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Investigation of the epigenetic response to the apoptotic effect of caspase-3 in colon cancer cell line (HT-29)

Kolon kanseri hücre hattında (HT-29) kaspaz-3'ün apoptotik etkisine epigenetik yanıtın incelenmesi

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Epigenetic response to the apoptotic effect of caspase-3
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BACKGROUND
Colorectal cancer represents the third most prevalent cause of cancer-related fatalities, attributable to its high rate of recurrence and mounting resistance to existing therapeutic interventions. The objective of this study was to undertake a comparative analysis of caspase-3, HDAC1 and HDAC2 gene expression levels in HUVEC and HT-29 cells, with a view to elucidating the interplay between apoptotic and epigenetic mechanisms.

METHODS
The study was conducted by culturing the HT-29 and HUVEC cell lines under appropriate conditions and performing real-time PCR to measure the gene expression levels of caspase-3, HDAC1, and HDAC2 in the cells.

RESULTS
The results obtained revealed a high level of caspase-3 activity and a low levels of HDAC1 and HDAC2 activity in the HUVEC cells.In contrast, a low level of caspase-3 activity and high levels of HDAC1 and HDAC2 activity were detected in the HT-29 cells.

CONCLUSION
In conclusion, the present study demonstrated that the epigenetic response to the apoptotic effect of caspase-3 in the colon cancer cell line (HT-29) and the HUVEC cell line was found to be associated with a negative correlation, suggesting that these genes may serve as potential biomarkers for colon cancer diagnosis and treatment.

KEYWORDS
Caspase-3, colon cancer, HT-29, HDAC1, HDAC2, HUVEC

ÖZ

AMAÇ
Kolorektal kanser, yüksek tekrarlama oranı ve mevcut tedavilere karşı artan direnç nedeniyle kanserle ilişkili ölümlerin üçüncü en yaygın nedenidir. Bu çalışmanın amacı, apoptotik ve epigenetik mekanizmalar arasındaki etkileşimi aydınlatmak amacıyla HUVEC ve HT-29 hücrelerinde kaspaz-3, HDAC1 ve HDAC2 gen ekspresyon seviyelerinin karşılaştırmalı bir analizini yapmaktır.

GEREÇ YÖNTEM
Çalışma, HT-29 ve HUVEC hücre hatlarının uygun koşullar altında kültüre edilmesi ve hücrelerdeki kaspaz-3, HDAC1 ve HDAC2 gen ekspresyon seviyelerini ölçmek için gerçek zamanlı PCR yapılmasıyla gerçekleştirilmiştir.

BULGULAR
HUVEC hücrelerinde yüksek kaspaz-3 aktivitesi, düşük HDAC1 ve HDAC2 aktivitesi bulunmuşken, HT-29 hücrelerinde düşük kaspaz-3 aktivitesi, yüksek HDAC1 ve HDAC2 aktivitesi bulunmuştur.

SONUÇ
Sonuç olarak bu çalışma kolon kanseri hücre hattında (HT-29) ve HUVEC hücre hattında kaspaz-3'ün apoptotik etkisine verilen epigenetik yanıtın negatif korelasyonla ilişkili olduğunu göstermiştir ve bu genlerin kolon kanseri tanı ve tedavisi için potansiyel biyobelirteçler olarak hizmet edebileceğini düşündürmektedir

ANAHTAR KELİMELER
HT-29, HDAC1, HDAC2, HUVEC, kaspaz-3, kolon kanseri.

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Epigenetics is defined as alterations in gene expression that are capable of being inherited both mitotically and/or meiotically, and which do not necessitate a change in the DNA sequence (1). In cancerous cells, there is frequently an occurrence of aberrant epigenetic and gene expression patterns, consequent to the perturbation of oncogenes and tumour suppressor genes. The potential for the reversal of epigenetic modifications renders the reprogramming of cancer cells through epigenetics, which is important in preventing, controlling, and treating cancers (2).

Histones and DNA interactions regulate the process of gene transcription, whereby the process of transcription is initiated or suppressed. There are several chemical modifications, particularly acetylation of lysine residues, which can alter the position of histones and affect gene transcription. Since excessive deacetylation of histones has been associated with the pathology of cancer diseases, it can be concluded that this process promotes the repression of tumour regulatory genes (3). Histone acetylation is a process that is subject to regulation by two enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs).

