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Research Article

Clinical Features and Survival Outcomes in Primary Intestinal Lymphoma: A Multicenter Retrospective Study

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Abstract

Objectives: Primary intestinal lymphoma (PIL) is a rare, heterogeneous extranodal malignancy, and data on its clinical course and survival in routine practice are scarce. We evaluated the clinical features, treatment patterns, and survival outcomes of patients with PIL in a multicenter cohort.

Methods: This multicenter retrospective study included 68 patients diagnosed with PIL between 2000 and 2013 at five tertiary oncology centers in Türkiye. Clinical, pathological, and treatment-related variables were collected from medical records. Overall survival (OS) and progression-free survival (PFS) were estimated by the Kaplan–Meier method and compared with the log-rank test; hazard ratios (HRs) were estimated with Cox regression limited to two covariates per model because of the small number of events.

Results: The median age was 45 years, and diffuse large B-cell lymphoma was the most common subtype. Most patients presented with early-stage disease. Over a median follow-up of 53 months, estimated 2-year PFS and OS were 61% (95% CI: 44–71%) and 66% (95% CI: 51–78%), respectively, and median OS was not reached. On univariate analysis, advanced stage, poor ECOG performance status, higher IPI score, and lack of treatment response were significantly associated with worse survival. ECOG performance status 3–4 remained associated with inferior OS after adjustment for stage (HR 8.80, 95% CI: 3.12–24.86). Surgery was associated with longer PFS in the log-rank analysis, but not in Cox regression, and no significant OS benefit was observed.

Conclusion: In this multicenter cohort, PIL survival was associated with established clinical risk factors. Because the number of events was small and most analyses were univariate, these findings should be regarded as exploratory real-world observations.

Keywords: Extranodal non-Hodgkin lymphoma, multicenter study, primary intestinal lymphoma, real-world data, survival outcomes

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Hodgkin and non-Hodgkin lymphomas (HL and NHL) are clonal lymphoproliferative disorders with distinct clinical features and account for 8% of malignancies.[1] Like Hodgkin disease, Non-Hodgkin lymphomas also originate in lymphoid tissues and can spread to other organs. However, NHL shows a greater tendency for extranodal spread compared to Hodgkin's disease.[2] While gastrointestinal involvement is common in extranodal NHLs, primary intestinal NHL is rare. Primary intestinal lymphomas account for 15-20% of gastrointestinal NHLs.[3]Although primary intestinal lymphomas are classified as GI lymphomas, they differ from GI NHLs due to their presentation at a younger age, the disease usually being at an advanced stage, their histologically aggressive nature, and the majority being diffuse large B-cell lymphoma (DLBCL).[4] Primary GI lymphomas are important because they differ from other lymphomas and other cancers located in the gastrointestinal tract in terms of evaluation, diagnosis, management, and prognosis.[5,6] Many studies have been conducted to determine the prognostic factors of primary GI lymphomas. However, the number of cases in these studies is quite small, and most have been treated with modalities based primarily on surgery.[7-11] The site of involvement, histological type, immunophenotypic characteristics, and stage are important in terms of treatment approaches. Since Isaacson and Wright introduced the term "mucosa-associated lymphoid tissue (MALT) lymphoma" into the literature in 1983, the diagnosis and treatment of primary gastrointestinal lymphomas have changed considerably over the past twenty years.[12] Due to their rarity, the optimal treatment regimen for primary intestinal lymphomas has not yet been established. Current treatment recommendations are based more on data from case series than on large randomized clinical trials.

Given the rarity and biological heterogeneity of primary intestinal lymphoma, comprehensive real-world data from multicenter settings remain limited, particularly from periods preceding widespread adoption of modern immunochemotherapy protocols. Therefore, the present study aimed to evaluate the clinical characteristics, treatment patterns, and survival outcomes of patients with primary intestinal lymphoma treated in routine practice across multiple tertiary centers in Türkiye.

