Short Communication

Association between Interleukin-1 Receptor Polymorphism and Human Herpesvirus 8 among Lymphoma Patients

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Abstract

Background: Human herpesvirus 8 (HHV-8) stimulates lymphoproliferation, by activating the signaling pathway of the interleukin-6 receptor, along with several other regulatory mechanisms. The presence of specific genetic variations governing immune responses can impact the promotion or suppression of malignant lymphoma. Polymorphisms in the gene cluster of interleukin-1 (IL-1) have been identified as significant contributors to the regulation of inflammation. **Objective:** This study aimed to determine the percentage HHV-8 and whether polymorphisms at IL-1 receptor antagonist (IL-1ra) locus modulate the risk of developing malignant lymphoma of a group of Iraqi patients in the Mid-Euphrates Sector, Iraq. **Materials and Methods:** A case-control study was conducted on 200 specimens obtained from patients with lymphoma and individuals without any apparent health conditions who served as the control group (considered normal individuals). The specimens were collected from various general hospitals and private clinics located in the Middle Euphrates region of Iraq. The study population included individuals aged between 17 and 75 years. Specimen collection took place between October 2022 and February 2023. Conventional polymerase chain reaction (PCR) was chosen for the detection of HHV-8 as well as IL-1ra gene polymorphism by sequencing. **Results:** According to PCR detection, 31 out of 64 (48.4%) of the specimens revealed PCR detection positivity for HHV-8, whereas 33 out of 64 (51.6%) specimens showed negative detection for HHV-8. The lymphoma which were most HHV-8-infected are related to the age stratum (56–75 years), accounted for 48%, whereas the age strata 15–35 years, and 36–55 years, each accounted for 23% and 29%, respectively. **Conclusion:** In view of the relatively small numbers included in our study, the present results indicate the possibility that HHV-8 and IL-1ra polymorphism may play a role in the tumor biology of lymphocyte and may contribute to their development.

Keywords: HHV-8, IL-1ra, lymphoma, PCR, polymorphism, sequencing

Introduction

Human herpesvirus 8 (HHV-8) infection is frequently found in cancerous lymphoid cells. The majority of primary effusion lymphoma (PEL) cases occur in individuals with weakened immune systems, particularly those infected with HIV, and often involve simultaneous infection with Epstein-Barr virus. The neoplastic tumor cells display various cytological features, ranging from immunoblastic to anaplastic morphology.[1]

Despite sharing cytomorphological similarities with PEL, HHV-8-negative effusion-based lymphoma represents a rare and underrecognized subset of non-Hodgkin's lymphoma. It possesses several unique clinicopathological features due to its predominant occurrence in older individuals and generally favorable prognosis. Unlike PEL, the neoplastic cells in HHV-8-negative effusion-based lymphoma demonstrate the expression of pan-B-cell markers.[2]

In later investigations, researchers discovered initially included as a negative control, a lymphoma sample obtained from an AIDS patient contained HHV-8 sequences.[3] Following this, a total of 193 lymphoma samples were subjected to screening from AIDS patients revealed eight

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_649_23

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Submission: 29-May-2023 **Accepted:** 29-Jun-2023 **Published:** 02-Feb-2024

How to cite this article: Al-Jawdhari AJA, Al-Alwany SHM. Association between interleukin-1 receptor polymorphism and human herpesvirus 8 among lymphoma patients. Med J Babylon 2023;20:875-81.

cases where HHV-8 DNA was present. These lymphomas initially known as body cavity-based lymphoma were subsequently renamed PEL. This particular type of lymphoma is exceptionally rare and primarily affects individuals infected with HIV-1. The primary location where it primarily develops is characterized by the presence of sizable serous cavities.[4] Additionally, this herpesvirus has been discovered to be linked to the plasmablastic form of multicentric Castleman's disease (MCD), characterized by the presence of hyperplastic lymph nodes. In addition, two types of excessive cell growth conditions were found in individuals diagnosed with MCD: MCD characterized by the presence of plasmablastic clusters, and diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) with HHV-8 infection.[5]

