX-2 positivity did not differ significantly between the histological subgroups in our study cohort, the intensity of COX-2 expression (referred to as COX-2 overexpression) was significantly associated with histological aggressiveness. This finding warrants further investigation, as it suggests that the impact of COX-2 expression on the clinical course of NHL may be more complex than initially thought.

One of the strengths of our study is its ability to differentiate the significance of COX-2 positivity and IHS scores in NHL. While COX-2 expression alone did not show a significant impact on overall survival, the association of IHS scores with histological aggressiveness provides a valuable perspective. This distinction suggests that focusing on IHS may provide a clearer understanding of prognosis in these patients. Furthermore, parameters such as PS and IPI, which are well-established prognostic factors, were also found to be significantly associated with overall survival in our analysis. This finding not only reinforces the reliability of our study data, but also demonstrates the robustness of our methodological approach and its consistency with previous research.

This study has several limitations. The first limitation is its retrospective nature. From a scientific perspective, the lack of data on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors during patient follow-up is a significant gap, as COX-2 inhibition could potentially alter the course of the disease, particularly in COX-2-positive patients. In addition, the small patient sample size may have contributed to the lack of statistically significant differences in overall survival and treatment response rates between the COX-2 negative and positive groups. Finally, considering that NHLs comprise a diverse range of over 20 different lymphoid tumours, the prognostic impact of COX-2 expression may differ between these specific types, a variable not explored in this investigation.

Conclusion

The results of this study indicate that COX-2 expression alone is not significantly associated with overall survival. However, increased COX-2 expression (overexpression) is associated with NHL aggressiveness through its association with higher IHS scores. These findings highlight the need for further research to elucidate the prognostic role of COX-2 in more detail, particularly through studies that comprehensively investigate IHS scores and include larger patient cohorts with prospective designs. It would also be beneficial for future studies to consider the potential effects of NSAID and COX-2 inhibitor use to provide more reliable evidence.

Disclosures

Ethics Committee Approval: This study was approved by the Marmara University Faculty of Medicine Ethics Committee (Date: 27.07.2007, No: 155).

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors covered all financial needs of this study.

Authorship Contributions: Concept – M.G.G., F.D.; Design – M.G.G., Y.B.T.; Supervision – F.D.; Materials – Y.B.T., B.S., B.T.C.; Data collection &/or processing – M.G.G., Y.B.T., B.S., B.T.C.; Analysis and/or interpretation – M.G.G.; Literature search – B.S., B.T.C., F.D.; Writing – Y.B.T.; Critical review – M.G.G., F.D.