Materials and Methods

Study Design and Setting

This retrospective, multicenter study included consecutive patients diagnosed with primary intestinal lymphoma between January 2000 and December 2013 at five tertiary oncology centers in Türkiye (İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Ankara Numune Training and Research Hospital, Dicle University Faculty of Medicine, Fırat University Faculty of Medicine, and Trakya University Faculty of Medicine). Patients were identified through medical oncology records and hospital databases. Eligible patients were those with histopathologically confirmed lymphoma involving the intestinal tract as the primary site of disease at diagnosis, without evidence of prior or concurrent systemic nodal lymphoma as the dominant presentation. Baseline demographic and clinical variables collected included age, sex, presenting symptoms, disease localization, histopathological subtype, Ann Arbor stage (Cotswolds modification), Eastern Cooperative Oncology Group (ECOG) performance status, and International Prognostic Index (IPI) score. For survival analyses, ECOG performance status was grouped as 0–2 versus 3–4; Ann Arbor stage as I–II, III and IV; and IPI risk as low (0–1), intermediate (2–3; low-intermediate and high-intermediate), or high (4–5). Laboratory parameters at diagnosis, including serum albumin, lactate dehydrogenase (LDH), and hemoglobin levels, were recorded. Treatment-related variables (surgical intervention, chemotherapy, radiotherapy, and treatment response) and follow-up data were obtained from medical records. Treatment response was assessed at the end of first-line treatment by radiological evaluation according to the standard response criteria in use at each center and was recorded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Patients with CR or PR were classified as responders and those with SD or PD as non-responders. Patients whose response was not evaluable or not documented were excluded from response-based analyses. Because response is determined after treatment has started, it was analyzed as an exploratory post-baseline variable rather than as a baseline prognostic factor. Patients with insufficient baseline clinical data were excluded. Patients without valid dates of diagnosis or last follow-up were retained in the descriptive analyses but were not included in the survival analyses.

Outcomes

The primary outcomes of the study were overall survival (OS) and progression-free survival (PFS). Overall survival (OS) was defined as the time from the date of diagnosis to death from any cause. Progression-free survival (PFS) was defined as the time from diagnosis to documented disease progression, relapse, or death from any cause, whichever occurred first. Patients without an event were censored at the date of last documented follow-up.

Follow-up duration was calculated from the date of diagnosis to the date of last documented contact or death, and the median follow-up was estimated with the Kaplan–Meier method. Survival analyses included patients with valid dates of diagnosis and last follow-up (58 patients for OS and 59 for PFS).

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation or median (range) for continuous variables and as frequencies and percentages for categorical variables. Group comparisons were performed using the chi-square test or Fisher's exact test for categorical variables and the Student's t-test or Mann–Whitney U test for continuous variables, as appropriate.

Survival curves were estimated with the Kaplan–Meier method, with 95% confidence intervals (CIs) calculated by Greenwood's formula, and compared with the log-rank test. Hazard ratios (HRs) with 95% CIs were obtained from Cox regression. Given the limited number of events (18 for OS, 26 for PFS), each Cox model was restricted to two covariates to avoid overfitting: ECOG performance status was adjusted for stage, and other variables were adjusted for IPI risk group (low vs. low-intermediate or higher). Exploratory subgroup analyses compared DLBCL with non-DLBCL histology, R-CHOP with CHOP, and diagnosis before versus from 2007 onward. A two-sided $p<0.05$ was considered statistically significant. Analyses were performed with SPSS version 22.0 and the lifelines package (version 0.30) in Python.

Ethical Approval

This study was approved by the Dr. Lütfi Kırdar Kartal Training and Research Hospital Scientific Research Ethics Committee on October 22, 2013 (Decision No: 6).

Results

A total of 68 patients with primary intestinal lymphoma were included in the study. The median age was 45 years (range: 13–81), and 69.1% (n=47) of the patients were male. At diagnosis, 28% (n=19) of patients had stage I disease, 60.3% (n=41) stage II, 4.4% (n=3) stage III, and 7.4% (n=5) stage IV. Most patients (63.2%, n=43) had an ECOG performance status of 0–1. B symptoms were present in 57.4% (n=39) of patients, and elevated serum LDH levels were observed in 52.9% (n=36). The most common presenting symptom was abdominal pain (52.9%), followed by weight loss (25.0%). The IPI score was low in 54.4% of patients, low-intermediate in 32.4%, high-intermediate in 10.3%, and high in 2.9% (Table 1).

Diagnosis was established by surgical biopsy in 47.1% of patients, endoscopic biopsy in 22.1%, and percutaneous biopsy in 5.9%. The small intestine was the most frequently involved site (29.4%), followed by the duodenum (14.7%), ileum (13.2%), and jejunum (11.8%). Diffuse large B-cell lymphoma (DLBCL) was the most common histopathological subtype (60.3%) (Table 2).