Interleukin-1 (IL-1) family includes IL-1α, IL-1β, and IL-1 receptor antagonists. The IL-1 gene cluster situated on chromosome 2q14 8 encodes proinflammatory cytokines that play a crucial role in inflammation and the immune response.[6] Multiple studies have suggested that IL-1 plays a significant role in cancer development, progression, angiogenesis, and metastasis.[7] IL1RN, a member of the IL-1 superfamily, acts as a competitive antagonist to the cell surface IL-1 receptor, controlling a multitude of immune and inflammatory reactions.[8] IL1RN is generated by various cellular entities, comprising immune cells, epithelial cells, and adipocytes.[9] The second intron of the IL1RN gene contains a variable number of tandem repeats polymorphism spanning 86 base pairs. Prior investigations have identified links between this polymorphism and specific types of cancer, although the findings have been inconclusive.[10-13] The objective of this study is to examine whether there exists a correlation between the IL1RN polymorphism and the likelihood of developing lymphoma in a subset of the Iranian population.

Materials and Methods

This study is designed as case-control study.

Study groups

A case-control study was conducted on 200 specimens obtained from patients with lymphoma and individuals without any apparent health conditions who served as the control group (considered normal individuals). Whole blood as well as gel tube blood specimens for viral genome extraction and total DNA extraction and serum, respectively:

1. Group of blood samples from patients with NHL.
2. Blood of apparently healthy persons as control group.

Sample collection

Blood samples will be gathered from individuals diagnosed with NHL as well as from apparently healthy individuals serving as the control group. The samples will be collected from both general hospitals and various private clinics located in Middle Euphrates, Iraq.

Sequencing of PCR products

The term DNA sequencing encompasses techniques used to determine the sequence of nucleotide bases (adenine, guanine, cytosine, and thymine) in a DNA molecule.[14] Initially, academic researchers obtained the first DNA sequences in the early 1970s using laboratory methods involving 2-dimensional chromatography. However, with the advancement of dye-based sequencing methods coupled with automated analysis, DNA sequencing has become more efficient and rapid. Understanding the DNA sequences of genes and other genomic regions has become crucial for fundamental research on biological processes and finds applications in various domains such as diagnostics and forensic investigations.

Total DNA extraction

DNA extraction kits were used to extract total genomic DNA from the blood samples of both the patients and the control groups.

Viral DNA extraction

Viral genomic DNA from blood patients and control groups was extracted by using a viral DNA extraction kit.

Measurement of concentration and purity of extracting DNA

By (Nano drop) at the absorbance at 260 nm and 280 nm respectively.

Can determine the DNA quantity and purity.

Statistical analysis

To detect the significance between the studied variables in this study, Chi-square test was applied, where all these statistical analyses were done by using the SPSS program, Version 24 (IBM, Armonk, New York, USA) where the $P < 0.05$ value was considered as significant one.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 7/17/1336 (including the number M220904 and the date in September 28, 2022) to get this approval.

Results

Age distribution of study groups

The studied blood specimens were related to patients with lymphoma whom their age ranged from 17 to 75 years (mean = 49.92 + 11.5 years), whereas their control

counterparts have a mean of 33.5 ± 13.4 years. However, on comparing the age of these two groups, no significant variations were detected ($P > 0.05$) [Table 1].

The gender of the studied patients with Lymphoma

The lymphoma male gender among our samples was constituting 36% whereas their female counterpart was 64%. The male-to-female ratio was 1.75:1, whereas, in the control group, male gender constituted 65% and the females 35%. The lymphoma patient and control group showed a non-significant difference (more than *P* 0.05) in statistical analysis [Table 2].

