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Original Article

Timing of multiple primary malignancies does not affect overall survival in lymphoma patients: a comparative study of 167 synchronous vs. metachronous cases

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Abstract: In recent years, growing attention has been paid to the clinical management and prognosis of lymphoma patients with multiple primary malignancies (MPMs). This study aimed to determine whether the timing of MPM diagnosis affects the clinical characteristics and prognosis of these patients. A total of 167 patients with lymphoma complicated by MPMs were retrospectively analyzed. Patients were divided into a synchronous cancer group (SC, interval ≤6 months between diagnoses) and a metachronous cancer group (MC, interval >6 months) based on the interval between the diagnoses of lymphoma and the second malignancy. Clinical characteristics were recorded and compared between the two groups. Overall survival (OS) was estimated using the Kaplan-Meier method, and independent prognostic factors were identified through a multivariate Cox proportional hazards regression analysis. No significant differences were observed in baseline clinical characteristics between the SC and MC groups. The 1-, 3-, and 5-year OS rates for the entire cohort were 94.01%, 74.25%, and 72.46%, respectively. Multivariate analysis revealed that aggressive lymphoma (hazard ratio [HR]=2.618; 95% confidence interval [CI], 1.169-5.863; P=0.026) and Ann Arbor stages III-IV (HR=5.793; 95% CI, 2.658-12.625; P<0.005) were independent predictors of poor prognosis. The temporal sequence of MPMs was not identified as a significant factor influencing OS. Overall, prognosis in patients with lymphoma with MPMs is determined primarily based on the biological behavior and treatment response of lymphoma, whereas the diagnostic interval and sequence of MPM occurrence do not appear to significantly affect long-term survival. These results highlight the importance of focusing on lymphoma-specific features and treatment response in prognostic evaluation of patients with lymphoma with MPMs.

Keywords: MPMs, lymphoma, synchronous cancers, metachronous cancers

Introduction

Multiple primary malignancies (MPMs) are defined as the synchronous or metachronous occurrence of two or more histologically distinct primary malignant tumors in the same patient [1]. The clinical diagnosis of MPMs usually adheres to the criteria proposed by Warren and Gates in 1932, which define synchronous tumors as those with an interval of ≤6 months between diagnoses and metachronous tumors as those with an interval of >6 months [2].

Lymphoma, a prevalent hematological malignancy, is associated with a markedly increased risk of developing second primary malignant tumors compared with the general population [3, 4]. The mechanisms underlying this elevated risk are multifactorial and not yet fully understood. First, lymphoma is often associated with systemic immunodeficiency, leading to compromised immune surveillance [5]. Second, anti-lymphoma treatments - including chemotherapy, radiotherapy, and targeted therapy - may have inherent carcinogenic potential. Furthermore, shared environmental exposures and genetic predispositions may simultaneously contribute to the development of both tumor types [6, 8, 9]. Advances in diagnostic techniques and therapeutic strategies have extended the sur-

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vival of patients with lymphoma. Although the occurrence of lymphoma complicated by solid tumors is rare, it presents complex challenges for clinical management [6]. A recent single-center study in China reported that the prevalence of synchronous solid tumors among 1,726 patients with lymphoma was approximately 2.03% [7].

Despite growing attention to the diagnosis and treatment of MPMs, systematic research specifically addressing lymphoma patients with MPMs remains limited. First, most prior studies are small case series and lack comprehensive analyses regarding the influence of MPM onset timing on prognosis in lymphoma patients [10]. Second, it remains unclear whether synchronous and metachronous MPMs differ in clinical presentation or require distinct management approaches. Similarly, the independent prognostic value of classification based on diagnostic time interval remains inconclusive [11, 12]. Evidence from studies in solid tumors suggests that synchronous malignancies are often associated with poorer outcomes, potentially reflecting more aggressive tumor biology or heightened genetic susceptibility [13]. However, definitive conclusions are lacking in the context of lymphoma with MPMs, and large-scale clinical investigations are still scarce.