Regarding treatment, 61.8% of patients underwent surgical intervention. Chemotherapy was administered to 86.8% of patients, most commonly CHOP- or R-CHOP-based regimens. Radiotherapy was used in a small subset of patients. Among those receiving chemotherapy, 45.6% completed six cycles (Table 3).

At the time of analysis, 23 patients (33.8%) had died. Among patients included in the survival analyses, 18 deaths and 26

Table 1. Clinical characteristics of patients

		Number (n)	Percentage (%)
Ann Arbor Stage (Cotswold Modification)	Stage I	19	28
	Stage II	41	60.3
	Stage III	3	4.4
	Stage IV	5	7.4
ECOG Performance Status	0	5	7.4
	1	38	55.9
	2	12	17.6
	3	9	13.2
	4	4	5.9
Initial symptom	Abdominal pain	36	52.9
	Weight loss	17	25.0
	Gastrointestinal bleeding	5	7.4
	Diarrhea	4	5.9
	Fatigue	3	4.4
	Fever	3	4.4
B symptom	Yes	39	57.4
	No	29	42.6
Elevated LDH	Yes	36	52.9
	No	32	47.1
>1 Extranodal site	Yes	7	10.3
	No	61	89.7
IPI Score	Low	37	54.4
	Low–Intermediate	22	32.4
	Intermediate-High	7	10.3
	High	2	2.9

ECOG: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; IPI: International Prognostic Index.

Table 2. Distribution of diagnostic methods, disease localization, and pathological subtypes among patients

		Number (n)	Percentage (%)
Diagnostic Method	Surgery	32	47.1
	Endoscopic biopsy	15	22.1
	Percutaneous biopsy	4	5.9
	Unknown	17	25.0
Localization	Small bowel	20	29.4
	Duodenum	10	14.7
	Ileum	9	13.2
	Jejunum	8	11.8
	Colon	6	8.8
	Cecum	5	7.4
	Other	10	14.7
Pathology	DLBCL	41	60.3
	B-cell	7	10.3
	MANTLE	6	8.8
	PTCL	6	8.8
	MALT	4	5.9
	Burkitt	4	5.9

Table 3. Distribution of treatments administered to patients

		Number (n)	Percentage (%)
Surgery	Yes	42	61.8
	No	26	38.2
Type of surgery*	Small bowel resection	17	40.4
	Right hemicolectomy	13	30.9
	Small bowel and colon resection	3	7.1
	Other	3	7.1
	Unknown	6	14.2
Chemotherapy–Radiotherapy	Chemotherapy	56	82.4
	Chemotherapy + Radiotherapy	3	4.4
	Radiotherapy	1	1.5
	No CT/RT	8	11.7
Chemotherapy regimen**	CHOP	28	47.4
	RCHOP	27	45.8
	Others	4	6.8

** Among the 42 patients who underwent surgery. **Among the 59 patients who received chemotherapy.*

PFS events were recorded. The median follow-up was 53 months (95% CI: 18–64; range, 5–157). The median PFS was 50 months (95% CI: 15.8–not reached), and the median OS was not reached. The estimated 2-year PFS and OS rates were 61% (95% CI: 44–71%) and 66% (95% CI: 51–78%), respectively (Fig. 1).

Progression-Free Survival

In univariate survival analyses using the log-rank test, advanced disease stage was significantly associated with inferior PFS; median PFS was 130 months in stage I–II patients, 18 months in stage III, and 4 months in stage IV patients (p=0.02). Poor ECOG performance status (3–4) was

