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RESEARCH ARTICLE

Cyclooxygenase-2 expression as a prognostic factor in pediatric classical Hodgkin lymphoma

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Abstract

Purpose Cyclooxygenase-2 (COX-2) is an inflammation-related enzyme that has been shown to have a role in tumor initiation, angiogenesis, and proliferation. It has been demonstrated that COX-2 expression is increased in many tumors and is a negative prognostic parameter. Our objective is to investigate the prognostic value of COX-2 expression in pediatric patients with classical Hodgkin lymphoma (CHL).

Methods This was a retrospective analysis in pediatric patients ($n=127$) diagnosed with CHL and treated at the pediatric oncology department, National Cancer Institute, Cairo University, January 2005–June 2013. We correlated COX-2 immunostaining in Reed–Sternberg (RS) cells with clinical variables and outcome.

Results COX-2 was expressed on 38.6% of RS cells. The median follow-up time was 48.4 months (range 4–114 months). The 5-year OS and PFS, in COX-2(+ve) versus COX-2(−ve) was 85.3% versus 96.0% ($p=0.248$) and 78.6% versus 84.3% ($p=0.354$), respectively. A multivariate analysis showed that COX-2(+ve) was not significantly associated with the 5-year OS (HR = 2.9; 95% CI 0.7–12.4, $p=0.149$) or with the 5-year PFS (HR = 1.4; 95% CI 0.6–3.2, $p=0.490$). High-risk patients in the COX-2(+ve) group had a significantly lower 5-year OS ($p=0.021$). The 5-year PFS was significantly lower in the COX-2(+ve) group with B symptoms ($p=0.023$) and bulky disease ($p=0.028$). Radiotherapy was given only to high-risk patients; survival was much better in radiation-treated children in both the Cox-2(+ve) and Cox-2(−ve) groups. The magnitude of the radiotherapy effect was also greater in the Cox-2(+ve) group, but this difference was not statistically significant.

Conclusion COX-2 expression showed a tendency to be a poor prognostic factor, but it failed to provide meaningful independent information. Further larger studies are needed to investigate COX-2 as a prognostic factor and potential therapeutic target.

Keywords COX-2 · Prognostic factor · Radiotherapy · Pediatric · Classical Hodgkin lymphoma

Introduction

Classical Hodgkin lymphoma (CHL) is defined by the World Health Organization (WHO) as a monoclonal lymphoid neoplasm composed of mononuclear Hodgkin cells and binucleated Reed–Sternberg (RS) cells residing in an infiltrate containing a variable mixture of nonneoplastic small lymphocytes, eosinophils, neutrophils, histiocytes, plasma cells, fibroblasts and collagen fibers [1]. The incidence of CHL varies widely worldwide and is based on geographic location as well as on socioeconomic and immunologic status. CHL accounts for approximately 7% of childhood cancers and 1% of childhood deaths in the United States, and it also accounts for approximately 10% of all lymphomas and 0.6% of all cancer diagnoses in developed countries annually [2].

Cytokines and chemokines in the milieu of CHL tissues are complex and interactive. This environment leads to heterogeneous background cellular composition and contributes to the proliferative and anti-apoptotic phenotype of RS cells. Understanding this biology is clinically important to implement therapies targeting disruption of this crosstalk between malignant cells and the microenvironment [3]. Different prognostic factors have been identified in CHL including

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stage, bulky disease, B symptoms, erythrocyte sedimentation rate (ESR), extra nodal extension, leukocyte count and male gender. Identification of new biological factors can allow further stratification of patients who may obtain a benefit from specific treatment regimens with the aim of reducing chemotherapy's late side effects [4].

