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CLINICOPATHOLOGICAL FEATURES OF ALK POSITIVE AND ALK NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA: A SINGLE INSTITUTE

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ABSTRACT

Background: Anaplastic large cell lymphoma (ALCL) is a rare and aggressive T-cell lymphoma, with limited information on its clinical and pathological characteristics in the Pakistani population.
Objective: The study aims to examine clinical, pathological, and prognostic factors in both ALK-positive and ALK-negative ALCL cases.
Materials and Methods: A total of 49 diagnosed cases from Shaukat Khanum Memorial Cancer Hospital over ten years (2013-2023) were analyzed for various clinical and prognostic factors.
Results: Out of 49 cases, 22 (44.9%) were ALK-positive and 27 (55.1%) were ALK-negative. The median age for ALK-positive patients was 12.5 years, while ALK-negative patients had a median age of 28 years. Notably, ALK-negative patients were younger than reported in other studies, potentially due to geographic differences.
Common symptoms included lymphadenopathy, observed in 12 cases of each subtype, with advanced clinical stage 4 being prevalent. Histological patterns were similar across subtypes.
Outcome Measures: The median overall survival was 12 months for ALK-positive and 15 months for ALK-negative cases, with progression-free survival of 34 months

for ALK-positive and 12 months for ALK-negative. There was no significant survival difference based on ALK status, although ALK-positive cases had better progression-free survival.
Conclusion: ALCL in Pakistan often presents at advanced stages and younger ages than global data suggests. ALK expression did not impact overall survival but correlated with longer progression-free survival in ALK-positive cases. The findings highlight the need for improved detection and treatment strategies in the region.

INTRODUCTION:

Anaplastic large cell lymphomas (ALCLs) are a group of mature T-cell-derived malignancies, sharing a common morphology yet having diverse pathogenesis and clinical manifestations. These tumors are marked by their large cells, which boast horse-shoe-shaped reniform nuclei and a rich eosinophilic cytoplasm, each cell glowing with the robust expression of CD30. In the ALK-positive variant, a defining t(2;5)(p23;q35) chromosomal rearrangement gives rise to the nucleophosmin-anaplastic lymphoma kinase protein, a marker so vividly expressed that it sets this form of lymphoma apart as a distinct entity(2). These lymphomas predominantly affect children and young adults, displaying a male predominance and often presenting at an advanced stage with significant extranodal involvement (5). Conversely, ALK-negative ALCLs reveal a different genetic landscape, marked by mutations in the JAK/STAT3 pathway and additional features such as DUSP22 gene rearrangements and TP63 expression (4). This variant typically emerges in older patients, with its peak incidence occurring in the sixth decade of life (1).

Despite extensive global research on anaplastic large cell lymphoma (ALCL), there remains a notable scarcity of studies focusing on its demographics, clinical characteristics, prognostic factors, and behavior within the Pakistani context. A critical gap exists in exploring the unique features of ALCL in our population, a gap that, if filled, could significantly refine diagnostic and therapeutic strategies to better meet the needs of our people. We posit that factors such as delayed diagnosis, restricted access to advanced treatment facilities, and disparities in healthcare infrastructure—when compared to Western settings—may complicate the management of ALCL in Pakistan. These challenges could adversely affect patient outcomes, underscoring the necessity for context-specific approaches to improve diagnosis, treatment, and long-term care.

This study endeavors to delve deeply into the demographics, pathological characteristics, and prognostic factors associated with ALCL in the Pakistani population. By identifying predictors of adverse outcomes within our own context, we aim to enrich our understanding of this condition and its impact on patient care. Moreover, this research aspires to contribute to the broader discourse on ALCL, particularly from the vantage point of resource-limited settings, thereby bridging a crucial gap in the global understanding of this malignancy.

Materials and methods:

Between 2013 and 2023, 49 in-house cases of anaplastic large cell lymphoma from the archives of Shaukat Khanum Memorial Cancer Hospital and Research Centre were reviewed through total population (universal sampling) technique. We retrospectively analyzed demographic, clinical, radiological, histopathological, and prognostic features for these cases, excluding those with primary cutaneous ALCL or lacking immunohistochemical evaluation. Clinical data assessed included patient age, sex, presentation site and biopsy results, nodal or extranodal involvement, other visceral organ involvement, PET CT findings, extent of

lymph node involvement, clinical symptoms, bone marrow involvement and clinical stage at presentation Prognostic factors included survival status, overall survival (OS), and progression-free survival (PFS).

