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Factors Associated with Lymphoma Recurrence Following Autologous Stem Cell Transplantation

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ABSTRACT

Introduction: Non-responsive or relapsed lymphoma patients may benefit from salvage chemotherapy or high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), an effective treatment, particularly in non-Hodgkin's and Hodgkin's lymphoma. This study aimed to investigate recurrence in these patients and identify associated risk factors.

Methods: A retrospective cohort study analyzed outcomes of lymphoma patients undergoing ASCT at Omid Hospital (2016-2020). Comprehensive data on demographics, treatment, underlying disease, recurrence, and pre-transplantation laboratory parameters were collected from hospital records. Follow-up from transplantation to February 2021 allowed for survival and recurrence evaluation using Kaplan-Meier and Cox regression. The study included patients without concurrent plasma cell disorders or other hematological malignancies for a focused lymphoma treatment outcome analysis.

Results: 49 lymphoma patients underwent ASCT (21 HL, 42.9%; 28 NHL, 57.1%). Gender distribution was similar (30 males, 61.2%; 19 females, 38.8%; P=0.774). Mean age at transplantation was 38.8 ± 11.15 years (P=0.519 between groups). Recurrence occurred in 14 patients (7 in each group; P=0.523), with a mean recurrence-free survival (RFS) of 25.2 months (95% CI: 21.44-28.96). HL patients had a lower mean RFS and a higher recurrence hazard ratio (HR: 1.25, 95% CI: 0.420-3.76), though not statistically significant (P=0.683). In NHL, older age significantly correlated with recurrence (P=0.030). While male gender and older age were associated with lower survival, only advanced age in NHL significantly predicted decreased survival (HR: 2.16, recalculated per 5-year increment, 95% CI: 1.63-2.45).

Conclusions: Advanced age significantly predicted reduced survival in NHL patients. Pre-transplant laboratory markers did not show a significant association with survival. Given the limited sample size and exploratory nature of this study, the results warrant validation in larger, multicenter cohorts.

Keywords:Lymphoma; Recurrence; Stem Cell Transplantation; Risk Factors

INTRODUCTION:

Lymphocytes, the primary effector cells of the immune system, can undergo neoplastic transformation, leading to a wide range of malignancies that may originate in or disseminate to virtually any anatomic site, not limited to lymphoid tissues (1). The primary lymphoid malignancies are non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), lymphoid leukemia, and plasma cell dyscrasias (2). HL is a relatively uncommon monoclonal lymphoid neoplasm characterized by Reed–Sternberg cells in an inflammatory context, while NHL includes a heterogeneous group of lymphoid malignancies that differ in histology and origin, molecular biology, clinical characteristics, and prognosis (3, 4). Based on biological and clinical research, HL is classified into two distinct categories, classical HL and nodular lymphocyte-predominant HL (NLPHL) (5).

The most common types of NHL include Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma, marginal zone lymphoma, and primary CNS lymphoma (6). The first-line treatment for the most common types of NHL generally consists of chemotherapy or chemoimmunotherapy, with the regimen and duration depending on the disease stage (7). Standard first-line regimens include CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), R-CHOP (rituximab as a chimeric anti-B cell monoclonal antibody is added to CHOP regimen), and the dose-adjusted R-EPOCH (including rituximab, etoposide, vincristine, adriamycin, cyclophosphamide, prednisolone) (8).

In classical HL, ABVD remains the most widely used first-line chemotherapy regimen (including adriamycin, bleomycin, vinblastine, and dacarbazine) (9).

For patients with treatment-resistant or relapsed lymphoma, salvage chemotherapy regimens (ST) or high-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) are therapeutic options (7, 10). ASCT is a valuable and effective treatment method with significant favorable outcomes in terms of the overal survival (OS) rate and the progression-free disease for patients with NHL and HL (11, 12).

Nevertheless, ASCT is associated with several important challenges. Post-transplant recurrence remains the major cause of treatment failure, and a considerable proportion of patients relapse despite achieving remission prior to ASCT (13, 14). Additional challenges include transplant-related toxicity, delayed or incomplete immune reconstitution, variability in patient selection, and the lack of reliable biomarkers to predict recurrence risk (15, 16, 17).