The HDACs referred to above can be categorised into four distinct classes: class I encompasses HDACs 1, 2, 3 and 8; class II comprises HDACs 4, 5, 6, 7, 9 and 10; class III consists of sirtuins (SIRT1-7); and class IV consists of HDAC 11, which exhibits characteristics of both class I and II HDACs. The delicate balance between histone acetylation and deacetylation is critical for the regulation of gene expression, and aberrant expression and mutations of genes encoding HDACs have been linked to various disorders, including those affecting critical cellular functions such as cell proliferation, cell cycle regulation and apoptosis, and, consequently, tumour development (4). In a variety of cancerous cell types, including colorectal cancer cells, histone deacetylase (HDAC) inhibitors have been shown to induce cell cycle arrest, cell differentiation and apoptosis, as well as decreasing metastasis (3,5). A significant number of studies have demonstrated that class I HDACs are overexpressed in cancerous cells and are particularly involved in the differentiation of colorectal cancer cells (6).

The Caspase family constitutes a cysteine protease family which exerts pivotal functions in the domains of programmed cell death and inflammation. (7). Increasing evidence reveals that caspase-3 has critical functions beyond apoptosis, performing pro-survival functions in malignant transformation and tumorigenesis. However, the mechanism of the non-apoptotic effect of caspase-3 in oncogenic transformation has remained unclear (7, 8).

In the present study, the HT-29 and HUVEC cell lines were examined. The purpose of the comparison of HT-29 and HUVEC cells is due to their widespread use in cancer research. These cell lines are of significant value in the context of understanding the growth, spread, and response of cancer cells to therapy.

The objective of the present study was to make a comparison between the levels of gene expression of Caspase-3, HDAC1, and HDAC2 in HUVEC and HT-29 cells, and to ascertain the association between apoptotic and epigenetic mechanisms. The extant literature does not yet include studies that compare the expressions of caspase-3 and HDAC1/2 in HUVEC cells and other cancer cells, including colon cancer. A review of extant literature reveals that studies in this field have been conducted by applying HDAC inhibitors or drug therapy. The present study provides novel information to the existing literature by addressing this gap in knowledge.

Materials and Methods

Cell culture

The human colon cancer cell lines (ATCC: HTB-38) and human umbilical vein endothelial cell lines (ATCC: CRL-1730) were opened under appropriate conditions and transferred into DMEM medium containing 20% foetal bovine serum (FBS), 1% penicillin-streptomycin, and 1% L-glutamine. The cells were then cultured in a 5% CO2 incubator at 37°C until a sufficient number of cells were harvested by changing the medium containing 10% FBS, 1% Pen-Strep, and 1% L-Glutamine when necessary.

RNA extraction and cDNA synthesis

The cells were seeded in 6-well plates at a density of 6x104 cells per well, with three replicates being used for each condition. Following a period of incubation, the cells were collected and subjected to a centrifugation process at 4000 rpm for 10 minutes at 4°C. Subsequent to this, the cells were transferred to 1,5 mL eppendorf tubes, and RNA isolation was performed. The RNA isolation process was conducted using

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the TRIzol reagent (RiboEx Kit; GeneAll Biotechnology, Seoul, Korea), following the manufacturer's instructions. The trisol step was utilised as the inaugural phase, designated as the lysis phase, with a view to enhancing the efficiency of the isolation process. Subsequently, The RNA isolation kit (GeneAll Biotechnology, Hybrid-R, Seoul, Korea), which is based on the spin column technique, was proceeded. The concentration and purity of the RNA were subsequently measured using the Nanodrop device Quibit (Invitrogen, Qubit4 Fluorometer). In this experiment, ABT, cDNA Synthesis Kit (Rnase Inh. High Capacity, Türkiye), was utilised for the synthesis of cDNA. The master mix was prepared in a total volume of 20 µl, and reverse transcription was performed. The processing steps were analyzed in the ProFlex thermal cycler at 25°C for 10 min, 37°C for 120 min, and 85°C for 5 min (1 cycle). The cDNA samples synthesized were stored at -80°C.