Data Analysis:

Data were entered and analyzed in SPSS version 29. For the descriptive statistics of categorical variables frequency and percentages were used and for the comparison of categorical variable chi-square test of independence was used. Hence the between the ALK status (positive/negative) and other variables: gender (male/female), patient status (dead/alive), disease progression (yes/no), lymph node involvement (inguinal, hilar, subcarinal, cervical, axillary, mediastinal, para-aortic, and extranodal), clinical presentation (lymphadenopathy and B symptoms, lymphadenopathy only, B symptoms only, skin involvement with lymphadenopathy, and abdominal pain), bone marrow involvement (positive/negative), and clinical stage (1-2/3-4) was assessed by using Chi square test of association/independence.. For (2x2) contingency table Fisher's Exact test was applied. The normality of the continuous variable like age was assessed using Shapiro Wilk's test of normality. It found to be non symmetrical hence, Mann Whitney test was applied to assess the significant differences. Kaplan-Meier survival analysis was conducted to compare the survival distribution by ALK status (positive and negative) for both the OS and PFS. The Log-Rank test was used to test the equality of survival distributions. OS was measured from diagnosis to death, while PFS was tracked from diagnosis until recurrence, relapse, or disease progression. Statistical analysis was performed using the SPSS-version 26. The p-Value ≤ 0.05 was considered significant.

Results:

Clinical features:

Table 1: Clinical features of ALK positive and ALK negative lymphoma

Clinical Features	ALK + ALCL n (%)	ALK – ALCL n (%)	p value
Total patients	22(44.9%)	27(55.1%)	
Male	16(32%)	23(46%)	0.311
Female	6(12%)	4(8%)	
alive	8(16%)	3(6%)	.046
Dead	14(28.5%)	24(48.9%)	
Progressive disease	8(16%)	14(28.5%)	.393
Lymph node involvement			0.516
Inguinal	13(26.5%)	11(22%)	
Hilar	0(0%0	1(2%)	
Subcarinal	1(2%)	0(0%)	
Cervical	12(24%)	5(10%)	
Axillary	13(26.5%)	4(8%)	
Mediastinal	1(2%)	2(4%)	
Para-aortic	2(4%)	1(2%)	
Extranodal presentation only	2(4%)	0(0%)	
Clinical presentation			0.569
Lymphadenopathy and B	6(12.2%)	7(14.2%)	

symptoms			
Lymphadenopathy only	12(24.4%)	12(24.4%)	
B symptoms only	1(2%)	5(10%)	
Skin involvement with lymphadenopathy	2(4%)	1(2%)	
Abdominal pain	1(2%)	2(4%)	
Bone marrow involvement			0.489
Positive	2(4%)	4(8%)	
negative	20(40.8%)	23(46.9%)	
Clinical stage			0.715
1-2	3(6%)	5(10%)	
3-4	19(38%)	22(45%)	

The estimated median age for ALK-positive ALCL was 12.5 years (±10.79 years), with an age range of 4 to 38 years and 54% of patients under 14 years old. In contrast, ALK-negative ALCL had a median age of 28 years (±19.43 years), ranging from 6 to 86 years, with only 11% under 14 years.

The most significant finding in clinical features was the difference in survival status between ALK-positive and ALK-negative groups ($p = 0.046$), with a higher mortality rate observed in ALK-negative patients (88.9%) compared to ALK-positive patients (63.6%). This suggests that ALK-negative ALCL may have a worse prognosis. However, no significant differences were found in disease progression, lymph node involvement, bone marrow infiltration, or clinical stage, indicating that ALK status alone may not be a strong determinant of these clinical parameters.

In ALK-positive cases, inguinal and axillary lymph nodes were the most commonly involved (n=13), followed by cervical lymph nodes (n=12), para-aortic lymph nodes (n=2), and mediastinal and subcarinal lymph nodes (n=1). Two ALK-positive patients had only extranodal presentation. For ALK-negative cases, inguinal lymph node involvement was the most frequent (n=11), followed by cervical (n=5), axillary (n=4), mediastinal (n=2), and para-aortic and hilar lymph nodes (n=1 each). No ALK-negative cases presented with extranodal disease exclusively

Both ALK-positive and ALK-negative ALCL cases presented with similar clinical features. Lymphadenopathy alone was the most common presentation (n=12), followed by lymphadenopathy with B symptoms (n=6 for ALK-positive, n=7 for ALK-negative), B symptoms only (n=1 for ALK-positive, n=5 for ALK-negative), skin involvement with lymphadenopathy (n=2 for ALK-positive, n=1 for ALK-negative), and abdominal pain (n=1 for ALK-positive, n=2 for ALK-negative). Bone marrow involvement was observed in 2 ALK-positive and 4 ALK-negative cases, while the remaining cases had no bone marrow involvement at presentation.