This study systematically characterized the clinicopathological features of lymphoma patients with MPMs using a well-defined, single-center retrospective cohort with a relatively large sample size. We specifically compared pathological features, survival outcomes, and prognostic factors between SC and MC groups. The significance and innovation of this study are reflected in three aspects. First, to the best of current knowledge, this study represents one of the largest cohorts to examine prognostic differences between SCs and MCs in lymphoma patients with MPMs, thereby evaluating the prognostic relevance of chronological classification in this population. Second, through multivariate Cox regression analysis, the study aimed to separate the effects of lymphoma-related factors from those associated with second tumors, identifying independent prognostic drivers that are not confounded by chronological classification. Third, the findings are expected to provide evidence to guide clinical decision-making. Specifically, if lymphoma-intrinsic characteristics are the dominant determinants of prognosis, standardized assessment and active treatment of lymphoma should remain a priority, even in the presence of a second primary malignancy. Ultimately, the study seeks to offer more precise clinical evidence for risk stratification, individualized therapy, and long-term follow-up in this high-risk population.

Materials and methods

Case collection

This single-center retrospective cohort study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (Approval No.: 2021KS046). Informed consent was waived for this study in accordance with relevant regulations. A total of 167 patients with concurrent lymphoma and at least one primary solid tumor of a distinct histological type were enrolled. All patients were admitted to the Department of Hematology of our hospital between January 2016 and December 2019.

Diagnostic and classification criteria

The diagnosis and classification of all lymphomas strictly followed the criteria outlined in the 5th edition of the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues (2022) [14]. Pathological typing and staging of concurrent solid tumors were performed based on the corresponding WHO classification criteria for specific organ systems [15-18]. The diagnosis for all patients was based on specimens obtained through surgical resection or biopsy and was confirmed through routine pathological morphological assessment and immunohistochemical staining. The pathological diagnosis of each patient was independently reviewed by at least two senior pathologists to reach a consensus; difficult or ambiguous cases were further reviewed and verified by an external expert.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) the first primary tumor was lymphoma confirmed through histopathology, (b) at least one concurrent tumor was a primary malignant tumor (including other hematological or solid tumors) confirmed through histopathology and distinct in histological type from lymphoma, and (c) all

tumors were confirmed as independent primary lesions, and the possibility of metastasis or recurrence was excluded.

The exclusion criteria were as follows: (a) missing clinical or pathological data and (b) concurrent tumors that were only precancerous lesions or benign tumors.

Data collection and definitions

Variables, including clinical characteristics of patients, treatment regimens, and outcomes, were collected. MPMs were classified as SC (interval ≤6 months) or MC (interval >6 months) according to Warren and Gates' criteria [2].

Efficacy evaluation and follow-up

The treatment response for lymphoma was assessed using imaging based on the Lugano classification criteria [19]. Responses were classified as complete remission (CR) or non-complete remission (NCR) based on the Lugano criteria. The treatment response for solid tumors was assessed based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST, version 2009) [20]. Follow-up was performed by reviewing our hospital's electronic medical records (both outpatient and inpatient records) and by contacting the patients through telephone. The follow-up was concluded on December 31, 2024.

Observation indicators

The primary endpoint of this study was overall survival (OS), defined as the interval from the date of lymphoma diagnosis to all-cause death or the last follow-up [21]. Secondary endpoints included: (1) Baseline clinical characteristics, including age, sex, family history of malignancy, lymphoma aggressiveness, Ann Arbor stage, systemic distribution of solid tumors, diagnostic sequence of MPMs, and patterns of multiple cancers; (2) Comparison of survival outcomes and identification of independent prognostic factors between patients with SCs and MCs; and (3) Analysis of survival differences among subgroups stratified according to MPM patterns.

