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Evaluation of Diagnosis Season and in Situ Hybridization EBER Results in Hodgkin Lymphoma: A Single Center Retrospective Study

Hodgkin Lenfomada Tanı Mevsimi ve in Situ Hibridizasyon EBER Sonuçlarının Değerlendirilmesi: Tek Merkezli Retrospektif Çalışma

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ABSTRACT Objective: Hodgkin lymphoma (HL) is a hematological malignancy with a generally favorable prognosis, yet its pathogenesis remains unclear, and unknown risk factors affecting incidence and mortality are still being explored. This study aimed to assess the influence of diagnosis season and the presence of in situ hybridization (ISH) Epstein-Barr encoded RNA (EBER) on HL survival. **Material and Methods:** We evaluated 232 HL patients treated at Ege University Faculty of Medicine Hematology Clinic from January 1, 1994, to December 31, 2023. **Results:** Among the 232 patients (41.4% female and 58.6% male), the mean age at diagnosis was 38.42 years (SD: 15.99), with a median age of 35. The most common subtype was nodular sclerosing (47%), followed by mixed cellularity (29.3%) and nodular lymphocyte predominant (NLP) (9.9%). EBER was detected in 45.7% of patients, while 54.3% were EBER negative. The highest diagnosis rate occurred in winter (30.6%), and the lowest in spring (19.8%). EBER presence did not vary by season, and no significant difference in overall survival times was found between EBER positive and negative patients (p=0.427). **Conclusion:** Our findings indicate that EBER positivity does not significantly impact the prognosis of HL, with no seasonal variability in EBER rates. The lack of significant survival differences suggests that EBER has limited relevance in HL management. These insights contribute to the understanding of HL's clinical practice and pathogenesis, highlighting areas for future research.

Keywords: Hodgkin disease; Epstein-Barr virus encoded RNA; seasons

ÖZET Amaç: Hodgkin lenfoma (HL), en iyi prognoza sahip hematolojik malignitelerden biridir. Bununla birlikte, HL'nin patogenezi tam olarak anlaşılmamış olup, HL insidansı ve mortalitesini etkileyebilecek potansiyel bilinmeyen risk faktörleri araştırılmaya devam etmektedir. Bu çalışmanın amacı, tanı mevsiminin ve in situ hibritizasyon (ISH) Epstein-Barr kodlu RNA (EBER) varlığının HL üzerindeki etkisini değerlendirmektir. **Gereç ve Yöntemler:** Bu çalışma, 1 Ocak 1994 ile 31 Aralık 2023 tarihleri arasında Ege Üniversitesi Tıp Fakültesi Hematoloji Kliniği'nde HL tanısı almış ve tedavi edilmiş 232 hastayı içermektedir. **Bulgular:** Bu çalışmada toplam 232 hasta (%41,4 kadın ve %58,6 erkek) değerlendirilmiştir. Tanı anındaki ortalama yaş 38,42 (SS: 15,99) olarak belirlenmiş, medyan yaş ise 35 bulunmuştur. HL'nin en yaygın alt tipi 47% ile nodüler sklerozan, ardından %29,3 ile karışık hücreli ve %9,9 ile nodüler lenfosit baskın (NLP) olarak saptanmıştır. EBER, hastaların %54,3'ünde yokken, %45,7'sinde tespit edilmiştir. En yüksek tanı oranı kış mevsiminde %30,6 olarak gözlemlenirken, en düşük oran bahar mevsiminde %19,8 olarak belirlenmiştir. EBER varlığı mevsimlere göre değişiklik göstermemiş ve EBER negatif ile pozitif hastalar arasında ortalama genel sağkalım sürelerinde istatistiksel olarak anlamlı bir fark bulunmamıştır (p=0,427). **Sonuç:** Çalışmamız, EBER pozitifliğinin Hodgkin Lenfoma (HL) prognozu üzerinde önemli bir etkisi olmadığını ortaya koymuştur. EBER pozitiflik oranları mevsimsel değişkenlik göstermemektedir. Bu bulgular, HL'nin klinik pratiği ve patogenezi hakkında önemli bilgiler sunmakta ve gelecekteki araştırmalar için yeni yönlerin belirlenmesine katkıda bulunmaktadır.