The majority of ALK-positive and ALK-negative cases were diagnosed at stage 4 (n=12 for ALK-positive, n=15 for ALK-negative), followed by stage 3 (n=7 for ALK-positive, n=4 for ALK-negative), stage 2 (n=2 for ALK-positive, n=4 for ALK-negative), and stage 1 (n=1). ALK-positive patients predominantly received the ALCL protocol, while ALK-negative patients were treated with CHOEP. Patients with progressive disease or those unresponsive to initial treatment were given second and third-line chemotherapy.

Table 2: PET CT findings of ALK positive and ALK negative ALCL

PET CT findings	Alk positive, n (%)	Alk negative, n (%)
Lymphadenopathy above and below the diaphragm	20(40.8%)	18(36.73%)
Bone	2(4%)	1(2%)
Skin	1(2%)	0(0%)
Lung	4(8.1%)	4(8.1%)
Pancreas	2(4%)	0(0%)
Spleen	0(0%)	1(2%)
Cervical lymphadenopathy only	0(0%)	2(4%)
Mediastinum	1(%)	4((8.1%)
Iliopsoas muscle involvement	0(0%)	2(4%)
Axillary lymphadenopathy only	1(2%)	1(2%)
Shoulder mass	1(2%)	0(0%)
Scalp mass	2(4%)	0(0%)

The PET CT findings revealed that lymphadenopathy above and below the diaphragm was more common in ALK-positive cases (90.9%) compared to ALK-negative cases (62%). Extranodal involvement was more frequent in ALK-positive cases, particularly affecting the lung, pancreas, and scalp, while ALK-negative cases had a greater frequency of spleen and iliopsoas muscle involvement. These findings highlight a broader extent of lymphatic and extranodal dissemination in ALK-positive ALCL, which may influence treatment approaches and prognosis.

Histological analysis of all cases was performed on H&E-stained slides. Anaplastic large cell lymphoma (ALCL) diagnosis was confirmed through cytomorphology and CD30 antigen expression via immunohistochemistry. Additional histological features assessed included lymph node architecture (whether partially or completely effaced), presence of hallmark cells (with pleomorphic horse-shoe shaped nuclei), predominant lymphoma cell type, and ALK expression. The expression of other T cell markers (CD2, CD3, CD4, CD5, CD7, and CD8) was also evaluated.

The most common architectural pattern observed was diffuse sheets of cells, followed by paracortical and sinusoidal patterns. Cell morphology predominantly featured hallmark cells (n=21 for ALK-positive ALCL and n=25 for ALK-negative ALCL). However, small cells, lymphohistiocytic cells, and monomorphic cells were present in smaller quantities (table 4)

Table 3: Histological and cytomorphological features

Architecture	ALK +ALCL	ALK - ALCL	P value
Sinusoidal pattern	1(2%)	2(4%)	1.00
Paracorticaldistribution	0(0%)	2(4%)	0.495
Diffuse sheets	21(42%)	25(51%)	1.000
Hallmark cells	16(32%)	22(44.9%)	0.510
Small cells	4(8%)	2(4%)	0.388
Lymphohistiocytic cells	2(4%)	3(6%)	1.000
Monomorphic cells	0(0%)	2(4%0	0.495

CD30 was positive in all cases. Other stains with variable positivity were CD3, CD4, LCA and EMA. Rare ALK + cases showed positive staining fo, c-myc, MUM1, CD43, granzyme and perforin (n=1). Rare ALK – cases showed expression of CD5, EBER,c-myc,CD 43 and CD99(n=1).(table 5)

Table 4: Immunohistochemical features

Positive stains	ALK +ALCL, n (%)	ALK –ALCL, n (%)	P value
CD30	22(44.9%)	27(55%)	0.499
CD3	4(8%)	7(14%)	0.849
CD 4	7(14%)	3(6%)	0.165
LCA	15(30%)	17(34%)	0.195
EMA	10(20%)	2(4%)	0.061