Statistical analysis

Statistical analysis was performed using the SPSS (version 25.0) and R (version 4.2.1) software. Continuous variables conforming to a normal distribution were expressed as the mean ± standard deviation (SD) and compared using the independent-sample t-test. Variables with a non-normal distribution were expressed as the median and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were expressed as numbers (percentages) and compared between groups using the chi-square test or Fisher's exact test as appropriate. The strength of association was assessed using Cramér's V coefficient. Values less than 0.1 indicate a weak association, 0.1-0.3 a moderate association, and ≥0.3 a strong association. Survival curves were plotted using the Kaplan-Meier (KM) method, and differences between groups were assessed using the log-rank test. Univariate and multivariate Cox proportional hazard regression models were used to identify independent factors influencing patient prognosis. Variables with a *P* value of <0.05 in the univariate analysis were included in the multivariate Cox model to calculate the hazard ratio (HR) and its 95% confidence intervals (CIs). Missing efficacy data (n=20; missing rate 11.9%) were addressed using multiple imputation with five imputations, and results were pooled according to Rubin's rules to account for imputation uncertainty. A *P* value of <0.05 was considered statistically significant.

Results

Comparison of baseline and disease characteristics

Baseline and clinical characteristics were compared between the SC and MC groups. Among the 167 patients included, 46 (27.5%) were classified as SCs, and 121 (72.5%) as MCs. The mean age of the entire cohort was 61.56 ± 12.21 years, with 89 men (53.3%). The two groups did not show significant differences in any baseline characteristics, including age, sex, presence of underlying diseases (hepatitis B, diabetes, and hypertension), history of smoking, family history of cancer, lymphoma aggressiveness (indolent vs aggressive), B symptoms, number of extranodal involvement sites, Ann Arbor stage, type of lymphoma, systemic distribution of solid tumors, diagnostic sequence, and type of multiple cancers (double vs triple) (P>0.05 for all; **Table 1**).