Despite known factors influencing outcomes, limited detailed studies are available on transplantation outcomes in Iranian lymphoma patients, highlighting the need to investigate recurrence and identify associated risk factors in this population following ASCT.

Methods:

This retrospective cohort study examined all lymphoma patients who underwent transplantation at Omid Hospital, affiliated with Isfahan University of Medical Sciences, between 2016 and 2020.

Demographic characteristics (age at lymphoma diagnosis, age at transplantation, gender), chemotherapy drugs and treatment duration, the interval between lymphoma diagnosis and transplantation, underlying diseases, history of drug use, incidence of recurrence, and pre-transplantation laboratory parameters (WBC, CRP, ESR, liver and kidney function tests) were obtained from the hospital Health Information System (HIS) and electronic medical records.

To assess post-transplant survival and recurrence, patients were followed up from the time of transplantation until February 2021.

Post-transplantation recurrence was diagnosed based on lymphadenopathy, lymph node biopsy, pathology results, and radiologic evidence of new or progressive lesions on PET/CT.

Relapse-free survival (RFS) was defined as time from inclusion to recurrence or death (18). In this study, disease free survival (DFS) and event-free survival (EFS) were considered equivalent to RFS.

Post-transplantation medications and recurrence intervals were also recorded. All lymphoma patients who underwent ASCT between 2016 and 2020 at Omid Hospital who did not have other plasma cell disorders or other hematological malignancies were included. Patients with incomplete files or who were unavailable for information completion were excluded.

The collected data were entered into SPSS V.23 and reviewed for completeness and accuracy. To summarize the findings, descriptive statistics such as means, standard deviations, and frequencies were calculated. Categorical variables were compared between groups using Chi-square or Fisher's exact tests, while Student's t-tests or Mann-Whitney U-tests were used for parametric and nonparametric continuous variables, respectively.

RFS was analyzed with Kaplan-Meier method, and Cox proportional hazards regression was used to calculate hazard ratios (HR), alongside descriptive statistics.

Results:

In our study, a total of 54 lymphoma patients underwent ASCT. After applying the eligibility criteria, 49 patients with complete medical records were included in the final analysis. Of these, 21 patients (42.9%) had HL, and 28 patients (57.1%) had NHL. In the entire cohort, 30 patients (61.2%) were male and 19 (38.8%) were female. There was no significant difference in gender distribution between the HL and NHL groups (P = 0.774).

The mean age at the time of ASCT was 38.8 ± 11.15 years (range: 17 to 63 years). The mean age at ASCT did not differ significantly between the HL and NHL groups (P = 0.519).

Various chemotherapy regimens were used. Specifically, Etoposide, Cytosar, and Melphalan were included in the regimen for all patients. CCNU(lomustine) was used in 26 patients, with no significant difference between the HL and NHL groups (P = 0.509). CCNU (lomustine) was used for 4 patients in the NHL group, while cyclophosphamide was administered to one patient in the HL group. Table 1 presents the chemotherapy regimens and demographic characteristics of the patients.

In this study, post-ASCT recurrence was observed in 14 patients (7 in the HL group and 7 in the NHL group), with no significant difference in frequency between the two groups (P = 0.523)

The mean RFS for all patients was 25.2 months (95% CI: 21.44, 28.96), assessed from the date of ASCT to documented event (Figure 1).

Comparison of RFS between the HL and NHL groups showed a lower mean RFS in HL patients compared to NHL patients (Table 2, Figure 2). The recurrence HR was also higher in HL patients (HR: 1.25, 95% CI: 0.42, 3.76); however, this difference was not statistically significant (P = 0.683).

Table 3 compares variables in patients with and without recurrence, stratified by lymphoma type. In the NHL group, patients who experienced recurrence were significantly older than those who did not (P=0.030). Nevertheless, no significant associations were observed with other variables.

RFS based on pre-ASCT laboratory factors (WBC, ESR,

Table 1. Chemotherapy regimens and demographic characteristics of the patients.