Quantitative real time PCR

For the real-time PCR analysis, the ABT 2X SYBR Mastermix kit (Türkiye) was utilised, with the master mix being prepared in a total volume of 20 µL in accordance with the manufacturer's instructions. The reaction was then performed on an Applied Biosystems QuantStudio5 Real-Time PCR instrument. The thermal cycling parameters for the PCR reaction included an initial denaturation step at 95°C for 300 seconds, followed by 40 cycles of denaturation at 95°C for 15 seconds and an annealing step at 60°C for 60 seconds. The samples were analysed in triplicate, and the specific primers utilised are listed in Table 1. Primers were specifically designed utilising primer3plus and the NCBI database. The designed primers have been validated using in silico primer analysis tools.

Table 1. Primers used in real time-qPCR

Primer name	Primer sequence 5′-3′
HS-GAPDH-F	AGGGCTGCTTTTAACTCTGGT
HS-GAPDH-R	CCCCACTTGATTTTGGAGGGA
HS-HDAC2-F	TTACTGATGCTTGGAGGAGGT
HS-HDAC2-R	TTCTGGAGTGTTCTGGTTTGT
HS-HDAC1-F	CCTGGAACTGCTAAAGTATCACC
HS-HDAC1-R	ACTCGTCATCAATCCCGTCT
HS-CASP3-F	ATTTGGAACCAAAGATCATACATGG
HS-CASP3-R	TTCCCTGAGGTTTGCTGCAT

Statistical analysis

All data was analyzed using IBM SPSS 25.0 (Chicago, USA) and GraphPad Prism (Version 8.02, USA). The data were determined to be normally distributed (Shapiro-Wilk test, $P>0.05$) and homogeneous (Levene's test). The data were presented as mean ± standard deviation (SD) of at least three independent experiments. Student T-test was used for statistical analyses of gene expressions between the two groups. In addition, the Tukey post-hoc test and two-way analysis of variance (ANOVA) test were used to compare gene expressions between HUVEC and HT29 cell lines. $p < 0.05$ was considered to be statistically significant.

Ethical statement and Informed consent

The present study does not include an ethical statement on account of the fact that its focus is a cell culture study. The requirement for informed consent was not applicable to this study due to the utilisation of cell lines.

Results

The present study set out to investigate the expression levels of the caspase-3, HDAC1, and HDAC2 genes in two different cell lines. The analysis was conducted using the HT29 and HUVEC cell lines. The gene expression levels of the abovementioned genes were then compared in these two groups of cells. The Student T-test results used in the statistical evaluation of gene expressions between the two groups are demonstrated in Table 2. The statistical analysis revealed that Caspase-3, HDAC1, and HDAC2 gene expression levels significantly differed between the HT29 and HUVEC cell lines ($p < 0.05$).

The analysis revealed a statistically significant decrease in the expression of the caspase-3 gene in the HT29 cell line compared to the HUVEC cell line. In addition, the analysis revealed a significant increase in the expression of the HDAC1 and HDAC2 genes in the HT29 cell line. The results of the study are presented in Figure 1.

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Table 2. Student T test results between the groups (F: F value, Sig: Significant, DF: Degree of Freedom)
Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
CASP3	Equal variances assumed	2.539	.186	3.506	4	.025	1.32333	.37748	.27529	2.37138
	Equal variances not assumed			3.506	2.841	.043	1.32333	.37748	.08313	2.56353
HDAC1	Equal variances assumed	2.551	.185	-4.533	4	.011	-1.10333	.24340	-1.77913	-.42754
	Equal variances not assumed			-4.533	2.594	.027	-1.10333	.24340	-1.95131	-.25536
HDAC2	Equal variances assumed	1.046	.364	-5.709	4	.005	-1.12000	.19619	-1.66470	-.57530
	Equal variances not assumed			-5.709	3.464	.007	-1.12000	.19619	-1.69957	-.54043