The cyclooxygenase enzyme and its end products, prostaglandins (PG) [5], have been thoroughly investigated for their association with various health conditions, including inflammation, thrombosis, arthritis, atherosclerosis and cancer. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandins. Some studies reported that the long-term use of NSAIDs, especially aspirin, can reduce cancer incidence, and most significantly, can reduce cancer mortality [6]. Cyclooxygenases have three known isoforms: COX-1, COX-2, and COX-3. COX-1 and COX-2 usually catalyze the rate limiting step of prostaglandin synthesis. COX-2 is induced by pro-inflammatory stimuli, growth factors, and tumor promoters to increase the rate of prostaglandin synthesis after tissue injury [5].

COX-2 overexpression has been consistently associated with malignant transformation of healthy tissue, cellular proliferation, invasiveness, and unfavorable outcome [7]. Cancers such as colorectal, lung [8], prostate [9], cervical [10], ovarian [11], bone [12], breast [13], gastric, pancreatic and certain head and neck squamous cell cancers were found to be associated with COX-2 overexpression [5]. Here, we aim to analyze COX-2 expression in pediatric patients diagnosed with classical Hodgkin lymphoma to explore its association with prognostic factors and patient outcome.

Materials and methods

Study population

This is a retrospective study that included 127 pediatric patients diagnosed with classical Hodgkin lymphoma who were treated at the National Cancer Institute, Cairo University. This study included patients who presented from January 2005 until June 2013, and patients were followed-up until August 2015. Clinical, radiological and laboratory data were collected from the patient's files. Staging was based on the Ann Arbor Staging Classification [14]. Risk assessment was performed initially: stages IA and IIA without bulky disease or extra nodal extension were considered to indicate low-risk patients; stage IA or IIA with bulky disease or extra nodal extension, stage IB or IIB, and stage IIIA were considered intermediate risk, and stage IIIB and IV indicated a high risk [15]. Our patients had been uniformly treated with 2–8 cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) with or without radiation therapy according to risk stratification. Response assessment and follow-up were based on the Cheson criteria [16]. Institutional Review Board (IRB) approval was obtained at our institute.

Histopathologic assessment

Archival paraffin blocks of all cases included in the study were obtained from the surgical pathology department at the National Cancer Institute, Cairo University. All hematoxylin & eosin (H&E) and immunohistochemically stained sections (CD15 and CD30) were reviewed to confirm the diagnosis and to classify the cases into histologic subtypes according to the WHO classification [17].

Immunostaining for COX-2 was performed using a mouse monoclonal antibody (clone SP21) and a Cell Marque and Bench Mark XT (Ventana) autostainer. Assessment of COX-2 immunostaining was performed using an Olympus light microscope (BX 51), and the percentage of positively stained RS cells was recorded by dividing the number of those cells by the total number of RS cells in five representative fields at 400× magnification. The staining of histiocytes within the CHL infiltrates served as an internal control. COX-2 is considered to be positive when more than 10% of HRS cells express this marker [18].

Statistical consideration

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 20. Numerical data were expressed as the mean and standard deviation, median and range as appropriate. Qualitative data were expressed as frequencies and percentages. The Chi-square (Fisher's exact) test was used to examine the relationship between qualitative variables as appropriate. The survival analysis was performed using the Kaplan–Meier method. Comparison between two survival curves was performed using the log rank test. p values < 0.05 were considered significant. Multivariate proportional hazards Cox regression was used to adjust for prognostic variables associated with OS and PFS. Regression was performed using R statistical environment (version 3.4.0) and the R package survival (version 2.41-3).