Variables	All patients	Hodgkin	non-Hodgkin	P-value
Age at time of transplantation, [mean ± SD]	38.8 ± 11.15	39.33 ± 11.73	38.39 ± 10.9	P=0.519
Gender, [N (%)]				P=0.774
Male	30 (61.2)	14 (66.7)	16 (57.1)	
Female	19 (38.8)	7 (33.3)	12 (42.9)	
Chemotherapy [N (%)]*				
Etoposide	49 (100)	21 (100)	28 (100)	-
Cytosar	49 (100)	21 (100)	28 (100)	-
Melphalan	49 (100)	21 (100)	28 (100)	-
CCNU (Lomustine)	26 (53.1)	10 (47.6)	16 (57.1)	P=0.509
Cyclophosphamide	1 (2)	1 (4.8)	0 (0)	P=0.429

* The number of positive cases is considered

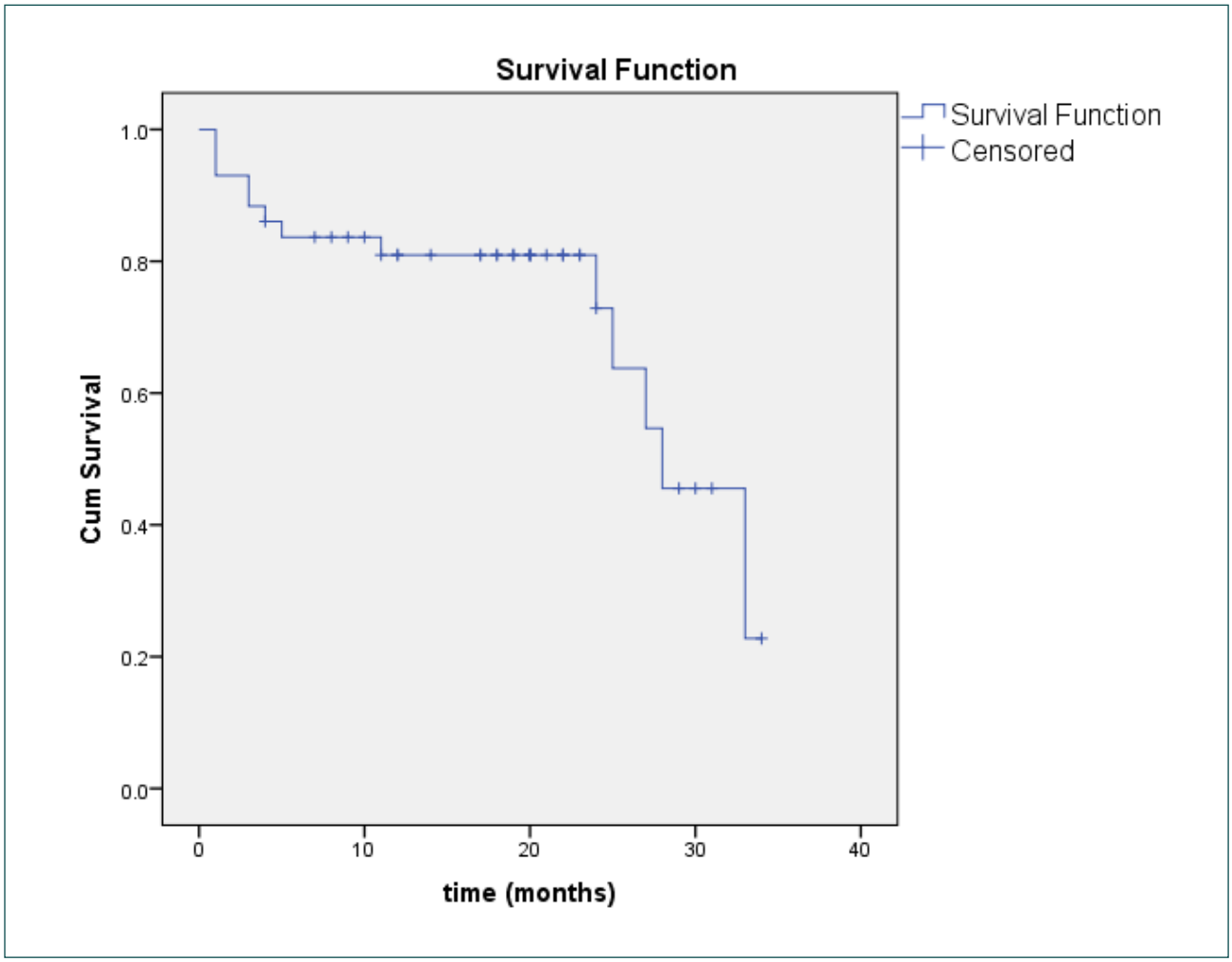

Figure 1: Kaplan-meier curve of recurrence free survival after ASCT

Table 2. Recurrence-free survival of patients by type of lymphoma

Patients	Mean of Recurrence-free survival			
	Mean	Std. Error	95% CI	
			Upper	Lower
All patients	25.2	1.91	21.44	28.96
Hodgkin	24.86	3.32	18.34	31.39
Non-Hodgkin	25.65	2.42	20.9	30.4