Anahtar Kelimeler: Hodgkin hastalığı; Epstein-Barr virus kodlanmış RNA; mevsimler

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Classical Hodgkin lymphoma was defined by Thomas Hodgkin in 1832 as a condition characterized by swelling of cervical lymph nodes, weight loss, and fever in young adults.[1] Hodgkin lymphoma (HL) is characterized by the presence of malignant Reed-Sternberg cells developed in the context of a non-neoplastic cell population consisting of T and B lymphocytes, along with the disruption of lymph node structure.[2] The World Health Organization classifies HL into 2 groups: classical HL and nodular lymphocyte-predominant HL (NLP HL). Classical HL is further subdivided into 4 subtypes: nodular sclerosing (NS), mixed cellularity (MC), lymphocyte-depleted (LD), and lymphocyte-rich (LR) HL. There are morphological, immunophenotypic, and clinical differences between NLP HL and classical HL.[3,4] The median age at diagnosis for classical HL is approximately 33 years. It is very rare in individuals younger than 12 years but is the most commonly encountered lymphoma in adolescents and young adults, appearing in patients over 80 as well. Classical HL exhibits a bimodal distribution, with the 1st peak occurring around ages 20-30 and the 2nd peak occurring between ages 50 and 70, a period more associated with Epstein-Barr virus (EBV) and having a lower treatment success rate compared to the 1st peak.[5]

EBV infections are thought to play a significant role in 25-40% of classical HL cases. This association is particularly observed in individuals with a history of immunosuppression, such as autoimmune diseases or Human Immunodeficiency Virus, and in malignancies arising from the transformation of low-grade B-cell lymphomas. Genome-wide studies provide strong evidence supporting an etiological link between EBV and classical HL.[6] However, there is limited information regarding the influence of other environmental risk factors. Nonetheless, a distinct incidence and risk profile exist based on factors such as age, race, gender, and socioeconomic status.[1] Siblings of the same sex have a 10-fold higher risk of developing HL, and the risk of HL development is significantly increased in monozygotic twins compared to dizygotic twins. These familial factors indicate a genetic basis for this disease.[3,7-10] The literature on the seasonal relationship of HL is very limited.

The Epstein-Barr encoded RNA (EBER)-1 (167 nucleotides) and EBER-2 (172 nucleotides) Ribonucleic acids (RNA) found in EBV-latently infected cells are transcribed by RNA polymerase III.[11-13] The exact function of EBER is not fully understood. Complexes with a protein called La have been defined, which may explain the predominantly nuclear localization of EBER-1 and EBER-2 identified by traditional in situ hybridization techniques.[14] Recent studies have revealed that EBERs are also found in the cytoplasm and share a similar distribution with the double-stranded RNA-activated protein synthesis inhibitor double-stranded RNA activated inhibitor (DAI).[15] DAI is induced by interferon treatment and plays a role in the host's viral defense. The formation of a complex between EBER-1 and DAI suggests the potential for the virus to evade the antiviral response. However, EBV strains carrying the EBER genes show low sensitivity to interferon-alpha or interferon-gamma. The function of a recently discovered protein associated with EBER, named EAP, is still unknown.[16-20] EBER genes have a high copy number (up to 10^6 per cell) in infected cells, and latent EBV infections can be detected in human tissues using appropriate oligonucleotide probes, contributing to the understanding of EBV-associated lymphoproliferative disorders.[21]

In recent years, the detection of EBER-1 and EBER-2 has become the gold standard for identifying latent EBV infections. The abundance and greater stability of these viral non-coding RNAs compared to messenger RNA (mRNA) make them ideal targets for in situ hybridization (ISH) studies. EBER detection can be successfully applied to both frozen and formalin-fixed, paraffin-embedded tissue sections.[22] EBER ISH has replaced DNA ISH in most laboratories for detecting latent EBV infections, although it should be noted that EBER expression relies on the active expression of the viral genome, and EBER-negative latency remains a theoretical possibility.[23] In some cases, cells suspected of harboring EBV were not found to be infected using appropriate methodologies. To confidently assign EBV infection to a specific cell type, double labeling techniques may be required to simultaneously detect viral DNA or gene products and cell lineage-specific gene prod-

ucts. Due to the heterogeneous nature of many EBV-associated lesions, gene expression analysis of EBV-infected cells in tissue sections is most effectively achieved using double labeling techniques.[24]