Table 1. Baseline clinical characteristics between the two groups

Variables	Total (*n*=167)	Synchronous malignancies (*n*=46)	Metachronous malignancies (*n*=121)	Statistic	*P*
Age, Mean ± SD	61.557 ± 12.212	61.935 ± 12.382	61.413 ± 12.195	t=0.246	0.806
Sex, n (%)				χ^2=0.266	0.606
Female	78 (46.707)	20 (43.478)	58 (47.934)		
Male	89 (53.293)	26 (56.522)	63 (52.066)		
Hepatitis B, n (%)				χ^2=0.000	1.000
No	155 (92.814)	43 (93.478)	112 (92.562)		
Yes	12 (7.186)	3 (6.522)	9 (7.438)		
Diabetes, n (%)				χ^2=1.378	0.240
No	144 (86.228)	42 (91.304)	102 (84.298)		
Yes	23 (13.772)	4 (8.696)	19 (15.702)		
Hypertension, n (%)				χ^2=1.034	0.309
No	122 (73.054)	31 (67.391)	91 (75.207)		
Yes	45 (26.946)	15 (32.609)	30 (24.793)		
Smoking history, n (%)				χ^2=0.902	0.342
No	118 (70.659)	35 (76.087)	83 (68.595)		
Yes	49 (29.341)	11 (23.913)	38 (31.405)		
Family history of tumors, n (%)				χ^2=1.794	0.180
No	144 (86.228)	37 (80.435)	107 (88.430)		
Yes	23 (13.772)	9 (19.565)	14 (11.570)		
Lymphoma aggressiveness, n (%)				χ^2=1.133	0.287
Indolent lymphoma	54 (32.335)	12 (26.087)	42 (34.711)		
Aggressive lymphoma	113 (67.665)	34 (73.913)	79 (65.289)		
Type of Lymphoma, n (%)				-	0.301
CLL/SLL	21 (12.568)	7 (15.221)	14 (11.569)		
DLBCL	92 (55.093)	25 (54.345)	67 (55.367)		
FL	17 (10.179)	2 (4.350)	15 (12.43)		
HL	6 (3.588)	1 (2.170)	5 (4.130)		
MALT	9 (5.390)	2 (4.351)	7 (5.791)		
MCL	3 (1.801)	0 (0.000)	3 (2.475)		
T cell	19 (11.376)	9 (19.574)	10 (8.255)		
B symptoms, n (%)				χ^2=0.185	0.912
A	92 (55.090)	25 (54.348)	67 (55.372)		
B	66 (39.521)	19 (41.304)	47 (38.843)		
NA	9 (5.389)	2 (4.348)	7 (5.785)		
Number of extranodal involvements, n (%)				-	0.819
0-1	136 (81.437)	37 (80.435)	99 (81.818)		
≥2	29 (17.365)	9 (19.565)	20 (16.529)		
NA	2 (1.198)	0 (0.00)	2 (1.653)		
Efficacy evaluation, n (%)				χ^2=0.069	0.966
CR	81 (48.503)	22 (47.826)	59 (48.760)		
NCR	66 (39.521)	18 (39.130)	48 (39.669)		
NA	20 (11.976)	6 (13.043)	14 (11.570)		
Diagnostic sequence of multiple primary malignant tumors, n (%)				χ^2=2.651	0.266
Non-hematological system tumors as the first primary malignancy	79 (47.305)	26 (56.522)	53 (43.802)		
Hematological system tumors as the first primary malignancy	28 (16.766)	5 (10.870)	23 (19.008)		
Synchronous occurrence of multiple primary malignant tumors	60 (35.928)	15 (32.609)	45 (37.190)		
Efficacy evaluation of non-hematologic tumors, n (%)				χ^2=2.399	0.301
CR	128 (76.647)	39 (84.783)	89 (73.554)		
NCR	24 (14.371)	4 (8.696)	20 (16.529)		
NA	15 (8.982)	3 (6.522)	12 (9.917)		
Type of multiple primary malignant tumors, n (%)				χ^2=0.000	1.000
Double primary cancers	154 (92.216)	42 (91.304)	112 (92.562)		
Triple primary cancers	13 (7.784)	4 (8.696)	9 (7.438)		

Whether multiple primary malignant tumors are in the same system, n (%)				χ^2=0.091 0.763
No	143 (85.629)	40 (86.957)	103 (85.124)	
Yes	24 (14.371)	6 (13.043)	18 (14.876)	
Ann Arbor, n (%)				χ^2=1.260 0.532
I-II	79 (47.305)	20 (43.478)	59 (48.760)	
III-IV	81 (48.503)	25 (54.348)	56 (46.281)	
NA	7 (4.192)	1 (2.174)	6 (4.959)	
Systems involved by multiple primary malignant tumors, n (%)				χ^2=8.621 0.125
Gastrointestinal tract tumors	54 (32.335)	19 (41.304)	35 (28.926)	
Breast cancer	34 (20.359)	8 (17.391)	26 (21.488)	
Reproductive system tumors	10 (5.988)	2 (4.348)	8 (6.612)	
Lung cancer	24 (14.371)	4 (8.696)	20 (16.529)	
Thyroid cancer	22 (13.174)	3 (6.522)	19 (15.702)	
Other system cancers	23 (13.772)	10 (21.739)	13 (10.744)	

t: t-test, Z: Mann-Whitney test, χ^2: Chi-square test, -: Fisher exact, SD: standard deviation, M: Median, CR: complete response, NCR: non-complete response, Q_1: 1st Quartile, Q_3: 3rd Quartile.

Correlation analysis

Correlation analysis using Cramer's V revealed a correlation coefficient of 0.221 between the involved systems of multiple primary malignant tumors and the types of lymphoma, indicating a moderate correlation. Fisher's exact test yielded a *P* value of 0.062, indicating that the correlation was not statistically significant (**Table 2**).

Description of event rates

The 1-, 3-, and 5-year OS rates for the entire cohort were 94.01%, 74.25%, and 72.46%, respectively (**Figure 1**; **Table 3**).