Distribution of the studied patients according to their age strata and gender

Regarding the age of lymphoma cases, 24/100 (24%) of them were between the age of 15–35 years (12 men and 12 women), 29/100 (29%) were between the age of 36–55 years (12 men and 17 women), and 47/100 (47%) were between the ages of 56–75 years (12 men and 35 women). The highest male and female frequencies (12 and 35, respectively) were found in the age group of those 56–75-years [Table 3].

Detection rates of HHV-8 by using PCR technique

Extraction of viral genome

Regarding the detection of viral DNA/RNA extraction kit to extract nucleic acid, it is found that 31 out of 64 (48.4%) of the specimens were containing the viral genome [Figure 1]. In contrast to the control group, five out of the (5%) postmortem specimens were having viral nucleic acid [Table 4]. The difference between the results of these two groups revealed a statistically significant difference ($P = 0.02$).

HHV-8 genome detection using conventional PCR

According to polymerase chain reaction (PCR) detection results, 48.4% (31 out of 64) of the specimens have HHV-8 genome, whereas 51.6 (33 out of 64) specimens showed negative results for HHV-8 genome detection, and as indicated in Table 5 and Figure 2. The statistical analysis of the differences between these two groups was significant ($P = 0.03$).

The HHV-8 results in blood specimens according to the age groups

The age strata (15–35 years), (36–55 years), and (56–75 years) each accounted for 23%; 29%; and 48%, respectively significant differences ($P < 0.05$) were found

Table 1: The age of patients with Lymphoma

Studying groups	*N*	Mean age	SD	SE	Min	Max
Lymphoma	100	49.92	11.5	2.2	17	75
Control	100	33.5	13.4	2.7	20	68
Statistical Analysis	Non-significant ($P > 0.05$) = 0.09					

Table 2: Distribution of study groups according to their gender

Gender	Lymphoma		Control		P-value
	No.	%	No.	%	
Male	36	36	35	35	0.4
Female	64	64	65	65	
Total	100	100	100	100	

Table 3: The categorization of individuals diagnosed with Lymphoma based on their age groups and gender

Age stratum of lymphoma patients	Gender		Total	
	Male	Female		
	No.	No.	No.	%
15–35	12	12	24	24
36–55	12	17	29	29
56–75	12	35	47	47
Total	36	64	100	100

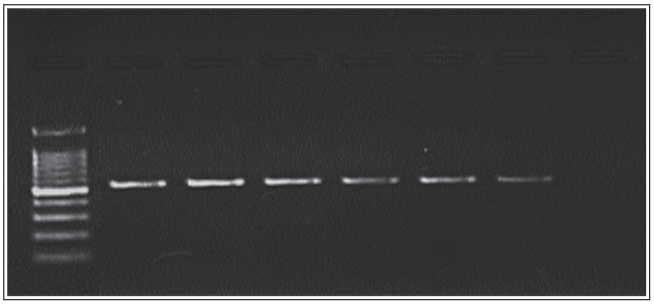

Figure 1: Extraction of HHV-8 genome from blood specimens, 1.5% agarose gel electrophoresis, TBE 1×, at 85 V for 60 min

Table 4: Viral genome detection in blood specimens

Viral genome		Lymphoma	AHC group†
Positive	*N*	31	5
	%	48.4%	5%
Negative	*N*	33	95
	%	51.6%	95%
Total	*N*	64	100
	%	100%	100%

†AHC means apparently health control

Table 5: The PCR results of HHV-8 DNA in Blood specimens of study groups

	Lymphoma *N*/%	AHC* *N*/%
Positive	31 (48.4%)	5 (5%)
Negative	33 (51.6%)	95 (95%)
Total	64 (100%)	100 (100%)

AHC* means apparently health control

Table 6: Frequency of HHV-8 PCR results among patients with lymphoma according to their age strata

Age stratum	Years	HHV-8			*P* value
		No.	Positive	Negative	
	15–35	15	6	9	ANOVA test $P = 0.04$ S. ($P < 0.05$)
		23%	40%	60%	
	36–55	18	8	10	
		29%	44.44%	55.56%	
	56–75	31	17	14	
		48%	54.84%	45.16%	
Total	64	31	33		
	%100	48.44%	51.56%		