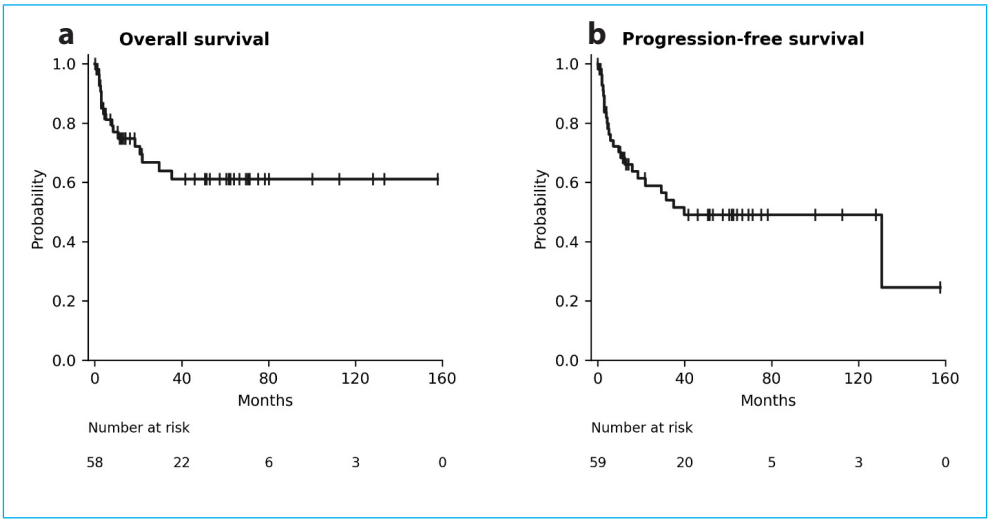

Figure 1. Kaplan–Meier estimates of **(a)** overall survival and **(b)** progression-free survival in patients with primary intestinal lymphoma. Vertical tick marks indicate censored observations; the number of patients at risk is shown below each panel.

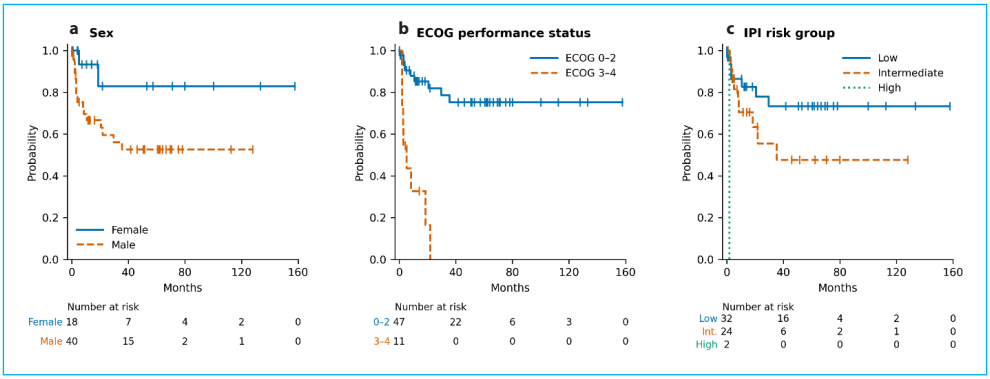

Figure 2. Kaplan–Meier estimates of overall survival by (a) sex (female vs. male; log-rank p=0.034), (b) ECOG performance status (0–2 vs. 3–4; p=0.001), and (c) IPI risk group (low, intermediate, and high; p=0.002). Vertical tick marks indicate censored observations; the number of patients at risk is shown below each panel. ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index.

strongly associated with worse PFS (median 4 months vs. 130 months for ECOG 0–2; p=0.001). Higher IPI scores were significantly associated with shorter PFS (p=0.001). Lack of treatment response was a major determinant of poor outcome, with a median PFS of 5 months in non-responders compared with 130 months in responders (p=0.001). Surgical treatment was associated with longer PFS in the log-rank analysis (p=0.046); however, this association did not reach statistical significance in Cox regression (HR 0.53, 95% CI: 0.24–1.15; p=0.106), and no significant difference in OS was observed.

Age, sex, tumor localization, presence of B symptoms, hemoglobin level, albumin level, and LDH level were not significantly associated with PFS.

Overall Survival

In univariate survival analyses, female sex was associated with better OS compared to male sex (p=0.034). Advanced disease stage was significantly associated with inferior OS; median OS was not reached in stage I–II patients, whereas it was 18 months in stage III and 7 months in stage IV patients (p=0.025). Poor ECOG performance status (3–4) was strongly associated with worse OS compared with ECOG 0–2 (median 4 months vs. not reached for ECOG 0–2; p=0.001). Higher IPI scores were significantly associated with shorter OS (p=0.002). (Fig. 2).

According to the International Prognostic Index (IPI), median OS was not reached in patients with low-risk scores, while it was 35 months and 5 months in patients with intermediate- and high-risk scores, respectively (p=0.002) (Fig. 2).