Comparison between groups

Kaplan-Meier analysis revealed no significant survival differences based on MPM pattern, system involvement, pathological type of the second tumor, or age. However, significant differences were observed in survival among patients with the presence of B symptoms and interim treatment response. The log-rank test indicated that all *P* values were <0.05 (**Figure 2**).

Cox regression analysis

To identify independent prognostic risk factors in lymphoma patients with second primary malignancies, univariate Cox regression analysis was first performed. Lymphoma aggressiveness, Ann Arbor stage, B symptoms, and treatment response (CR vs NCR) were statistically significant in the univariate analysis (P<0.05) and were subsequently included in the multivariate Cox model. Results indicated that aggressive lymphoma and NCR in treatment evaluation were significant independent prognostic risk factors (**Table 4**).

Discussion

In this systematic analysis of 167 lymphoma patients with second primary cancers, we characterized the clinical features and prognostic factors of this specific population. Our findings indicate that within the complex context of MPMs, key disease characteristics of lymphoma, such as pathological type, aggressiveness, stage, and treatment response, remain the primary factors driving long-term survival. Conversely, the temporal sequence of second primary tumors is not an independent prognostic factor.

The absence of significant differences in baseline characteristics between the SC and MC groups suggests that disease burden and clinical phenotypes at initial diagnosis may be similar. This finding is partially consistent with that of a study by Jiang et al. [10], suggesting that prognostic assessment for these patients should prioritize the intrinsic biological characteristics of tumors rather than relying solely on the chronological order of the tumors [22].

The observed OS rates indicate that patients with lymphoma complicated by MPMs who receive standardized management at specialized centers can achieve favorable survival outcomes, particularly during the early stages of

Table 2. Correlation analysis between lymphoma pathological types and multiple primary malignancies

		Systems involved by multiple primary malignant tumors					
		Gastrointestinal tract tumors	Breast cancer	Reproductive system tumors	Lung cancer	Thyroid cancer	Other system cancers
Type of lymphoma	CLL/SLL	9	2	0	5	2	3
	DLBCL	28	23	9	13	11	8
	FL	6	5	0	2	2	2
	HL	1	1	0	0	1	3
	MALT	1	2	1	2	3	0
	MCL	1	1	0	0	1	0
	T cell	8	0	0	2	2	7
Fisher test		0.062					
Cramer's V		0.221					

CLL/SLL: Chronic lymphocytic leukemia/small lymphocytic lymphoma, DLBCL: Diffuse large B-cell lymphoma, FL: Follicular lymphoma, HL: Hodgkin lymphoma, MALT: Mucosa-associated lymphoid tissue lymphoma, MCL: Mantle cell lymphoma, T cell: T-cell lymphoma.

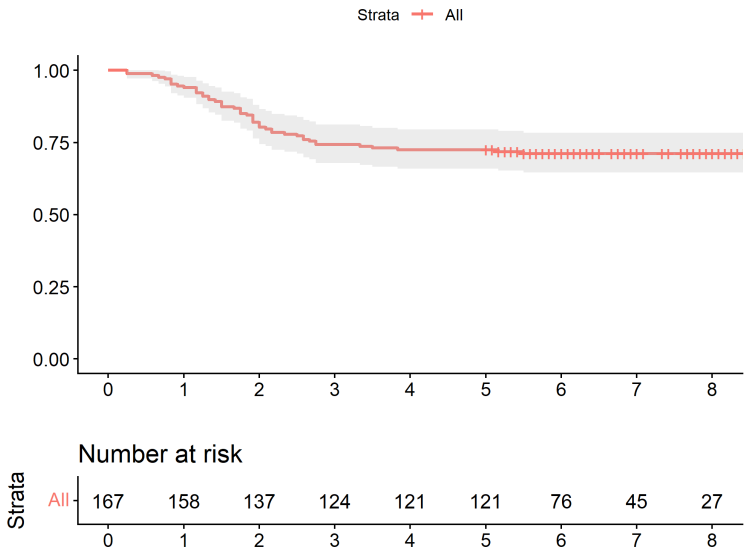

Figure 1. Kaplan-Meier analysis of overall survival (OS) for the enrolled patients.