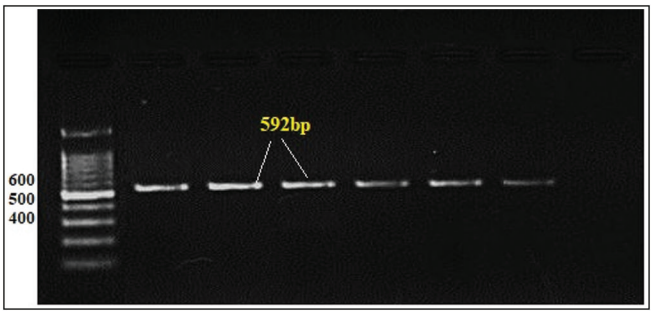

Figure 2: The PCR patterns detection of HHV-DNA (592 bp) in patients with lymphoma: the lanes from 1 to the 9 refers to HHV-8 DNA samples; The electrophoresis conditions: agarose of 1.5, 85 V, 20 m Amp for 1 h (5 μL in each well), and later on the stained with a red safe solution

when these age groups were compared statistically [Table 6].

Genotyping of IL-1R gene polymorphisms

The target sequences of the studied groups, amplified by sequencing technique, are summarized in Table 7 and represented in Figure 3.

In patients with NHL and AHC groups, the occurrence rate of GG and AG genotypes is being examined, reaching 30.7%, 20%, 24%, and 8%, respectively. This frequency was significantly higher in patients compared to the control group. Specifically, the GG genotype had a 2.489 times higher rate (OR = 2.489), In contrast to the GA and AA genotypes observed in the analyzed groups, the frequency of the AA genotype in patients with NHL and AHC groups was found to be 45.3% and 72% respectively. These results indicate a decrease in the occurrence of this genotype among patients when compared to the control group.

The statical analysis presented in Table 7 revealed a strong correlation between the IL-1R gene polymorphism and Iraqi patients, indicating high significance.

Discussion

PEL predominantly impacts individuals who have a significantly compromised immune system, particularly individuals living with HIV. There have been a few instances where PEL has been observed in individuals with conditions such as malignancy, cirrhosis, or those who have undergone organ transplantation.[15,16] The uncontrolled growth of cells infected with HHV-8 is associated with the onset of the disease.[17]

HHV-8, a gamma herpesvirus, exhibits varying prevalence depending on geographic regions and specific exposures. It is frequently found in equatorial areas, such as Africa and South America, where more than 50% of the population has been exposed to the virus. The occurrence of the condition in the Mediterranean area, Middle East, and the Caribbean is moderate, with rates ranging from 5% to 20%. However, in North America, Northern Europe, and Asia, the virus has a low prevalence, affecting less than 5% of the population.[15] In the same regions, men exhibit a notably higher seroprevalence compared to women. The main mode of transmission for HHV-8 is saliva, but it can also be transmitted to a lesser extent through injection drug use, blood transfusions, and organ transplantation. Among various population groups in the United States, HIV-positive men who have sex with men face the highest risk, with seroprevalence rates reaching as high as 30%. ADditionally, transplant patients have an estimated seroprevalence of 15%.[15] Available evidence supports the observation that the transmission of HHV-8 through a solid organ transplant is substantiated.[16,18]Our patient did not possess any identified risk factors for HHV-8. Among the limited number of cases reported in transplant recipients, most have been observed in regions where HHV-8 is more prevalent compared to the United States. Given the information provided, there is a reasonable possibility that the HHV-8 in this particular situation might have originated from the donor and been transmitted through the transplanted organ. However, it was not feasible to obtain conclusive verification.