Results

Clinicopathologic characteristics

A total of 127 children with CHL were included in this analysis with a median age of 9 years (range 2–18 years). The percentages of males and females were 87/127 (68.5%) and 40/127 (31.5%), respectively, with a ratio of 2.1:1. B symptoms, bulky disease, and extra nodal disease were observed in 28.3%, 22%, and 22% cases, respectively. Patients were staged as stage I, II, III and IV in 18.9%, 37.8%, 26% and

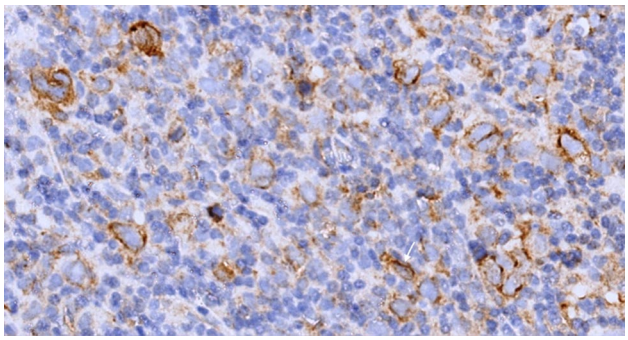

Fig. 1 A case of classical Hodgkin lymphoma of the mixed cellularity type with positive COX-2 expression in Reed–Sternberg cells (×400 original magnification)

17.3%, respectively. Moreover, 36.2%, 36.2% and 27.6% patients were classified as low, intermediate and high risk, respectively. Of all cases, 46.4%, 44.9% and 8.7% were subtyped as mixed cellularity, nodular sclerosis and lymphocyte-rich types, respectively, and no lymphocyte-depleted cases were included in our cohort.

COX-2 immunostaining

COX-2 expression was detected either in the cytoplasm or the cell membrane of RS cells (Fig. 1) in 49/127 (38.6%) cases. The association between COX-2 and clinicopathologic variables is shown in Table 1. Higher COX-2 expression was noted among cases characterized by age younger than 5 years (51.7%), male gender (39.1%), occurrence of B symptoms (47.2%), bulky disease (50%), extra nodal involvement (50%), nodular sclerosis subtype (45.6%), advanced stage (41.8%), and intermediate (45.7%)/high risk (42.9%), but the difference in expression was not statistically significant.

Patient follow-up

Patients were followed-up for a median of 48.4 months (range 4–114 months) and had a 5-year OS rate of 91.3%. The correlation between clinicopathological variables and the 5-year OS is listed in Table 2. The best estimates were achieved in patients younger than 5 years (100%), in those where extra nodal involvement was absent (96.5%), patients with stage I disease (100%), and those classified as low (97.3%)/intermediate risk (97.8%). In contrast, the worst estimates were noted among patients older than 11 years (79.1%), those with extra nodal involvement (70.7%), patients with stage IV disease (62.9%), and those classified as high risk (72.6%). These differences were statistically significant at $p=0.028$, $p=0.001$, $p=0.001$ and $p=0.003$. Better estimates were observed for the mixed cellularity subtype, stage II/III disease, cases where B symptoms were absent and cases where bulky disease was absent. However, these differences were not significant.

Table 1 Association between COX-2 and clinicopathological variables

	COX-2				*p* value
	Negative		Positive		
	No.	%	No.	%	
Age (years)					
< 5	14	48.3	15	51.7	0.194
5–11	30	65.2	16	34.8	
> 11	34	65.4	18	34.6	
Gender					
Male	53	60.9	34	39.1	0.784
Female	25	62.5	15	37.5	
B symptoms					
No	59	64.8	32	35.2	0.153
Yes	19	52.8	17	47.2	
Bulky					
No	64	64.6	35	35.4	0.170
Yes	14	50.0	14	50.0	
Extra nodal involvement					
No	64	64.6	35	35.4	0.170
Yes	14	50.0	14	50.0	
Pathology					
Lymphocyte-rich	7	63.6	4	36.4	
Mixed cellularity	40	67.8	19	32.2	0.275
Nodular sclerosis	31	54.4	26	45.6	
Stage					
Early (I, II)	46	63.9	26	36.1	0.454
Advanced (III, IV)	32	58.2	23	41.8	
Risk group					
Low	33	71.7	13	28.3	0.226
Intermediate	25	54.3	21	45.7	
High	20	57.1	15	42.9	

COX-2 cyclooxygenase-2

The 5-year PFS was 82.2%, and Table 2 shows its relationship to other clinicopathological variables. The best survival was achieved in patients with absence of extra nodal involvement (85.4%), stage I disease (95.7%), non-bulky disease (86.2%) and low risk (90.6%). In contrast, the worst survival was achieved among patients with extra nodal involvement (71.4%), stage IV disease (63.6%), bulky disease (67%), and high risk (70.5%). These differences were statistically significant at $p=0.033$, $p=0.012$, $p=0.036$ and $p=0.027$.