Table 3. Kaplan-Meier analysis of overall survival (OS) for the enrolled patients

Time	os	95% CI
1 Year	94.01%	90.48%-97.68%
3 Years	74.25%	67.91%-81.19%
5 Years	72.46%	65.99%-79.56%

treatment. However, the plateau phase observed in the survival curve after 3 years suggests that long-term survival continues to face persistent challenges, such as disease recurrence, progression of second tumors, and treatment-related complications [23-25]. Multivariate analysis revealed two robust independent prognostic factors. Aggressive lymphoma and failure to achieve CR at interim evaluation were identified as risk factors for survival. These findings are highly consistent with established classical prognostic models for lymphoma [26, 27]. In univariate Cox regression analysis, Ann Arbor stage and B symptoms were significantly associated with prognosis; however, they lost statistical significance in the multivariate model ($P > 0.05$), suggesting that their prognostic influence is likely mediated by lymphoma aggressiveness and treatment response. To further investigate the impact of lymphoma-related factors on prognosis, pathological subtypes were collected from the 167 enrolled patients. During data preparation, high collinearity was observed between lymphoma pathological subtype and lymphoma aggressiveness. To mitigate the adverse effects of multicollinearity on model stability and parameter estimation, the pathological subtype variable was excluded from the final Cox regression model. Instead, lymphoma aggressiveness was retained as a