Figure 2 demonstrates a differential expression between each other of the Caspase-3, HDAC1, and HDAC2 gene expressions observed between the HUVEC and HT29 cell lines. In the HUVEC cell line, the expression level of the caspase-3 gene was determined to be the highest in comparison to the expression levels of the HDAC1 and HDAC2 genes. A statistically significant difference was detected ($p < 0.05$). A negative correlation was observed between the caspase-3/HDAC1 and caspase-3/HDAC2 genes, and it was noted that there was a statistically significant difference between them ($p < 0.05$). No statistically significant relationship was found between the expression levels of the HDAC1 and HDAC2 genes ($p > 0.05$). In the HT29 cell line, the expression level of the caspase-3 gene was determined to be the lowest in comparison to the expression levels of the HDAC1 and HDAC2 genes, and a statistically significant difference was identified between them ($p < 0.05$). A negative correlation was observed between the caspase-3/HDAC1 and caspase-3/HDAC2 genes and it was noted that there was a statistically significant difference between them ($p < 0.05$). However, no statistically significant difference was found between the expression levels of the HDAC1 and HDAC2 genes ($p > 0.05$).

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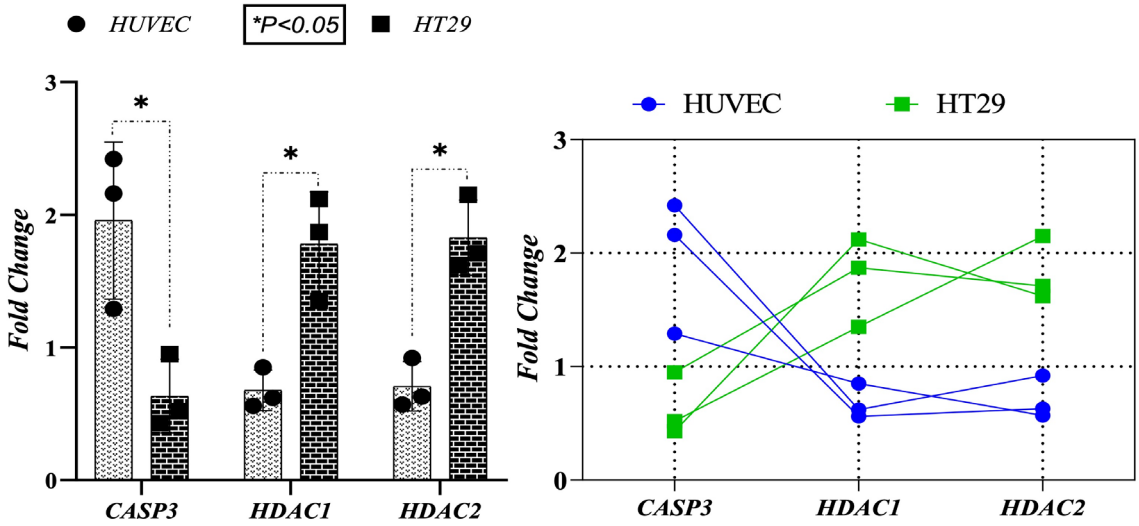

Figure 1. Caspase-3, HDAC1 and HDAC2 gene expression levels in HUVEC and HT29 cell lines. The results were presented as the mean ± standard deviation (SD) of three independent experiments (n = 3).