In our recent study, we took the initiative to examine the connection between the IL1R polymorphism and the likelihood of developing lymphoma within an Iranian community. Our findings demonstrated a noteworthy correlation between the IL1R polymorphism and a reduced risk of lymphoma among the individuals we

Table 7: Distribution of genotypes and the odds ratio of IL-1R gene polymorphisms were compared between NHL patients and individuals with AHC

Genotype IL-1R (rs)		Study groups		Total	*P* value	OR	95% CI for OR	
		NHL	AHC				Lower	Upper
AA	*N*	34	18	52	0.02	0.551	0.371	0.812
	%	45.3	72	52				
GG	*N*	23	5	28	0.03	2.489	1.342	1.630
	%	30.7	20	28				
AG	*N*	18	2	20	0.02	0.234	0.493	0.459
	%	24	8	20				
TOTAL	*N*	75	25	100				
	%	100	100	100				

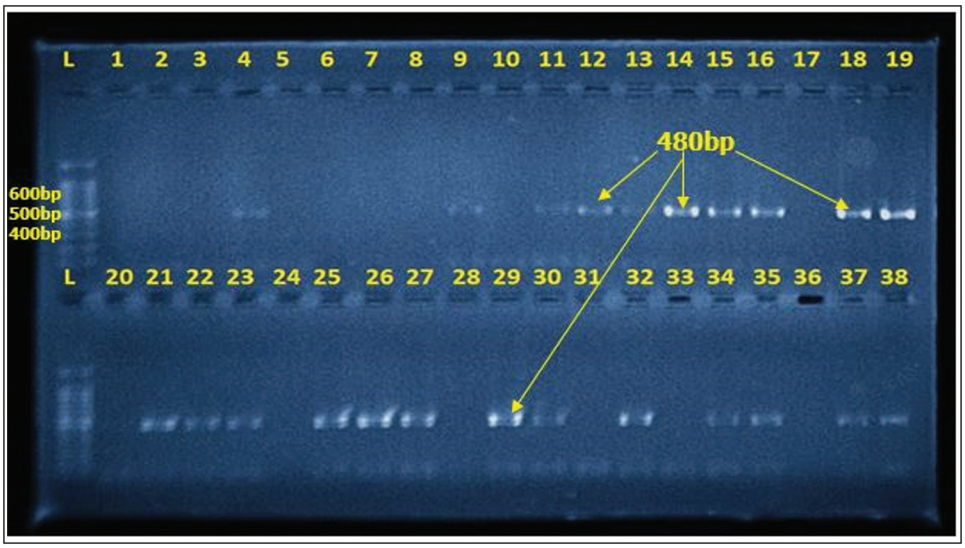

Figure 3: Agarose gel electrophoresis of an amplified product patterns of *IL-1R1*. Electrophoresis conditions, 1.5% agarose, 85 V, 20 mA for 1 h (5 μL in each well), stained with red safe solution

studied. Specifically, the IL1RN 1/2 genotype exhibited a decreased risk for both NHL and HL. These outcomes align with previous research suggesting that the IL-1RN *2 genotype may be linked to a lower prevalence of breast cancer, and the IL1RN 2 allele was observed to marginally decrease the risk of breast cancer.[19]

Similarly, In the Hu study, it was observed that the IL-1RN 2 allele's presence was linked to a notable reduction in the likelihood of developing lung cancer. This finding implies that the allele may offer a protective effect against the disease.[20]

The study revealed elevated levels of IL1RN in the serum of patients with lung and colorectal cancer, gynecological carcinoma, and HL when compared to the serum of control subjects. This suggests that this protein plays a crucial role in the initiation and progression of tumor growth.[20]

On the contrary, Ibrahimi and colleagues demonstrated a correlation between the 1/2 and 2/4 genotypes of IL1RN and susceptibility to colorectal cancer (CRC). Furthermore, they found that the presence of allele 2 in IL-1RN is linked to an increased risk of CRC as indicated by the CRC risk.[21]

Furthermore, there were no notable variations observed in the IL-1RA gene polymorphism between individuals diagnosed with hepatocellular carcinoma and the control group.[22]