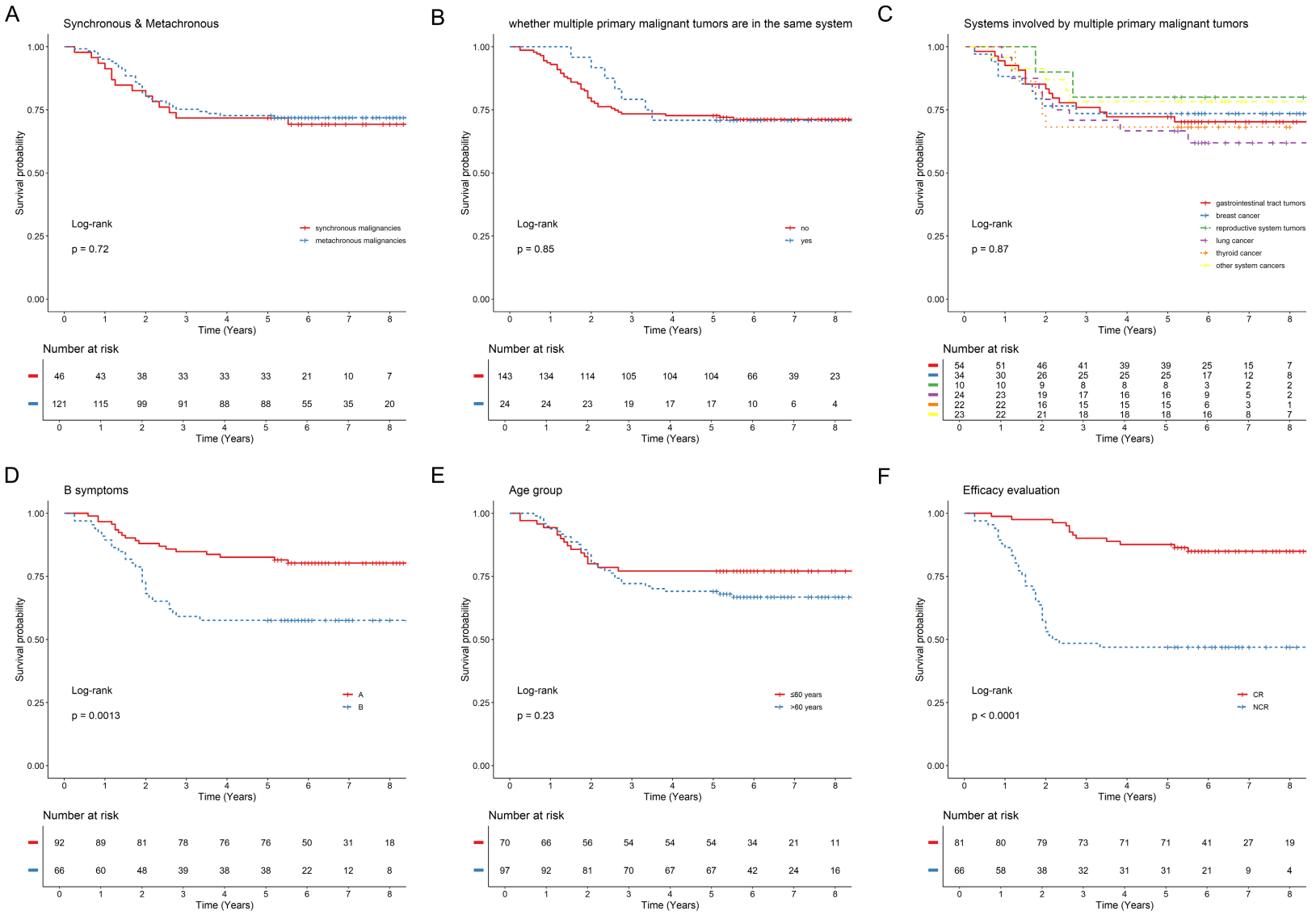

Figure 2. Kaplan-Meier analysis of overall survival (OS) for patients. A. Kaplan-Meier analysis of overall survival (OS) between synchronous malignancies group and metachronous malignancies group. B. Kaplan-Meier analysis of overall survival (OS) between the group of lymphoma and MPMs involved the same system and the group of lymphoma and MPMs involved the different system. C. Kaplan-Meier analysis of overall survival (OS) in the different pathological type of MPMs. D. Kaplan-Meier analysis of overall survival (OS) between the group with A symptom and the group with B symptom. E. Kaplan-Meier analysis of overall survival (OS) between

the patients aged ≤60 years and the patients aged >60 years. F. Kaplan-Meier analysis of overall survival (OS) between complete response (CR) group, defined as a complete response (CR) after four courses of RCHOP therapy, and the non-complete response (NCR) group, defined as failure to achieve a CR after four courses of RCHOP therapy.

Table 4. Univariate and multivariate Cox regression analysis

Variable	Univariable		Multivariable	
	CI	*P* value	CI	*P* value
Sex (Ref=female)	1.049 (0.585-1.881)	0.869		
Age	1.019 (0.994-1.045)	0.128		
Hepatitis B (Ref=No)	0.816 (0.246-2.712)	0.735		
Diabetes (Ref=No)	1.06 (0.465-2.415)	0.888		
Hypertension (Ref=No)	0.766 (0.383-1.529)	0.441		
smoking history (Ref=No)	0.668 (0.334-1.334)	0.246		
Family history of tumors (Ref=No)	1.447 (0.687-3.048)	0.323		
Lymphoma aggressiveness (Ref=indolent lymphoma)	2.337 (1.109-4.925)	0.026	2.618 (1.169-5.863)	0.021
Ann Arbor (Ref=I-II)	2.535 (1.335-4.816)	0.005	1.123 (0.54-2.338)	0.749
B symptoms (Ref=A)	2.684 (1.451-4.966)	0.002	1.483 (0.753-2.92)	0.245
Number of extranodal involvements (Ref=0-1)	1.805 (0.914-3.564)	0.087		
efficacy evaluation (Ref=CR)	5.551 (2.811-10.962)	<0.001	5.793 (2.658-12.625)	<0.001
Efficacy evaluation of non-hematologic tumors (Ref=CR)	1.514 (0.742-3.089)	0.246		
Diagnostic sequence of multiple primary malignant tumors (Ref=non-hematological system tumors as the first primary malignancy)	0.712 (0.281-1.801)	0.464		
Hematological system tumors as the first primary malignancy	1.273 (0.683-2.373)	0.438		
Synchronous occurrence of multiple primary malignant tumors	0.928 (0.4-2.152)	0.858		
Systems involved by multiple primary malignant tumors (Ref=gastrointestinal tract tumors)	0.627 (0.138-2.851)	0.537		
Breast cancer	1.292 (0.557-2.996)	0.543		
Reproductive system tumors	1.121 (0.449-2.799)	0.803		
Lung cancer	0.704 (0.250-1.981)	0.497		
Thyroid cancer	1.423 (0.549-3.686)	0.459		
Other system cancers	0.925 (0.406-2.108)	0.849		
Type of multiple primary malignant tumors (Ref=double primary cancers)	0.894 (0.471-1.694)	0.725		
Whether multiple primary malignant tumors are in the same system (Ref=No)	0.925 (0.406-2.108)	0.849		
Synchronous malignancies_metachronous malignancies (Ref=synchronous malignancies)	0.894 (0.471-1.694)	0.725		