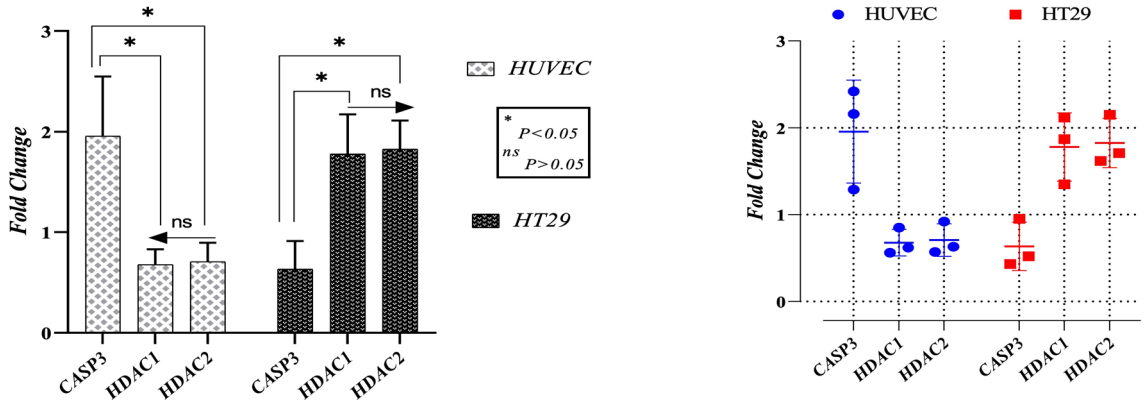

Figure 2. Evaluation between each other of Caspase-3, HDAC1 and HDAC2 gene expressions in the HUVEC and HT29 cell lines. The results were presented as the mean ± standard deviation (SD) of three independent experiments (n = 3).

Discussion

Carcinogenesis is a multi-stage process in which cells obtain various critical properties as a result of genetic instability and alterations in gene expression (9). While colorectal cancer is the second leading cause of cancer-related deaths, it is the fourth most frequently diagnosed cancer type worldwide (10). It has been established that HDACs are not functioning correctly in cases of cancer. Consequently, several HDAC inhibitors are currently being investigated for their potential use as cancer chemotherapeutics (11). A plethora of scientific studies have demonstrated that there is an increase in HDAC activity in cases of colon cancer (9, 12-15). It has been reported that HDAC inhibitors can induce apoptosis in various cancer cell lines, including those derived from breast cancer (MCF-7), lung cancer and colon cancer (HCT116) (16). HDAC has been shown to function as a strong negative regulator of apoptosis and autophagy in tumourigenesis. The process of

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permeabilisation of the HDAC inhibitor results in the negative regulation of cancer progression, achieved by the inactivation of cytosolic HDAC.

This, in turn, leads to the activation of both apoptotic and autophagic pathways. It has been established that HDAC inhibition promotes extrinsic apoptosis by activating caspase 8 through the cell death receptors FADD, TRADD, TRAIL, and TNF. Furthermore, it has been demonstrated that HDACs are capable of suppressing the expression of anti-apoptotic proteins, including Bcl-2, Bcl-XL, and Mcl-1. This suppression, in turn, has been observed to stimulate the expression of pro-apoptotic proteins, such as Bax, Bad, Bid, Bak, NOXA, and PUMA (17). Studies performed in HT-29 cells in different years, showed that the active form of caspase-3 increased 24 hours after HDAC inhibitors were applied (18,19). In a 2023 study, HDAC inhibitors were similarly applied to HCT-116 and HT-29 cells. The results demonstrated that the levels of cleaved forms of PARP, caspase 3, caspase 8, and caspase 9 increased in both cells 24 hours after application. It is evident that these findings are consistent with our own (20). In a further study, it was noted that activation of caspase-3 and poly (ADP-ribose) polymerase 1 (PARP1) increased in HCT116 colon cancer cells treated with 5-fluorouracil. Following the suppression of HDAC1, it was established that the enhanced activation of caspase-3 was markedly repressed in cells treated with 5-fluorouracil (21). In a study by Min et al., in MCF-7 breast cancer cells, for the increased HDAC activity, HDAC inhibitors were used, and it was emphasised that these inhibitors activated caspase-3/7 and may induce caspase-dependent apoptosis partially through the mitochondrial pathway accompanied by an increased rate of cytochrome C release (16). Many studies have reported that the level of HDAC1 expression increases in colorectal cancer tissue in comparison with normal tissue (22).