References

1. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999;49(1):33-64.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3):209-49.
3. Crofford LJ. COX-1 and COX-2 tissue expression: implications and predictions. J Rheumatol Suppl 1997;49:15-9.
4. Shaftel SS, Olschowka JA, Hurley SD, Moore AH, O'Banion MK. COX-3: a splice variant of cyclooxygenase-1 in mouse neural tissue and cells. Brain Res Mol Brain Res 2003;119(2):213-5.
5. Hashemi Goradel N, Najafi M, Salehi E, Farhood B, Mortezaee K. Cyclooxygenase-2 in cancer: A review. J Cell Physiol 2019;234(5):5683-99.
6. Sano H, Kawahito Y, Wilder RL, Hashiramoto A, Mukai S, Asai K, et al. Expression of cyclooxygenase-1 and -2 in human colorectal cancer. Cancer Res 1995;55(17):3785-9.
7. Ohno R, Yoshinaga K, Fujita T, Hasegawa K, Iseki H, Tsunozaki H, et al. Depth of invasion parallels increased cyclooxygenase-2 levels in patients with gastric carcinoma. Cancer 2001;91(10):1876-81.
8. Brodie AM, Lu Q, Long BJ, Fulton A, Chen T, Macpherson N, et al. Aromatase and COX-2 expression in human breast cancers. J Steroid Biochem Mol Biol 2001;79(1-5):41-7.
9. Atula T, Hedström J, Ristimäki A, Finne P, Leivo I, Markkanen-Leppänen M, et al. Cyclooxygenase-2 expression in squamous cell carcinoma of the oral cavity and pharynx: association to p53 and clinical outcome. Oncol Rep 2006;16(3):485-90.
10. Erkanli S, Bolat F, Kayaselcuk F, Demirhan B, Kuscu E. COX-2 and survivin are overexpressed and positively correlated in endometrial carcinoma. Gynecol Oncol 2007;104(2):320-5.
11. Chen YJ, Wang LS, Wang PH, Lai CR, Yen MS, Ng HT, et al. High cyclooxygenase-2 expression in cervical adenocarcinomas. Gynecol Oncol 2003;88(3):379-85.
12. Khuri FR, Wu H, Lee JJ, Kemp BL, Lotan R, Lippman SM, et al. Cyclooxygenase-2 overexpression is a marker of poor prognosis in stage I non-small cell lung cancer. Clin Cancer Res 2001;7(4):861-7.
13. Mohammed SI, Knapp DW, Bostwick DG, Foster RS, Khan KN, Masferrer JL, et al. Expression of cyclooxygenase-2 (COX-2) in human invasive transitional cell carcinoma (TCC) of the urinary bladder. Cancer Res 1999;59(22):5647-50.
14. Kajita S, Ruebel KH, Casey MB, Nakamura N, Lloyd RV. Role of COX-2, thromboxane A2 synthase, and prostaglandin I2 synthase in papillary thyroid carcinoma growth. Mod Pathol 2005;18(2):221-7.
15. Ladetto M, Vallet S, Trojan A, Dell'Aquila M, Monitillo L, Rosato R, et al. Cyclooxygenase-2 (COX-2) is frequently expressed in multiple myeloma and is an independent predictor of poor outcome. Blood 2005;105(12):4784-91.
16. Trojan A, Tinguely M, Vallet S, Seifert B, Jenni B, Zippelius A, et al. Clinical significance of cyclooxygenase-2 (COX-2) in multiple myeloma. Swiss Med Wkly 2006;136(25-26):400-3.
17. Cetin M, Buyukberber S, Demir M, Sari I, Sari I, Deniz K, et al. Overexpression of cyclooxygenase-2 in multiple myeloma: association with reduced survival. Am J Hematol 2005;80(3):169-73.
18. Hazar B, Ergin M, Seyrek E, Erdogan S, Tuncer I, Hakverdi S. Cyclooxygenase-2 (Cox-2) expression in lymphomas. Leuk Lymphoma 2004;45(7):1395-9.
19. Koh YW, Park C, Yoon DH, Suh C, Huh J. Prognostic significance of COX-2 expression and correlation with Bcl-2 and VEGF expression, microvessel density, and clinical variables in classical Hodgkin lymphoma. Am J Surg Pathol 2013;37(8):1242-51.
20. Gallouet AS, Travert M, Bresson-Bepoldin L, Guilloton F, Pangault C, Caulet-Maugendre S, et al. COX-2-independent effects of celecoxib sensitize lymphoma B cells to TRAIL-mediated apoptosis. Clin Cancer Res 2014;20(10):2663-73.
21. Economopoulos T, Papageorgiou S, Dimopoulos MA, Pavlidis N, Tsatalas C, Symeonidis A, et al. Non-Hodgkin's lymphomas in Greece according to the WHO classification of lymphoid neoplasms. A retrospectiveanalysis of 810 cases. Acta Haematol 2005;113:97-103.
22. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987-94.
23. McCarty KS Jr., Miller LS, Cox EB, Konrath J, McCarty KS Sr. Estrogen receptor analyses. Correlation of biochemical and immunohistochemical methods using monoclonal antireceptor antibodies. Arch Pathol Lab Med 1985;109:716-21.
24. Ferrandina G, Lauriola L, Zannoni GF, Distefano MG, Legge F, Salutari V, et al. Expression of cyclooxygenase-2 (COX-2) in tumour and stroma compartments in cervical cancer: clinical implications. Br J Cancer 2002;87(10):1145-52.
25. Zhang H, Sun XF. Overexpression of cyclooxygenase-2 correlates with advanced stages of colorectal cancer. Am J Gastroenterol 2002;97(4):1037-41.
26. Richardson CM, Richardson D, Swinson DE, Swain WA, Cox G, O'Byrne KJ. Cyclooxygenase-2 protein levels are independent of epidermal growth factor receptor expression or activation in operable non-small cell lung cancer. Lung Cancer 2005;48(1):47-57.
27. de Pedro M, Baeza S, Escudero MT, Dierssen-Sotos T, Gómez-Acebo I, Pollán M, et al. Effect of COX-2 inhibitors and other non-steroidal inflammatory drugs on breast cancer risk: a meta-analysis. Breast Cancer Res Treat 2015;149(2):525-36.
28. Taketo MM. Cyclooxygenase-2 inhibitors in tumorigenesis (Part II). J Natl Cancer Inst 1998;90(21):1609-20.
29. Kardosh A, Soriano N, Liu YT, Uddin J, Petasis NA, Hofman FM, et al. Multitarget inhibition of drug-resistant multiple my-

eloma cell lines by dimethyl-celecoxib (DMC), a non-COX-2 inhibitory analog of celecoxib. Blood 2005;106(13):4330-8.
30. Zhang M, Abe Y, Matsushima T, Nishimura J, Nawata H, Muta K. Selective cyclooxygenase 2 inhibitor NS-398 induces apoptosis in myeloma cells via a Bcl-2 independent pathway. Leuk Lymphoma 2005;46(3):425-33.
31. Prince HM, Mileshkin L, Roberts A, Ganju V, Underhill C, Catalano J, et al. A multicenter phase II trial of thalidomide and celecoxib for patients with relapsed and refractory multiple myeloma. Clin Cancer Res 2005;11(15):5504-14.
32. Paydas S, Ergin M, Erdogan, S, Seydaoglu, G. Cyclooxygenase-2 expression in non-Hodgkin's lymphomas. Leuk Lymphoma 2007;48(2),389-95.
33. Aktas S, Kargi A, Olgun N, Diniz G, Erbay A, Vergin C. Prognostic significance of cyclooxygenase-2 expression in pediatric Hodgkin and non-Hodgkin lymphomas with or without Epstein-Barr virus latent infection. Comp Clin Pathol 2008;17(2):125–31.
34. Zaky AH, Elsers D, Bakry R, Abdelwanis M, Nabih O, Hafez R, et al. Prognostic value of accumulative expression of COX-2 and p53 in small and diffuse large B cell lymphoma. Pathol Oncol Res 2020;26,1183-90.