The 5-years OS in COX-2-positive patients was lower than that in COX-2-negative patients (85.3% versus 96.0%). Moreover, the 5-year PFS in COX-2-positive patients was lower than that of COX-2-negative patients (78.6% versus 84.3%). However, the *p* values for OS and PFS were not

Table 2 Five-year OS and PFS of each clinicopathological variables in the whole group

	No.	5-year OS		5-year PFS	
		(%)	*p* value	(%)	*p* value
Age group					
< 5	29	100		84.9	
5–11	46	97.4	0.028	88.6	0.159
11	52	79.1		75.5	
Gender					
Male	87	92.9	0.275	84.4	0.399
Female	40	89.9		75.8	
B symptoms					
No	91	94.0	0.449	85.6	0.080
Yes	36	84.6		73.9	
Bulky					
No	99	93.6	0.170	86.2	0.036
Yes	28	84.9		67	
Extra nodal involvement					
No	99	96.5	0.001	85.4	0.033
Yes	28	70.7		71.4	
Pathology					
Lymphocyte-rich	11	88.9		79.5	
Mixed cellularity	59	93.2	0.766	80	0.845
Nodular sclerosis	57	89.6		85.5	
Stage					
I	24	100		95.7	
II	48	95.2	0.001	83.6	0.012
III	33	97.0		83.6	
IV	22	62.9		63.6	
Risk					
Low	46	97.3		90.6	
Intermediate	46	97.8	0.003	82.5	0.027
High	35	72.6		70.5	
COX-2 stain in RS					
Negative	78	96	0.248	84.3	0.354
Positive	49	85.3		78.6	
Multivariate analysis[a]					
Age	1.5 (1.2–1.9)		0.0007	—	—
Risk					
Intermediate	2.2 (0.2–25.1)		0.528	1.7 (0.5–5.9)	0.433
High	9.3 (1.1–80.6)		0.043	3.8 (0.9–15.3)	0.062
B symptoms	—		—	1.0 (0.4–3.1)	0.933
COX-2 + stain in RS	2.9 (0.7–12.4)		0.149	1.4 (0.6–3.2)	0.490

OS overall survival; *PFS* progression-free survival; *COX*-2 cyclooxygenase-2; *RS* Reed–Sternberg *HRs* hazard ratios; *CI* confidence interval

[a]Values in multivariable analysis are HRs (95% CI)

significant ($p = 0.248$ and 0.354 for 5-years OS and 5-year PFS, respectively) (Fig. 2a, b).

The multivariate analysis in Table 2 shows no significant association between COX-2 positivity and 5-year OS after adjusting for age and risk (HR = 2.9; 95% CI 0.7–12.4, $p = 0.149$). Similarly, the association between the 5-year PFS and COX-2 expression was not statistically significant after adjusting for risk and the presence of B symptoms (HR = 1.4; 95% CI 0.6–3.2, $p = 0.490$). Therefore, COX-2 expression failed as an independent poor prognostic factor. However, high-risk patients, independently, showed a significant association with a worse 5-year OS (HR = 9.3; 95%