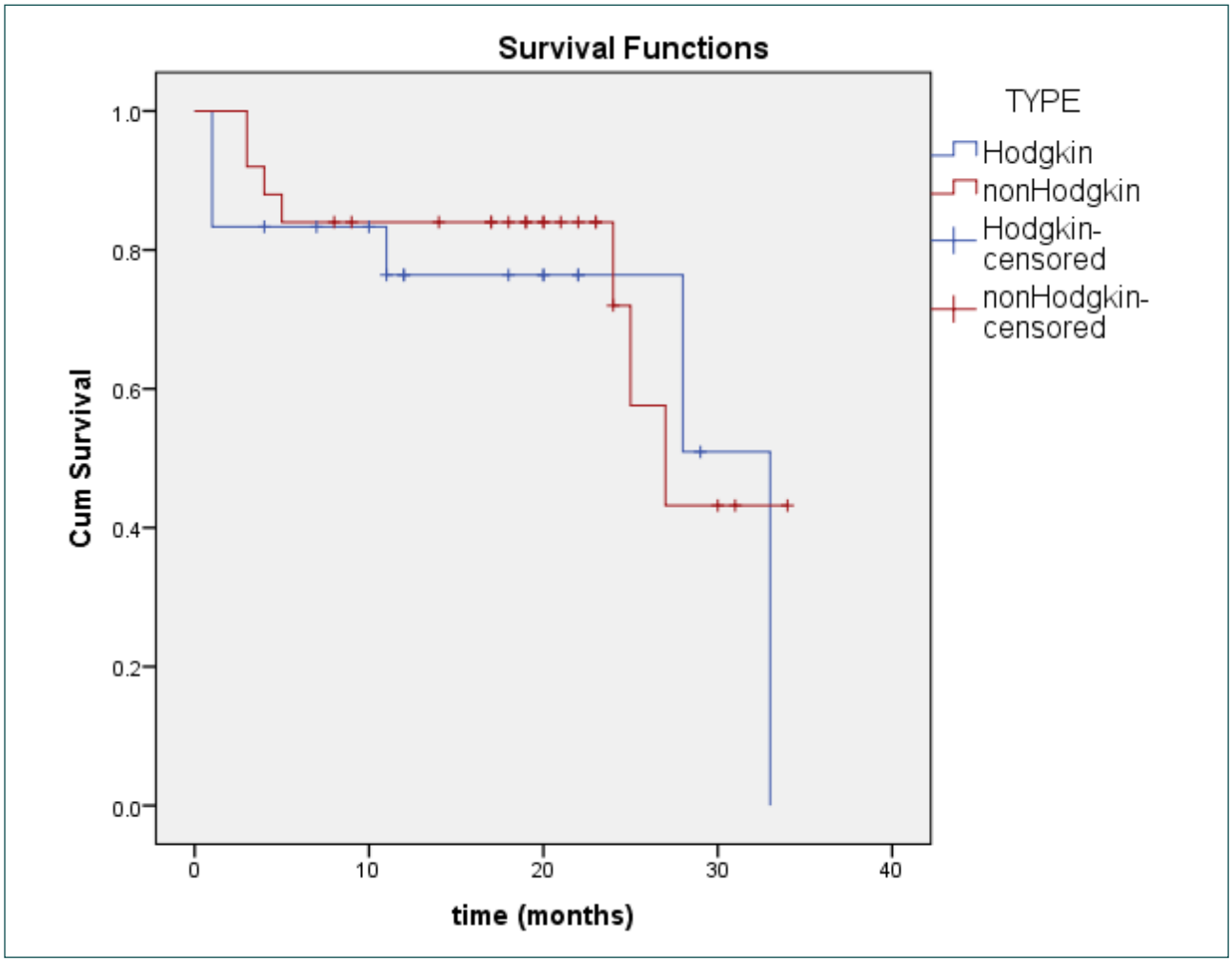

Figure 2: Kaplan-Meier curve of recurrence free survival after ASCT by type of lymphoma

and CRP) and demographic variables (gender and age), by lymphoma type, is presented in Table 4.

Despite the findings that male gender in HL patients is associated with lower survival rates and a higher HR compared to females, and that in NHL patients males exhibited shorter survival times than females, none of these observations reached statistical significance.

In NHL patients, advanced age was associated with decreased survival. The HR for age was recalculated per 5-year increment (HR: 2.16, 95% CI: 1.63, 2.45) indicating a substantially higher risk of mortality with increasing age.

Nonetheless, none of the laboratory factors before ASCT demonstrated a statistically significant impact on patient survival.

Discussion:

The foundational role of ASCT in the management of relapsed or refractory HL and aggressive NHL is well-established (19, 20). Recent studies have confirmed the survival benefit of ASCT in relapsed or refractory lymphoma. For instance, Wullenkord et al. reported a 3-year progression-free survival (PFS) of approximately 63% and an overall survival (OS) of 68% in patients with aggressive NHL undergoing ASCT (14). Additionally, Mariotti et al.'s study further underscores the utility of ASCT even in heavily pre-treated HL patients who achieve disease response (22). This cohort study aimed to assess the rate of recurrence following ASCT and to identify associated clinical and demographic risk factors.