The uncertainty regarding potential risk factors that may affect the incidence and mortality of HL continues. Investigating seasonal diagnosis and incidence and mortality models related to EBER presence can help in understanding both the pathogenesis of the disease and its risk factors. This study aims to assess the impact of the diagnosis season and EBER presence on the survival of patients with HL.

MATERIAL AND METHODS

In this retrospective study, patients diagnosed with HL and treated at the Department of Hematology, Ege University School of Medicine, between January 1, 1994, and December 31, 2023, were included. The date of diagnosis was defined according to the pathology report as the month, day, and year when HL was first diagnosed. The results of ISH EBER in the pathology reports were evaluated. The EBER status was evaluated at the time of diagnosis in 232 patients. Cases were grouped according to the season of diagnosis and the presence of EBER. Additionally, response to first-line therapy, as well as autologous and allogeneic stem cell transplantation treatments, were recorded to identify relapsed/refractory (R/R) HL cases. The relationship between progression-free survival and overall survival (OS) in relation to the season of diagnosis and EBER status was also investigated.

The study was conducted in accordance with the principles of the Helsinki Declaration. Ethical approval for this study was obtained from the Ege University Medical Research Ethics Committee (date: September 5, 2024, no: 24-9T/2).

STATISTICS

The patient data collected within the scope of the study were analyzed using IBM Statistical Package for the Social Sciences (SPSS 23.0-IBM, NY, United States). Chi-square analysis was employed for the comparison of categorical variables across seasons. The Log Rank (Mantel-Cox) test was used to compare overall and progression-free survival times based on the variables. Results were considered statistically significant when the p value was <0.05.

RESULTS

A total of 232 patients were included in the study, of which 41.4% (96 individuals) were female and 58.6% (136 individuals) were male. The mean age at diagnosis was 38.42 years, with a standard deviation of 15.99. The median age was determined to be 35 years, and the age range was between 2 and 80 years. When examining the distribution by subtype, the most frequently encountered HL subtype was nodular sclerosing at 47%, followed by mixed cellularity at 29.3% and nodular lymphocyte predominant (NLP) at 9.9%. The lymphocyte-depleted type was observed in 5 patients, representing 2.2%.

When classified by stage groups, 58.4% of patients were classified as early stage, while 41.6% were classified as advanced stage. According to EBER test results, EBER was not detected in 54.3% of patients, while it was detected in 45.7%. In terms of seasonal distribution, the highest proportion of patients (30.6%) was found in the winter, whereas the lowest proportion (19.8%) was observed in spring. Based on first-line treatment responses, 87.9% of patients showed a complete response, 9.9% had a relapse, and 2.2% were refractory. Autologous stem cell transplantation was performed on 9.5% of patients, while allogeneic stem cell transplantation was performed on 0.4%. Survival outcomes indicated that 95.7% of patients survived while 4.3% of patients passed away. Among the patients, 9.9% had NLP and 90.1% had classical HL. The mean OS time was 5.70±4.59 years, with a median of 4.56 years. The survival time ranged from 0.06 to 28.01 years. The progression-free survival (PFS) time was 2.87±2.63 years, with a median of 2.20 years, and the PFS time ranged from 0.37 to 11.85 years (Table 1).