Ref: Reference.

core predictive variable, effectively reflecting differences in tumor biological behavior.

Furthermore, in this cohort, the Hodgkin lymphoma (HL), follicular lymphoma (FL), and Marginal Zone Lymphoma (MZL) subtypes were associated with better survival outcomes compared with CLL/SLL. Although CLL/SLL, FL, and MALT are all classified as indolent lymphomas, patients with CLL/SLL appear to have a higher risk of developing secondary tumors following treatment.

Although this study identified aggressive lymphoma as an independent adverse prognostic factor, the risks associated with indolent lymphoma and second primary tumors also merit close attention. In this study, among the 21 patients with CLL/SLL, 14 (66.7%) presented with metachronous malignancies. Studies have shown that the occurrence of secondary cancers is frequently associated with a poor prognosis and is one of the leading causes of mortality in patients with CLL/SLL [28]. CLL/SLL typically occurs in the elderly population, and the incidence rate of most tumors increases with age [29]. Significant advances have been made in CLL/SLL treatment over the past decade. Consequently, as survival has improved, the incidence of secondary cancers has also increased significantly [30-32]. The patients with CLL/SLL included in this study were predominantly treated with alkylating agents and nucleoside analogs. Whether the introduction of novel agents - such as rituximab, BTK inhibitors, and Bcl-2 inhibitors [33, 34] - will further increase the incidence of secondary malignancies merits further investigation.

Despite these findings, this study has certain limitations. The retrospective design may introduce selection bias and unmeasured confounding factors. Although the sample size is relatively large for this type of study, it limits the depth of analysis for certain subgroups. Furthermore, the classification of SCs and MCs is based on the time of clinical diagnosis, which may not accurately reflect the true biological synchrony of the tumors. With the development of multicenter collaborations and novel treatment regimens, larger sample sizes will be included in future studies, leading to a more comprehensive and refined understanding of lymphoma complicated by MPMs.

Conclusion

In conclusion, this study provides important real-world evidence for understanding the clinical challenge of lymphoma complicated by MPMs. Our findings strongly suggest that the prognosis of lymphoma complicated by MPMs is primarily determined by lymphoma-specific factors, such as subtype, aggressiveness, and treatment response. The presence of a second primary cancer should not detract from the need for standardized assessment and aggressive treatment of the lymphoma. Clinical decision-making should be based on a comprehensive, individualized evaluation of both (or multiple) tumors. Future studies should integrate prospective large-sample cohorts with molecular profiling to elucidate the interaction mechanisms between lymphoma and second primary cancers and explore optimal integrated treatment strategies [1, 35].

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Disclosure of conflict of interest

None.

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