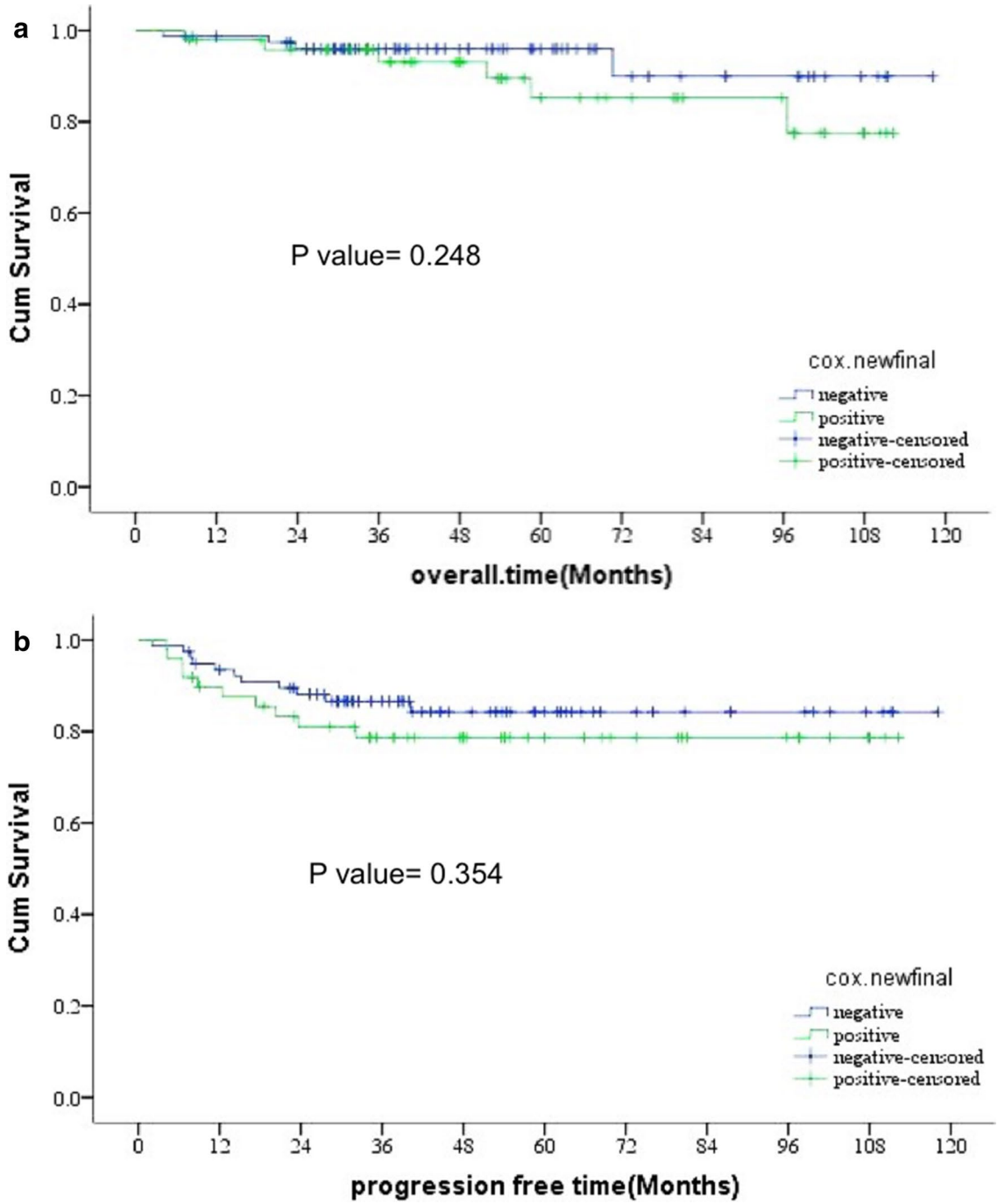

Fig. 2 Five-year OS (**a**) and PFS (**b**) of patients with COX-2-positive and COX-2-negative expression

CI 1.1–80.6, $p = 0.043$) compared with low-risk patients. Additionally, older age as an independent factor was associated with a worse 5-year OS (HR = 1.5; 95% CI 1.2–1.9, $p = 0.0007$).