There was no significant difference in EBER positivity among NLP HL patients according to season ($p=0.28$). There was no significant difference in EBER positivity among classical HL patients according to season ($p=0.933$). There was no significant difference in EBER positivity among lymphocyte-rich type patients according to season

TABLE 1: Distribution of demographic and clinical characteristics of patients

	n/X̄±SD	%/median (minimum-maximum)
Gender		
Female	96	41,4
Male	136	58,6
Age	38.42±15.99	35.00 (2.00-80.00)
Sub type		
Classical hodgkin lymphoma of undetermined subtype	15	6.5
Lymphocyte rich	12	5.2
Nodular sklerosing	109	47
Mixed cellular	68	29.3
Nodular lymphocyte predominant	23	9.9
Lymphocyte poor	5	2.2
Stage		
Stage 1	9	3.9
Stage 2	126	54.5
Stage 3	52	22.5
Stage 4	44	19
Stage group		
Early	135	58.4
Late	96	41.6
EBER		
Negative	126	54.3
Positive	106	45.7
Season		
Winter	71	30.6
Spring	46	19.8
Summer	58	25
Autumn	57	24.6
First line treatment of response		
Relapse	23	9.9
Refractory	5	2.2
Complete response	204	87.9
Autologous stem cell transplantation		
No	210	90.5
Yes	22	9.5
Allogeneic stem cell transplantation		
No	231	99.6
Yes	1	0.4
Mortality		
Alive	222	95.7
Ex	10	4.3
Classical hodgkin lymphoma		
No	23	9.9
Yes	209	90.1
OS	5.70±4.59	4.56 (0.06-28.01)
PFS	2.87±2.63	2.20 (0.37-11.85)

SD: Standard deviation; EBER: Epstein-Barr encoded RNA; OS: Overall survival; PFS: Progression-free survival

(p=0.33). There was no significant difference in EBER positivity among nodular sclerosing subtype patients according to season (p=0.926). There was no significant difference in EBER positivity among mixed cellular subtype patients according to season (p=0.838). Regardless of subtype differentiation, there was no significant difference in EBER positivity according to season (p=0.656). EBER positivity rates were 46.5% in winter, 43.5% in spring, 51.7% in summer, and 40.4% in autumn (Table 2).

According to EBER, there was no significant difference in mean OS time (p=0.427) (Figure 1). The mean survival time for EBER-negative patients was 23.1 years, while for EBER-positive patients, it was 22.3 years. According to EBER, there was no significant difference in mean progression-free survival time (p=0.364) (Figure 2). The mean PFS for EBER-negative patients was 11 years, while for EBER-positive patients, it was 5.3 years. There is no difference in mean OS time and disease-free survival times by season (p values: 0.786, 0.385) (Figure 3, Figure 4). There is no difference in OS times based on stage status and autologous stem cell transplantation status (p values: 0.180, 0.191) (Table 3).

DISCUSSION

The impact of seasonal variations and EBER expression on the pathogenesis and prognosis of HL remains largely unexplored. This study endeavors to address this critical knowledge gap by conducting a rigorous investigation into the seasonal incidence of HL and a comprehensive assessment of the prognostic significance of EBER expression. Through a meticulous analysis of these variables and a critical appraisal of existing literature, we aim to elucidate the intricate interplay between these factors and their potential influence on patient outcomes. These findings will contribute valuable insights into the multifaceted prognostic landscape of HL, ultimately enhancing our understanding of this complex malignancy.

The role of seasonal responses on HL is supported by a limited number of studies in the literature. These studies have generally been conducted in northern countries, particularly Norway, Sweden, England, and Scotland. In research by Douglas et al.