The relatively modest RFS highlights the ongoing risk of

Table 3. Compares the variables studied in patients with and without recurrence, categorized by lymphoma type

Lymphoma type	Variables	Recurrence		P-value
		Yes	No	
Hodgkin	Gender. N (%)			P=0.743
	Male	5 (71.4)	9 (64.3)	
	Female	2 (28.6)	5 (35.7)	
	Age. [mean ± SD]	39.86 ± 14.49	39.07 ± 10.7	P=0.889
	WBC. [mean ± SD]	4198.0 ± 1060	5266.3 ± 1660	P=0.212
	ESR. [mean ± SD]	18.4 ± 7.09	27.73 ± 27.02	P=0.691
	CRP. [mean ± SD]	5.3 ± 3.66	6.4 ± 6.12	P=0.955
Non-Hodgkin	Gender. N (%)			P=0.418
	Male	3 (42.9)	13 (61.9)	
	Female	4 (57.1)	8 (38.1)	
	Age. [mean ± SD]	46.0 ± 13.17	35.86 ± 9.02	P=0.030
	WBC. [mean ± SD]	5858.3 ± 1990	5226.4 ± 1930	P=0.502
	ESR. [mean ± SD]	30.6 ± 25.95	16.8 ± 25.77	P=0.483
	CRP. [mean ± SD]	6.78 ± 36.17	5.58 ± 8.53	P=0.319

Table 4. Cox regression analysis of factors associated with recurrence-free survival by lymphoma type

Lymphoma type	Variables	HR	95% CI		P-value
			Upper	Lower	
Hodgkin	Gender (Male to female)	3.084	0.322	29.581	P=0.329
	Age*	0.961	0.880	1.050	P=0.383
	WBC	1.000	0.999	1.000	P=0.851
	ESR	0.971	0.889	1.060	P=0.506
	CRP	1.005	0.819	1.233	P=0.963
Non- Hodgkin	Gender (Male to female)	0.520	0.114	2.367	P=0.329
	Age*	2.16	1.63	2.45	P=0.048
	WBC	1.000	1.000	1.001	P=0.803
	ESR	1.016	0.990	1.042	P=0.533
	CRP	1.025	0.921	1.141	P=0.646

*The hazard ratio for age was recalculatedper 5-year icrement

relapse despite ASCT, particularly in HL patients (95% CI: 21.44 to 28.96) (13).