Out of 22 ALK positive patients, 14 patients had died at the time of data analysis. Similarly, out of 27 ALK negative patients, 24 patients had died. The median overall survival was 12 months for ALK-positive cases and 15 months for ALK-negative cases. The combined median survival for both groups was 15 months. Log-Rank test results showed no statistically significant difference in overall survival based on ALK status (Chi-Square = 0.563, df = 1, p = 0.453), indicating that ALK status did not significantly affect overall survival in this study. (Figure 1 and table 5)

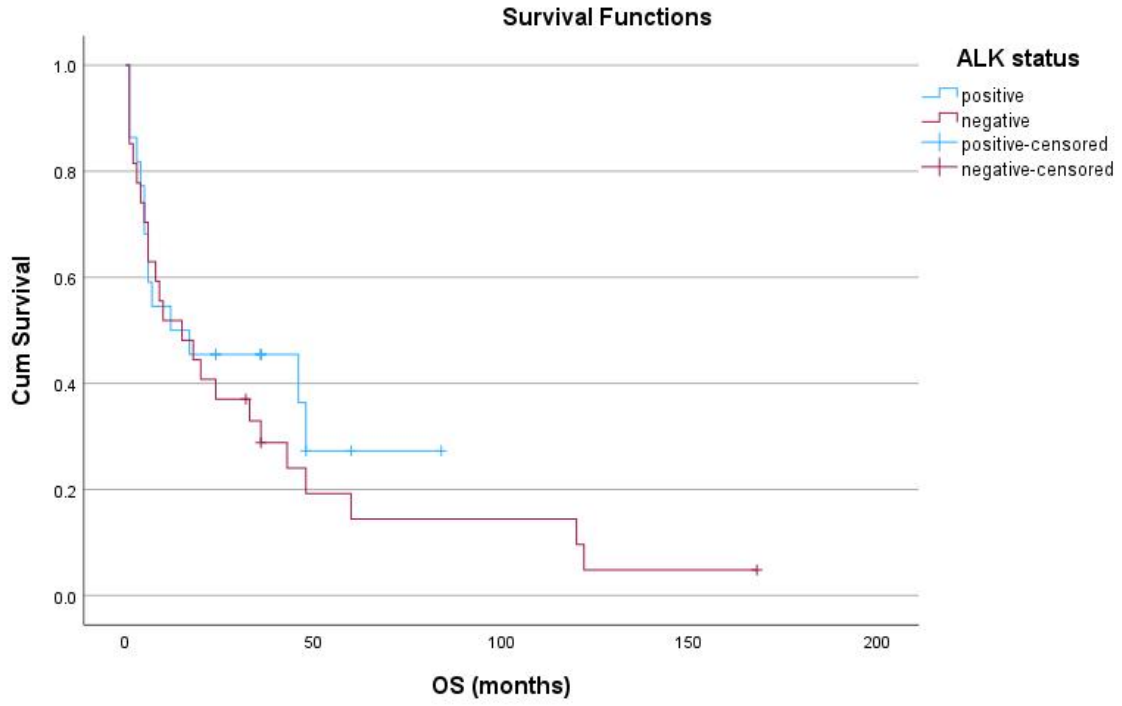

Figure 1: Overall survival (months) of ALK positive and ALK negative anaplastic large cell lymphoma

The median progression-free survival (PFS) was 34 months for ALK-positive cases and 12 months for ALK-negative cases, with the overall average PFS for all cases being 24 months. The Log-Rank test indicated no statistically significant difference in progression-free survival between ALK-positive and ALK-negative groups (Chi-

Square = 0.953, df = 1, p = 0.329). (Figure 2 and table 5)