To the best of our knowledge, there have not been any documented findings on the connection between the IL-1R polymorphism and lymphoma. Nevertheless, a combined examination of three studies revealed a positive correlation between IL1RN rs2637988 and a heightened susceptibility to NHL.[23] Likely, the heightened susceptibility to shorter immune responses may be augmented, leading to an increased chance of esophageal cancer in a Northwest Han Chinese population. Conversely, a reduced likelihood of developing esophageal cancer in the same population is associated with various genetic variations in IL-1RN, including rs3181052, rs452204, and rs315919.[24] There

is mounting evidence indicating that long-lasting inflammation could potentially increase the likelihood of developing different types of cancer. Inflammation and immune responses are significantly impacted by cytokines, which also have the ability to influence cancer vulnerability.[25] Among these cytokines, IL-1 is particularly noteworthy as it has been demonstrated to promote tumor growth, angiogenesis, invasiveness, and metastasis in diverse cancer types.[25] IL-1RN, in contrast, has the capacity to modify the levels of IL-1 expression and compete for binding sites on IL-1 receptors, thereby modulating the effectiveness of IL-1 signaling and immune as well as inflammatory responses associated with IL-1.[23] In spite of the compelling findings, our research is subject to certain constraints. These limitations encompass the examination of a relatively modest sample size and the consideration of gene-environment interactions. Additionally, we acknowledge the absence of data regarding the expression levels of IL-1RN in the serum of both lymphoma patients and control groups.

Conclusion

The following conclusions are obtained from the present study.

Highest age-specific frequency was noticed in patients with Hodgkin lymphoma in the age stratum of ≤40 years, whereas, in patients with Non-Hodgkin was in age stratum of (61–80 years). The ratio of female patients whom suffering from Hodgkin and non-Hodgkin lymphoma was higher than their male counterparts. The presence of HHV-8 in both of HL and NHL groups of blood may indicate the importance of such contribution in the etiologic development of HL and NHL. Interleukin-1R gene polymorphisms did consider a risk for HL and NHL Patients.