TABLE 2: Comparison of EBER status according to seasons

	EBER	Winter	Spring	Summer	Autumn	Total	Test statistics	p value
Nodular lymphocyte predominant	No	5 (71.4)	3 (100)	1 (33.3)	8 (80)	17 (73.9)	3.835	0.280
	Yes	2 (28.6)	0 (0)	2 (66.7)	2 (20)	6 (26.1)		
Classical hodgkin lymphoma	No	33 (51.6)	23 (53.5)	27 (49.1)	26 (55.3)	109 (52.2)	0.435	0.933
	Yes	31 (48.4)	20 (46.5)	28 (50.9)	21 (44.7)	100 (47.8)		
Lymphocyte rich	No	0 (0)	2 (66.7)	3 (75)	2 (66.7)	7 (58.3)	3.429	0.330
	Yes	2 (100)	1 (33.3)	1 (25)	1 (33.3)	5 (41.7)		
Nodular sklerosing	No	24 (64.9)	14 (60.9)	18 (62.1)	14 (70)	70 (64.2)	0.468	0.926
	Yes	13 (35.1)	9 (39.1)	11 (37.9)	6 (30)	39 (35.8)		
Mixed cellular	No	4 (21.1)	3 (25)	3 (15.8)	5 (27.8)	15 (22.1)	0.848	0.838
	Yes	15 (78.9)	9 (75)	16 (84.2)	13 (72.2)	53 (77.9)		
Lymphocyte poor	No	2 (66.7)	1 (100)	1 (100)	---	4 (80)	---	---
	Yes	1 (33.3)	0 (0)	0 (0)	---	1 (20)		
Total	No	38 (53.5)	26 (56.5)	28 (48.3)	34 (59.6)	126 (54.3)	1.614	0.656
	Yes	33 (46.5)	20 (43.5)	30 (51.7)	23 (40.4)	106 (45.7)		

*Chi-square test, frequency (percentage); EBER: Epstein-Barr encoded RNA

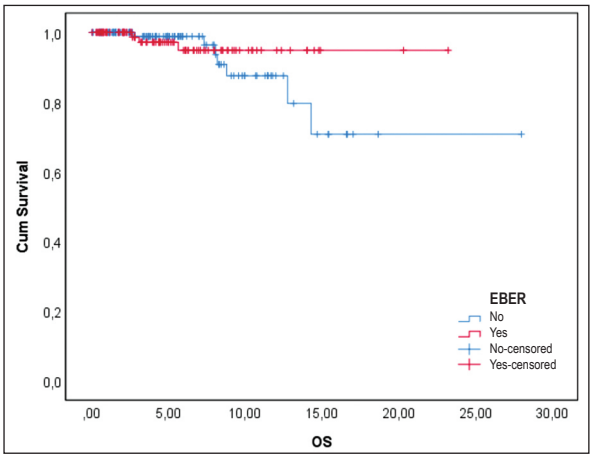

FIGURE 1: Survival curve of OS according to EBER status
EBER: Epstein-Barr encoded RNA; OS: Overall survival

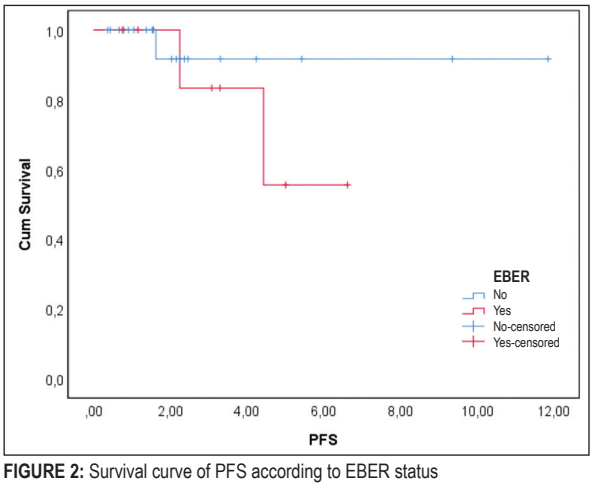

FIGURE 2: Survival curve of PFS according to EBER status
EBER: Epstein-Barr encoded RNA; PFS: Progression-free survival

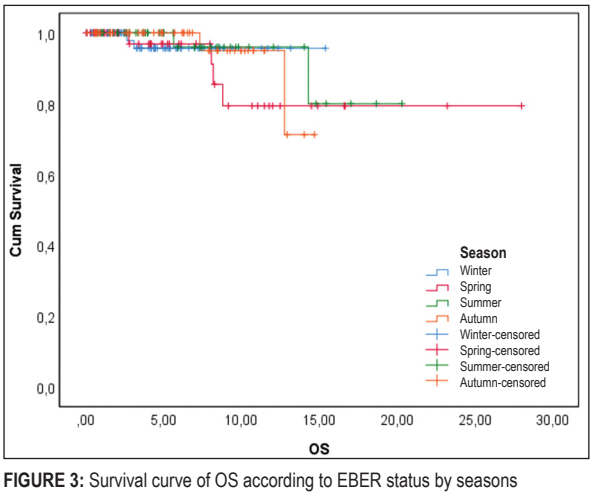

FIGURE 3: Survival curve of OS according to EBER status by seasons
EBER: Epstein-Barr encoded RNA; OS: Overall survival