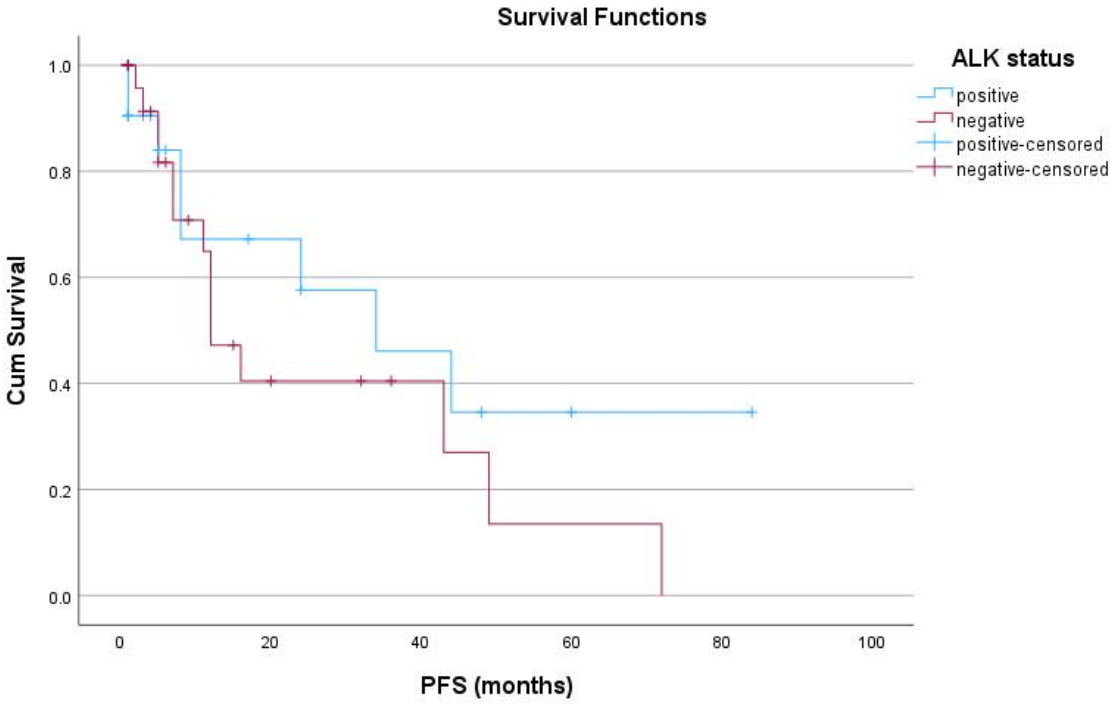

Figure 2: Progression free survival curves of ALK positive and ALK negative anaplastic large cell lymphoma

Table 5: Survival Statistics of ALK positive and ALK negative ALCL.

Statistics	Group	Survival (95% Confidence Interval)	
		Overall	**Progression free**
Est. Mean Survival Time (Months)	**ALK(+)**	12.00±18.762	34.00±13.225
	ALK(-)	15.00±7.789	12.00±2.409
	Total	15.00±6.299	24.00±15.275
	P-value	0.453	0.329
5 year survival rate (%)	**ALK(+)**	27.3%	34.9%
	ALK(-)	14.4%	13.5%

Interpretation: The 5 year overall survival rate for ALK positive cases was 27.3 % and for ALK negative cases was 14.4%.Similarly,the 5 year progression free survival for ALK positive cases was 34.9 % and for ALK negative cases was 13.5%. The survival analysis did not demonstrate a statistically significant difference in overall survival (p = 0.453) or progression-free survival (p = 0.329) between ALK-positive and ALK-negative cases. Although ALK-positive patients had a longer median progression-free survival (34 months) compared to ALK-negative patients (12 months), this difference was not statistically significant. These results suggest that factors beyond ALK status, such as disease stage, treatment response, and potential genetic

variations, may influence survival outcomes in ALCL patients. The absence of a significant survival benefit for ALK-positive cases emphasizes the need for further research into additional prognostic biomarkers and optimized therapeutic strategies for both subtypes.

Discussion:

Through this study we have identified several similarities and differences with respect to the clinical and histopathological features in both subtypes of ALCL. Like many studies conducted previously, the median age of presentation of AlK +ALCL was younger than that of ALK-ALCL.(7,8,10,15,16,,20,22). Also the median age of presentation for ALK - ALCL in our study was much younger than other studies(3,8,7,15, 9,25,26,27). The younger age of presentation in ALK – ALCL as compared to other studies can be attributed to geographic variations in age distribution as our study included patients exclusively from Pakistan. There was a statistically significant difference in the age of presentation between the ALK + and ALK – cases, comparable to study by YanFang Wang et al and many others (11, 14,15).

In this study, the majority of cases presented with lymphadenopathy alone (n=24), followed by lymphadenopathy with B symptoms (n=13), and B symptoms alone (n=6). Cervical lymphadenopathy was the most common presentation, consistent with previous studies (31). Notably, skin involvement with lymphadenopathy and abdominal pain were observed as initial complaints in a few cases (n=3 each), which contrasts with other studies where B symptoms and skin involvement were more prevalent at presentation (8, 11, 14). The frequency of extranodal disease presentation was also lower (n=2) compared to the study by Lakshmiah et al. (14).