Table 3 shows the 5-year OS and PFS and their relationship to COX-2 and other clinicopathological variables. Patients with COX-2 positivity exhibited a low 5-year OS if they were high risk (74.5%) and intermediate risk (69.4%) compared with patients who were low risk (95.8%); this difference was significant ($p = 0.021$). The 5-year PFS was significantly low in COX-2-positive patients who presented with B symptoms versus no B symptoms and bulky versus nonbulky disease (68.3% versus 88.7%, $p = 0.023$) and (66.5% versus 87.6%, $p = 0.028$). Other clinicopathological variables such as age, gender, extra nodal involvement, pathology, and

Table 3 Five-year OS and PFS in relation to COX-2 and other clinicopathological variables

	5-year OS (%)				5-year PFS (%)			
	Cox −ve		Cox + ve		Cox −ve		Cox + ve	
	Rate	*p* value	Rate	*p* value	Rate	*p* value	Rate	*p* value
Age (years)								
≤ 5	100		100		75.0		87.1	
6–10	100	0.294	95.2	0.092	90.0	0.494	87.8	0.297
≥ 11	91.1		81.4		76.4		74.4	
Gender								
Male	94.1	0.204	92.5	0.699	87.1	0.216	82.9	0.872
Female	87.8		90.7		59.6		81.9	
B Symptoms								
No	94.3	0.744	94.2	0.188	80.3	0.916	88.7	0.023
Yes	83.3		86.1		83.9		68.3	
Bulky								
No	94.2	0.736	92.7	0.151	83.9	0.634	87.6	0.028
Yes	75.0		88.2		66.7		66.5	
Extra nodal involvement								
No	100	< 0.001	94.3	0.112	85.0	0.063	85.8	0.179
Yes	77.8		82.6		66.7		73.7	
Pathology								
Lymphocyte-Rich	100		83.3		100		68.6	
Mixed cellularity	88.9	0.586	96.6	0.750	75.2	0.512	83.9	0.767
Nodular sclerosis	93.8		87.8		88.2		84.4	
Stage								
Early (I, II)	100	0.061	95.4	0.099	87.7	0.143	87.1	0.161
Advanced (III, IV)	82.6		84.5		75.4		75.4	
Risk								
Low	100		95.8		89.4		83.9	
Intermediate	100	0.116	69.4	0.021	85.5	0.101	85.2	0.116
High	68.9		74.5		68.0		65	
Radiotherapy								
No	78.3	0.016	74.9	< 0.001	73.3	0.141	63.1	0.002
Yes	100		100		85.3		90.5	

COX-2 cyclooxygenase-2; *OS* overall survival; *PFS* progression-free survival

stage showed lower 5-year OS and PFS rates in COX-2-positive versus COS-2-negative patients, but the differences did not reach statistical significance.

The relationship between radiotherapy (RT) and COX-2 expression is shown in Table 3; the 5-year OS and PFS in COX-2-positive patients who received radiation therapy versus those who did not were 100% versus 74.9% ($p < 0.001$) and 90.5% versus 63.1% ($p = 0.002$), respectively. The 5-year OS and PFS of COX-2-negative patients who received radiation therapy versus those who did not were 100% versus 78.3% ($p = 0.016$) and 85.3% versus 73.3% ($p = 0.141$), respectively.

Discussion

Classical Hodgkin lymphoma (CHL) is a malignancy that is associated with a storm of inflammatory cytokines that leads to the formation of a certain microscopic environment composed of a minority of malignant cells and an abundance of inflammatory cells. It was also assumed that cyclooxygenase-2, a major participant in inflammation, has a relationship with disease characteristics [19]. Many studies investigated the role of COX-2 in CHL and its association with increased proliferation and angiogenesis

through increases in the expression of angiogenic factors such as prostaglandin E2 (PGE2), which is a strong inducer of vascular endothelial growth factor (VEGF) [19, 20]. In addition, COX-2 was found to be associated with the induction of anti-apoptotic mechanisms such as upregulation of B-cell lymphoma-2 (bcl-2) and the promotion of invasion through induction of some matrix metalloproteinases [21, 22].