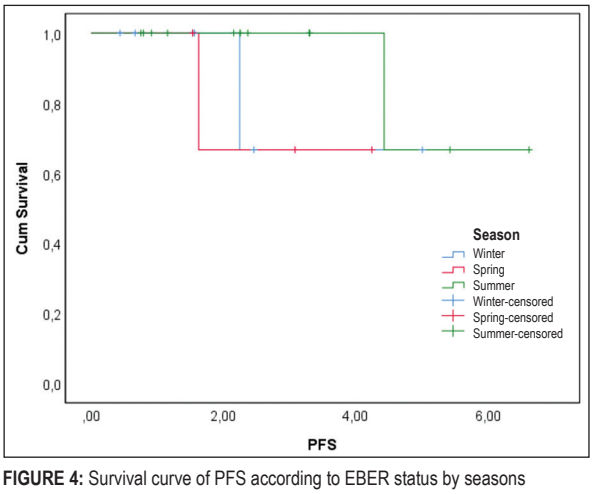

FIGURE 4: Survival curve of PFS according to EBER status by seasons
EBER: Epstein-Barr encoded RNA; PFS: Progression-free survival

TABLE 3: Comparison of overall and progression-free survival time according to variables

	Median overall survival time (%95 CI)	5-year survival rate	p value*	Median disease-free survival time (%95 CI)	5-year disease-free survival rate	p value *
EBER						
No	23.1 (19.5-26.6)	98.9%	0.427	11 (9.4-12.6)	91.7%	0.364
Yes	22.3 (21.2-23.4)	97.2%		5.3 (3.8-6.7)	55.6%	
Season						
Winter	14.9 (14.1-15.6)	95.7%		4.1 (2.6-5.6)	66.7%	
Spring	23.8 (20-27.5)	96.9%	0.786	3.4 (2-4.8)	66.7%	0.385
Summer	18.8 (16.8-20.8)	100.0%		5.9 (4.7-7.1)	66.7%	
Autumn	13.9 (12.9-14.9)	100.0%				
Stage group						
Early	17.5 (16.2-18.8)	100.0%	0.180	---	---	---
Late	24.2 (21-27.4)	95.4%		---		
Autologous stem cell transplantation						
No	24.2 (21.2-27.2)	99.3%	0.191	---	---	---
Yes	14.7 (12.3-17.2)	90.0%				

*Log Rank (Mantel-Cox) test; EBER: Epstein-Barr encoded RNA

it was shown that nodular sclerosing HL peaked in March and displayed a marked annual circulation rhythm. Neilly et al. observed a peak in March in their study of all cases in Scotland.[25,26] In one of two studies from Sweden, a higher diagnosis of HL was found in the elderly group in February, while the other study did not find a significant relationship between the season of diagnosis and OS.[27,28] Seasonal variations in ultraviolet radiation are evident in Scandinavian countries, and it is not possible to produce vitamin D from ultraviolet-B radiation during the winter months. Porojnicu et al. demonstrated that the effects of vitamin D and its derivatives become more pronounced at higher latitudes and that diagnosis during winter could increase the risk of additional mortality, suggesting a protective role for vitamin D in HL.[29] A recent study from Türkiye found no relationship between HL and seasonality, but highlighted the importance of vitamin D deficiency and viral infections.[30] In our study, the findings regarding the season of diagnosis are noteworthy, with the highest percentage (30.6%) of patients diagnosed in winter. This suggests, consistent with the literature, that vitamin D deficiency may be a contributing factor.