PET CT findings revealed that 77% of cases had lymphadenopathy both above and below the diaphragm, with rare extranodal sites such as the lung, liver, spleen, pancreas, jejunum, soft tissue mass, and bone. This finding aligns with the advanced clinical stage observed, as 90% of cases presented with stage 4 disease. This is similar to the clinical stage 4 prevalence reported in studies by Kerry J. Savage et al. (8, 3, 7, 15, 19). Clinical stage is a critical prognostic factor, as noted in the study by K.C. Lakshmaiah (14) and is considered the most significant factor by YA-FANG WANG et al. (11, 8). Despite this, our study did not find a statistically significant relationship between clinical stage and overall survival between the ALK-positive and ALK-negative subtypes, likely due to the overall poor outcomes and limited effectiveness of systemic treatments for both subtypes.

Our study indicates that bone marrow involvement was more common in ALK-negative ALCLs compared to ALK-positive ALCLs, consistent with findings by Yan-Fang Wang et al. (11). This contrasts with another study where ALK-positive ALCLs exhibited more frequent bone marrow involvement (8). Similar to previous research (8, 14), the majority of cases in our study showed hallmark cells, with small and lymphohistiocytic cells being less common. Furthermore, CD3 positivity was more prevalent in ALK-negative ALCLs (14% vs. 8%), while EMA positivity was higher in ALK-positive ALCLs (20% vs. 4%), aligning with earlier studies (13, 21).

Our results show that ALK status did not significantly affect overall survival, consistent with several studies where ALK status had no impact on survival in patients under 40 years of age (1, 9, 15). This contrasts with American studies (12, 6) where ALK-positive ALCLs demonstrated better 5-year overall survival compared to ALK-negative ALCLs. Research on the Chinese population indicated that ALK expression correlated with improved survival in patients under 14 years

but not in adults (11). However, our Cox regression analysis did not reveal statistically significant results to support this trend. Nonetheless, ALK-positive cases exhibited better progression-free survival compared to ALK-negative cases in our study. Previous studies have highlighted that age is a significant factor influencing survival outcomes (8), with pediatric patients in Asian populations generally showing better overall survival than adults (14). Our study's limited sample size may have affected the statistical significance of age-related survival differences.

Our study has several limitations. First, it did not incorporate recent molecular advancements in ALK-negative ALCL classification, such as prognostic markers like DUSP22 and p63, which could provide deeper insights into survival outcomes (2, 4). The traditional histological approach may not fully capture the complexity of ALCL, underscoring the need for more precise diagnostic methods and biomarkers.

The generally poorer outcomes for ALK-negative ALCL can be attributed to the disease's genetic heterogeneity, highlighting the need for more targeted therapeutic strategies (1). Despite this, ALK-negative ALCLs have been shown to have better outcomes compared to peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) (4).

Wang et al. (29) suggested that suppressor Tregs in ALK-positive ALCL might inhibit the anti-tumor immune response, potentially diminishing the impact of ALK expression. Beltran et al. (30) found that while ALK expression in DLBCL has a favorable prognostic role, ALK-negative DLBCL has a more aggressive clinical course. This indicates that the prognostic value of ALK could be influenced by other unknown factors. Additionally, factors such as performance status, IPI scores, and beta2-microglobulin levels have been shown to affect outcomes in ALCL (9, 15). CD Welk et al. identified minimal residual disease, minimal disseminated disease, ALK antibody titers, and histologic subtype as significant risk factors in pediatric ALCL (18).

Future research should explore whether clinical stage and biomarkers could surpass ALK status in prognostic value. Studies have suggested that ALK-positive ALCL cells may exhibit higher apoptosis in response to chemotherapy compared to ALK-negative cells (17). ALK inhibitors might offer novel therapeutic options for some solid tumors (28). Additionally, BCL2 expression, almost exclusive to ALK-negative ALCL, is associated with poorer prognosis (23, 24). Further investigation into BCL2 and other markers like Ki67 will require larger sample sizes and appropriate funding to comprehensively assess their roles in ALCL.

Conclusion:

In conclusion, our study reveals distinct clinical features in Pakistani patients with ALCL, such as a higher clinical stage and a younger age at presentation for ALK-negative ALCL, compared to global data. These findings highlight the prognostic importance of age and underscore the need to consider ethnic and geographic factors in hematologic malignancies. To better understand these variations, future research should involve larger, multinational, and multi-institutional cohorts, allowing for stratification based on specific prognostic features and tailored therapeutic options. Additionally, raising awareness among families about ALCL symptoms is crucial for facilitating early medical intervention, particularly in low- to middle-income countries.

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