Ohsawa et al., Barisik et al., and Hazar et al. observed cytoplasmic COX-2 expression in RS cells in 7/10 (70%), 49/54 (80%), and 15/31 (48%) of CHL cases, respectively [19, 20, 23]. In our study, COX-2 expression was detected in 49/127 (38.6%) of CHL cases, which was similar to the frequency reported by Mestre et al. (89/242 or 37% of HL cases) [21].

Although, no agreement has been established among researchers regarding the association between COX-2 expression and histopathologic subtype. However, our study revealed the highest COX-2 expression among the nodular sclerosis type (26/57 or 45.6%). This result is similar to results in other studies performed by Barisik et al. and Mestre et al. which also showed high COX-2 expression among the nodular sclerosis subtype (88.4% and 62%, respectively) [21, 22].

Constitutional manifestations associated with CHL, including drenching night sweats, unexplained fever, and weight loss, are assumed to occur due to cytokine release from RS cells and inflammatory cells in the surrounding microenvironment. In our study, patients who presented with B symptoms exhibited COX-2 positivity versus negativity in 47.2% and 52.8% ($p=0.153$), respectively. Similar results were presented by Mestre et al. as patients with B symptoms with early-stage HL exhibited COX-2 positivity and negativity in 33% and 29%, respectively ($p=0.65$). Those with advanced-stage HL exhibited COX-2 positivity and negativity in 58% and 54%, respectively ($p=0.65$) [21]. In our study, bulky disease showed equal expression of COX-2 positivity versus negativity (50% versus 50%), while nonbulky disease showed COX-2 positive and negative expression of 35.4% and 64.6%, respectively ($p=0.170$). Similarly, Mestre et al. showed that bulky disease with positive versus negative COX-2 expression in early- and advanced-stage HL was 33% versus 28% ($p=0.53$) and 26% versus 29% ($p=0.74$), respectively [21].

Mestre et al. showed that COX-2 was more highly expressed in advanced- versus early-stage HL (43% versus 32%) [21]. Similarly, in our study, COX-2 was more highly expressed in advanced- versus early-stage disease (41.8% versus 36.1%; $p=0.454$). Moreover, COX-2 was more highly expressed in patients who were intermediate and high risk versus low risk (45.7% and 42.9% versus 28.3%; $p=0.226$). Although COX-2 was more highly expressed in advanced-stage HL and in high-risk patients, the P value was not statistically significant.

In June 2012, Mestre et al. found that COX-2 expression was associated with inferior outcome; the 5-year OS in cases of positive and negative COX-2 expression was 73% and 91% ($p<0.001$), respectively, and by multivariate analysis, COX-2 expression (HR = 2.95; CI 1.53–5.7, $p=0.001$) was independently associated with a low 5-year OS [21]. In the same study, the 5-year PFS in cases of positive and negative COX-2 expression was 60% and 79% ($p=0.003$), respectively, and by multivariate analysis, COX-2 expression (HR = 1.91; CI 1.17–3.14, $p=0.010$) was independently associated with a low 5-year PFS [21]. Our study showed similar values; the 5-year OS in cases of positive and negative COX-2 expression was 85.3% and 96% ($p=0.248$), respectively, and by multivariate analysis, COX-2 expression (HR = 2.9; 95% CI 0.7–12.4, $p=0.149$) was independently associated with a low 5-year OS. In addition, the 5-year PFS in cases of positive and negative COX-2 expression was 78.6% and 84.3% ($p=0.354$), respectively, and by multivariate analysis, COX-2 expression (HR = 1.4; 95% CI 0.6–3.2, $p=0.490$) was independently associated with a low 5-year PFS. Although our values showed a trend toward a lower 5-year OS and PFS with positive COX-2 expression, our p values were nonsignificant. Therefore, this single biomarker failed to provide meaningful independent information.