Infectious mononucleosis is associated with an increased risk of HL and provides significant data on the role of EBV in the development of HL. However, it remains unclear whether this relationship is restricted only to the EBV-positive HL subgroup. A study conducted in Denmark and Sweden examined the history of mononucleosis and childhood socioenvironmental characteristics in 586 classical HL patients and 3,187 control individuals. The tumor EBV status of 499 cases was determined using IH and Polymerase Chain Reaction techniques. The findings indicated that infectious mononucleosis is associated with EBV-positive HL but not with EBV-negative HL.[31] In another study based on these results, seasonal variations related to the onset of symptoms in childhood HL were examined, and the role of EBV status was investigated. Previous research identified a notable peak in HL onset in December, while this study did not observe any seasonal variation in pediatric HL patients. However, within the EBV-positive subgroup, a significant increase in symptom onset was noted in July and August.[32] This supports the hypothesis that primary EBV infections may influence the emergence of HL symptoms.[33] In the EBV-negative subgroup, no seasonal variation was observed, but the onset of symptoms was more frequently noted during the winter months. This suggests that EBV-negative HL may be associated with an as-yet unidentified infectious agent.[34] Furthermore, the distribution of EBV-positive and EBV-negative patients

in the population may influence the seasonal effects on HL. A methodological contribution of the study is the use of the symptom onset date to determine the disease onset. The study suggests that this approach better reflects an accurate disease pattern, and addressing the variability caused by the waiting period between symptom onset and diagnosis could yield more accurate results. However, in our study, the EBER positivity rates did not show seasonal-based changes. Since our study was based on the pathology acceptance date rather than the symptom date, this may have posed a limitation for our research. Additionally, the differing frequency of primary EBV infections in adult cases could also have been a limiting factor in our analysis. This indicates that the role of EBV in the development of HL may be more complex and cannot be explained by a single seasonal model.

There are many hematopoietic and non-hematopoietic malignancies associated with EBV infection. In particular, EBV is frequently detected in the neoplastic cells of mixed cellular classical HL, some T-cell lymphomas, immunosuppressed diffuse large B-cell lymphomas, and Burkitt lymphoma. However, the neoplastic cells of NLP HL are generally considered to be EBV-negative.[35] In our study, the most frequently observed HL subtype among EBER-positive cases was nodular sclerosing HL, at 47%. EBER positivity was detected in 6 out of 17 NLP HL cases. Due to the limited number of cases and studies related to EBER positivity in NLP HL, further research is necessary to understand the underlying mechanisms and implications of EBV in this particular subtype of the disease.

The prognostic value of EBER positivity remains a controversial topic; however, our study's results demonstrate that the presence of EBER has a limited effect on lymphoma. Progression-free survival analyses did not show a significant difference concerning EBER positivity. In this context, the average progression-free survival period for EBER-positive patients was determined to be 5.3 years, while it was 11 years for EBER-negative patients. This situation suggests that the role of EBER in HL might interact more with treatment responses or the progression of the disease in conjunction with other factors, rather than having a direct prognostic impact at the time of diagnosis.

CONCLUSION

In conclusion, the data from this study reveal that the impact of EBER positivity and seasonality on survival outcomes in HL presents a more complex relationship. Understanding the interactions of multifactorial influences on a heterogeneous disease like HL is crucial for guiding future research. In this context, further studies conducted on a larger patient population may provide clearer insights into the role of EBER and seasonal variations. Our findings contribute to clinical practice and offer new perspectives on the pathogenesis of HL.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Damla Çağla Patır, Özlem Limoncu, Mahmut Töbü, Nur Soyer;* ***Design:*** *Güray Saydam, Fahri Şahin;* ***Control/Supervision:*** *Filiz Vural;* ***Data Collection and/or Processing:*** *Nazan Özsan, Mine Hekimgil, Derya Demir;* ***Analysis and/or Interpretation:*** *Damla Çağla Patır, Ajda Güneş;* ***Literature Review:*** *Damla Çağla Patır;* ***Writing the Article:*** *Damla Çağla Patır;* ***Critical Review:*** *Mahmut Töbü;* ***References and Fundings:*** *Mahmut Töbü, Güray Saydam;* ***Materials:*** *Mine Hekimgil.*

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