However, another study found no significant difference between colorectal cancer tissue and normal tissue (23). In a study by Cao et al., it was demonstrated that the expression of HDAC1 was elevated in colorectal cancer tissues in comparison with normal tissues (24). Similarly a study by Huang et al. showed that the expression level of HDAC1 was elevated in colorectal cancer samples in comparison to normal mucosa. Moreover, these findings were found to be significantly associated with the survival outcomes of patients diagnosed with colorectal cancer (25). A separate study likewise emphasised that HDAC1 increases the survival, proliferation and transformation of colorectal cancer cells (26). As demonstrated by Qi et al., HDAC2 expression is significantly elevated in colorectal cancer in comparison to adjacent normal mucosa. The study further elucidates that high HDAC2 expression is associated with reduced survival and liver metastasis, as well as with higher T-stages. Additionally, the study emphasises that the downregulation of HDAC2 impedes cell migration and invasion (27). In a further study, HDAC2 was observed to be significantly overexpressed in both adenoma and colorectal cancer (28). In the course of our study, we discovered that the expression levels of HDAC1 and HDAC2 were significantly elevated in the colon cancer cell line HT29 in comparison to the HUVEC cell line. This increase was found to be statistically significant ($p < 0.05$).

The data obtained in the present literature review to determine the effect of the apoptotic regulator caspase-3 on HT29 and HUVEC cells were in the form of a comparison of colon cancer and HUVEC cells by applying a medical agent. For instance, in a study conducted in 2018, colorectal cancer cells and HUVEC cells were exposed to titanium dioxide nanoparticles at different doses, and RT-PCR was used to evaluate the expression of P53, Bax, Bcl-2, and caspase-3. Titanium dioxide nanoparticles had no significant effect on HUVECs, but caused a significant increase in caspase-3 expression in HT29 cells (29). In another study, the induction of apoptosis with Gentiopicroside in HCT116 colon cancer cells via Bax/Bcl2 and caspase-3 was observed, and the study demonstrated that gentiopicroside exerts a cytotoxic effect on colorectal cancer cells (30). In a previous study on colon cancer, the emphasis was placed on the fact that oncogenic alterations rendered cancer cells resistant to apoptosis. It was thus hypothesised that the activation of alternative cell death pathways might provide new therapeutic options. In addition, the genetic loss of caspase-3 in colon cancer cells was shown to increase susceptibility to DNA-damaging agents through RIP1-dependent necrosis, without abandoning apoptosis (31). Flanagan et al. reported that patients suffering from colorectal cancer who exhibited reduced levels of activated caspase-3 experienced a greater duration of disease-free survival (32). Nevertheless, recent studies have presented a more intricate profile of caspase-3 in the context of cancer development and therapeutic interventions. These studies have suggested that

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contrary to its role as a tumour suppressor, caspase-3 promotes carcinogenesis following cellular exposure to chemicals and radiation (7, 33). A study was conducted to ascertain whether caspase-3 activity could serve as a prognostic biomarker for colorectal cancer. Enzyme activity was correlated with clinical parameters, and elevated caspase-3 activity in tumours was found to be significantly associated with an increased risk of distant recurrence (34). The results of our present study demonstrate that there is a statistically significant decrease in the expression level of caspase-3 in HT29 colon cancer cells in comparison with HUVEC cells and that there is a statistically significant difference between the HUVEC and HT29 cell lines ($p < 0.05$).

In the present study, owing to restrictions in financial resources, the number of repetitions, which is generally regarded as the minimum level for statistical analysis in scientific research and biological studies, was constrained to three. This study was conducted in a setting in vitro. While in vitro experiments offer valuable insights, they might not entirely replicate the intricate interactions observed in living organisms. Consequently, there is a necessity for further in vitro and in vivo studies to be conducted in this area.

In conclusion, the present study demonstrated that the epigenetic response to the apoptotic effect of caspase-3 in the colon cancer cell line (HT-29) and the HUVEC cell line was found to be associated with a negative correlation between the caspase-3/HDAC1 and caspase-3/HDAC2 genes, suggesting that these genes may serve as potential biomarkers for colon cancer diagnosis and treatment. The combination of therapies employing HDAC inhibitors in the treatment of cancer has the potential to result in a substantial increase in patient survival time. Furthermore, the elevated expression of HDACs and the diminished expression of caspase3 may serve as promising biomarker candidates for the early diagnosis of the condition and monitoring prognoses. A number of HDAC inhibitors are already in clinical use for the treatment of various types of cancer, including lymphoma.

Conflict of interest

The authors declare no conflict of interest.

The contributions of the authors

VG designed, conceived and performed the research. TK performed statistical analysis. VG and TK confirm the raw data's authenticity. All authors read and approved the final manuscript.

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