COX-2 was more highly expressed in patients < 5-year of age than those aged 5–11 and > 11 years: 15/29 (52%), 16/46 (35%) and 18/52 (35%), respectively (Table 1). However, the multivariate analysis in Table 2 showed that older age, as an independent factor, was associated with a worse 5-year OS (HR = 1.5; 95% CI 1.2–1.9, $p=0.0007$). No significant association was observed between positive COX-2 expression and 5-year OS after adjusting for age and risk (HR = 2.9; 95% CI 0.7–12.4, $p=0.149$).

Mestre et al. also published an article in May 2015 about the effect of radiotherapy (RT) on COX-2-positive patients with early Hodgkin lymphoma [24]. Patients with COX-2 expression who received RT versus no RT had a significantly better 5-year PFS (80% versus 54%, $p=0.008$), while patients with negative COX-2 expression who received RT versus no RT had a nonsignificant better 5-year PFS (90% versus 79%, $p=0.13$). They demonstrated that RT overcomes the negative prognostic effect associated with COX-2 expression and acts in a chemotherapy-independent manner. In our study, radiotherapy was given only to high-risk patients. Survival is much better in radiation-treated children in both the Cox-2-positive and Cox-2-negative groups (5-year OS is 100% and 100%; 5-year PFS is 90.5% and 85.3%; $p=0.695$). The magnitude of the effect of radiotherapy is larger in the Cox-2-positive group, but this value is not significant enough to demonstrate the interaction between Cox-2 expression status and radiation therapy.

Many studies were performed to explore the role of COX-2 in hematolymphoid malignancies. Ladetto et al. reported COX-2 expression as a poor prognostic factor in multiple myeloma and suggested an interaction between COX-2 and IL-6, which is a major biomarker involved in the pathogenesis of multiple myeloma [25]. Actually, both COX-2 and IL-6 upregulate each other in a biologic loop. Interestingly, IL-6 is reported to be an unfavorable prognostic marker of CHL [26]. This may explain the negative prognostic impact of COX-2 on CHL.

Given the importance of the probability that COX-2 is a prognostic biomarker and that it may play an important pathogenic role in CHL [21], it could be used as a therapeutic target, since it was already used in solid tumors with promising efficacy [27]. It was also found that COX-2 inhibitors have been entered in some trials as a prophylaxis for the development of this disease. This was performed in adults by Chang et al. when they demonstrated that long-term aspirin use (and no other non-steroidal anti-inflammatory drugs) can protect against the development of CHL [16].

Conclusion

Assessment of COX-2 expression as a prognostic factor is a potential area of research in many cancer patients with either solid or hematologic malignancies. Many studies were performed in adult patients, but few have been performed in pediatric patients. In our study, COX-2 expression showed a tendency to be a poor prognostic factor, but the data did not reach statistical significance. By multivariate analysis, COX-2 expression failed to be an independent poor prognostic factor. The 5-year OS and PFS were lower, significantly in some variants and nonsignificantly in other variants, in patients with COX-2 positivity than patients with negative expression. Radiotherapy effects in COX-2-positive CHL pediatric patients did not provide evidence that RT can ameliorate the effect of COX-2 expression. Given the difficulty in drawing conclusions for the evaluation of the meaning of COX-2 expression in pediatric patients with classical Hodgkin's disease, more studies are needed to determine the real value of this inflammatory enzyme. These studies may initiate a new era of potential therapeutic targets to inhibit the overexpression of this marker in RS cells to improve outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical standards The IRB approved Dr. Ahmed Hussein Al Gammal to conduct this study at the National Cancer Institute - Cairo University.

Informed consent None.

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