Acknowledgments

The authors thank the laboratory staff at Al-Hillah City Hospitals (Mirgian, and Imam AL-Sadiq Teaching), and Medical city hospitals in Baghdad (Baghdad Teaching, and National Center for Educational Laboratories) in Iraq for processing clinical specimens to facilitate research requirements.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Dai H, Cherian R, Mathur S. Primary body cavity-based large B-cell lymphoma in an HIV and HHV-8 negative, HCV positive patient: A case report and literature review. Lab Med 2014;45:136-40.
2. Wu W, Youm W, Rezk SA, Zhao X. Human herpesvirus 8-unrelated primary effusion lymphoma-like lymphoma: Report of a rare case and review of 54 cases in the literature. Am J Clin Pathol 2013;140:258-73.
3. Chang Y, Moore P. Twenty years of KSHV. Viruses 2014;6:4258-64.
4. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med 1995;332:1186-91.
5. Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, *et al*. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 1995;86:1276-80.
6. Zuo X, Li M, Yang Y, Liang T, Yang H, Zhao X, *et al*. Interleukin gene polymorphisms in Chinese Han population with breast cancer: A case-control study. Oncotarget 2018;9:17994-8001.
7. Ma L, Zhou N. Association between an insertion/deletion polymorphism in IL-1A gene and cancer risk: A meta-analysis. Onco Targets Ther 2015;9:1-6.
8. Wang T, Feng Y, Zhao Z, Wang H, Zhang Y, Zhang Y, *et al*. IL1RN polymorphisms are associated with a decreased risk of esophageal cancer susceptibility in a Chinese population. Chemotherapy 2019;64:28-35.
9. Hashemi M, Bahari G, Sarhadi S, Eskandari E, Narouie B, Taheri M, *et al*. 4-bp insertion/deletion (rs3783553) polymorphism within the 3'UTR of IL1A contributes to the risk of prostate cancer in a sample of Iranian population. J Cell Biochem 2018;119:2627-35.
10. Yigit M, Degirmencioglu S, Ugurlu E, Yaren A. Effect of serum interleukin-1 receptor antagonist level on survival of patients with non-small cell lung cancer. Mol Clin Oncol 2017;6:708-12.
11. Niedzwiecki S, Stepien T, Kuzdak K, Stepien H, Krupinski R, Seehofer D, *et al*. Serum levels of interleukin-1 receptor antagonist (IL-1ra) in thyroid cancer patients. Langenbecks Arch Surg 2008;393:275-80.
12. Wu S, Hu G, Chen J, Xie G. Interleukin 1beta and interleukin 1 receptor antagonist gene polymorphisms and cervical cancer: A meta-analysis. Int J Gynecol Cancer 2014;24:984-90.
13. Camargo MC, Mera R, Correa P, Peek RM, Fontham ETH, Goodman KJ, *et al*. Interleukin1beta and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: A meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1674-87.
14. Rawtani D, Hussain CM, eds. Modern Forensic Tools and Devices: Trends in Criminal Investigation. John Wiley & Sons; 2023.
15. Ariza-Heredia EJ, Razonable RR. Human herpes virus 8 in solid organ transplantation. Transplantation 2011;92:837-44.
16. Luppi M, Barozzi P, Santagostino G, Trovato R, Schulz TF, Marasca R, *et al*. Molecular evidence of organ-related transmission of Kaposi sarcoma-associated herpesvirus or human herpesvirus-8 in transplant patients. Blood 2000;96:3279-81.
17. Nador RG, Cesarman E, Chadburn A, Dawson DB, Ansari MQ, Sald J, *et al*. Primary effusion lymphoma: A distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood 1996;88:645-56.
18. Testa A, Baiocchini A, Comandini UV, Falasca L, Nardacci R, Maritti M, *et al*. Fatal sclerosingperitonitis associated with primary effusion lymphoma after liver transplantation: A case report. Transplant Proc 2010;42:3849-53.
19. Lee KM, Park SK, Hamajima N, Tajima K, Choi J-Y, Noh D-Y, *et al*. Genetic polymorphisms of interleukin-1 beta (IL-1B) and IL-1 receptor antagonist (IL-1RN) and breast cancer risk in Korean women. Breast Cancer Res Treat 2006;96:197-202.
20. Hu Z, Shao M, Chen Y, Zhou J, Qian J, Xu L, *et al*. Allele 2 of the interleukin-1 receptor antagonist gene (IL1RN*2) is associated with a decreased risk of primary lung cancer. Cancer Lett 2006;236:269-75.
21. Ibrahimi M, Moossavi M, Mojarad EN, Musavi M, Mohammadoo-Khorasani M, Shahsavari Z. Positive correlation between interleukin-1 receptor antagonist gene 86bp VNTR polymorphism and colorectal cancer susceptibility: A case-control study. Immunol Res 2019;67:151-6.

22. Tak KH, Yu GI, Lee MY, Shin DH. Association between polymorphisms of interleukin 1 family genes and hepatocellular carcinoma. Med Sci Monit 2018;24:3488-95.
23. Hosgood HD 3rd, Purdue MP, Wang SS, Zheng T, Morton LM, Lan Q, *et al*. A pooled analysis of three studies evaluating genetic variation in innate immunity genes and non-Hodgkin lymphoma risk. Br J Haematol 2011;152:721-6.
24. Guven Karatas S, Bayrak R, Sahin Balcik O, Yalçın KS, Atıcı E, Akyıldız U, *et al*. Human immunodeficiency virus (HIV)-negative and human herpes virus8 (HHV-8)-positive primary effusion lymphoma: A case report and review of the literature. Turk J Haematol 2013;30:67-71.
25. Jones D, Ballestas ME, Kaye KM, Gulizia JM, Winters GL, Fletcher J, *et al*. Primary-effusion lymphoma and Kaposi's sarcoma in a cardiac-transplant recipient. N Engl J Med 1998;339:444-9.