A trend toward lower survival and higher HR in male patients with HL was observed, although not statistically significant (P = 0.329).

This pattern is consistent with prior studies reporting gender-related disparities in HL outcomes, which have been attributed to hormonal, genetic, and immunologic differences affecting treatment responsiveness and immune recovery (22, 23). The lack of statistical significance in our cohort may reflect the limited sample size rather than the absence of a true association.

Analysis of variables in patients with and without recurrence, categorized by lymphoma type, revealed that within the NHL group, older individuals experienced significantly more recurrences (P = 0.030). The inferior post-transplant outcomes in older patients may reflect age-related immune decline, increased comorbidity burden, and reduced tolerance to high-dose chemotherapy (24).

Age-related immunosenescence, characterized by thymic involution, accumulation of senescent T cells, and chronic low-grade inflammation, reduces immune surveillance of residual malignant cells (25). Senescent CD8+ T cells exhibit diminished proliferation, effector cytokine production, and cytotoxic activity (26). Furthermore, age-associated clonal hematopoiesis of indeterminate potential (CHIP) and epigenetic aging of hematopoietic stem cells may impair post-transplant immune reconstitution (27, 28). These findings highlight the importance of considering age in candidate selection for ASCT, as well as the need for tailored post-transplant surveillance and supportive care strategies for older patients.

Our findings align with those of Pasvolsky et al., demonstrating superior OS in younger ASCT recipients and highlighting the importance of long-term surveillance for late complications such as second primary malignancies (29).

The conditioning regimens used in our cohort, including high-dose etoposide, cytarabine (Cytosar), melphalan, CCNU, and cyclophosphamide, reflect the continued importance of high-dose chemotherapy as an essential component of successful ASCT preparation (30, 31). Concurrently, the role of post-ASCT maintenance and consolidation therapies is being actively investigated. These approaches aim to eradicate any residual disease and prevent relapse (32).

In addition, emerging evidence emphasizes the prognostic value of minimal residual disease (MRD), the tumor microenvironment (TME), and the kinetics of immune reconstitution in predicting relapse and long-term outcomes after ASCT (33–35). Incorporating these biomarkers into routine assessment could substantially refine post-transplant risk stratification.

Similarly, the absence of a significant association between pre-transplant laboratory parameters, including CRP and ESR, and survival contrasts with prior reports, which may be attributable to the limited statistical power of our study (36, 37). The small cohort size represents the most critical limitation of this study, substantially reducing statistical power and the ability to detect nuanced associations. Therefore, non-significant findings may reflect type II error rather than true absence of association. Future studies with larger sample sizes are needed to confirm these preliminary observations.

Our study provides insights into recurrence rates and RFS within our patient cohort. However, the landscape of post-ASCT lymphoma management is quickly evolving (38). Data regarding disease stage, chemosensitivity, genetic markers, and pre-transplant prognostic indices (e.g., aaIPI, PET-CT SUVmax) were not available for analysis, which limits the ability to fully assess their prognostic impact.

To build on these findings and gain a more complete understanding, future research should focus on prospective, multicenter studies incorporating comprehensive molecular profiling, such as PET-CT SUVmax and ctDNA. Additionally, future investigations should prioritize integrating MRD monitoring into standard practice, assessing the effectiveness of new post-transplant treatments for specific risk categories, further clarifying the significance of the TME and immune system recovery, understanding the long-term risks of SPMs, and emphasizing patient-centered outcomes to improve the care and long-term health of lymphoma survivors after autologous transplantation.

Conclusions:

Advanced age was the only statistically significant factor associated with reduced survival in NHL patients. No significant associations were observed for the pre-transplantation laboratory factors. Other findings were descriptive and should be interpreted cautiously due to limited sample size.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

Author Contributions: MS, MG and SADT wrote the first draft of the manuscript. MS conceived the study, conducted data analysis, and contributed to the manuscript revision and editing. MG and AA interpreted the statistical analyses. SHT and SADT contributed to the conception, study design, supervision, project administration, and manuscript revisions. SADT and SHT contributed to data collection. All of the authors critically revised the manuscript. The authors read and approved the final manuscript.

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