Lack of treatment response was also significantly associated with inferior OS, with a median OS of 10 months in non-responders, while median OS was not reached in responders (p=0.008). (Fig. 3). No statistically significant associations were observed between OS and age, tumor localization, B symptoms, surgical treatment, hemoglobin level, albumin level, or LDH level.

Cox Regression Analysis

Cox regression results are shown in Table 4. After adjustment for stage, ECOG performance status 3–4 remained associated with inferior OS (HR 8.80, 95% CI: 3.12–24.86; p<0.001) and PFS (HR 3.85, 95% CI: 1.64–9.01; p=0.002), whereas stage lost statistical significance. Non-response remained associated with shorter OS (HR 7.04, 95% CI: 1.65–29.95; p=0.008) and PFS (HR 5.20, 95% CI: 1.77–15.26;

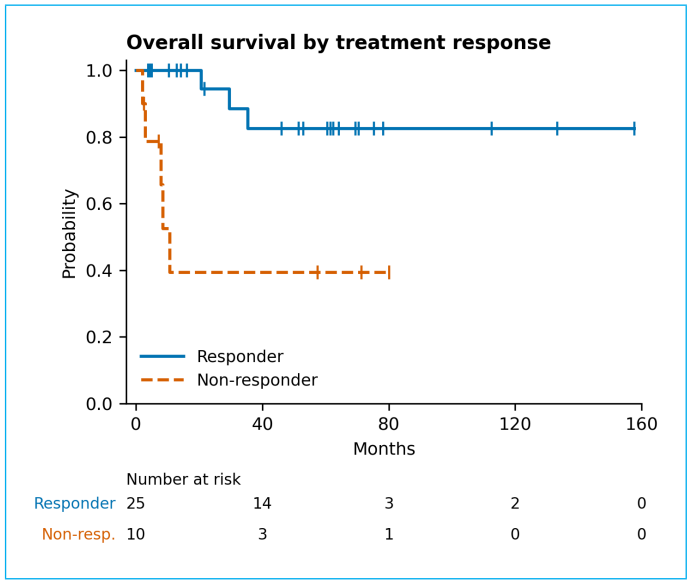

Figure 3. Kaplan–Meier estimates of overall survival according to response to first-line treatment (responders, complete or partial response, vs. non-responders, stable or progressive disease; log-rank p=0.008). Vertical tick marks indicate censored observations; the number of patients at risk is shown below the panel.

Table 4. Cox regression analysis for overall and progression-free survival

Variable	OS, univariable HR (95% CI)	OS, adjusted HR (95% CI)	PFS, univariable HR (95% CI)	PFS, adjusted HR (95% CI)
Female vs. male	0.25 (0.06–1.10) p=0.066	0.27 (0.06–1.18)[a] p=0.081	0.52 (0.20–1.40) p=0.197	0.61 (0.23–1.66)[a] p=0.335
Age >60 vs. ≤60 years	1.26 (0.41–3.85) p=0.682	–	0.84 (0.29–2.45) p=0.746	–
Stage III–IV vs. I–II	3.39 (1.18–9.72) p=0.023	2.47 (0.84–7.26)[b] p=0.101	2.84 (1.12–7.19) p=0.028	2.30 (0.89–5.94)[b] p=0.086
B symptoms, yes vs. no	2.29 (0.82–6.44) p=0.115	2.53 (0.90–7.15)[a] p=0.079	2.03 (0.88–4.66) p=0.097	2.31 (1.00–5.36)[a] p=0.050
ECOG 3–4 vs. 0–2	9.86 (3.54–27.47) p<0.001	8.80 (3.12–24.86)[b] p<0.001	4.26 (1.85–9.83) p<0.001	3.85 (1.64–9.01)[b] p=0.002
Elevated LDH, yes vs. no	0.99 (0.39–2.51) p=0.983	–	1.39 (0.61–3.14) p=0.432	–
IPI ≥low-intermediate vs. low[c]	2.41 (0.93–6.26) p=0.071	–	3.28 (1.40–7.67) p=0.006	–
DLBCL vs. non-DLBCL	0.64 (0.25–1.62) p=0.348	0.62 (0.25–1.57)[a] p=0.317	0.69 (0.32–1.49) p=0.342	0.62 (0.28–1.34)[a] p=0.223
Surgery, yes vs. no	0.72 (0.28–1.86) p=0.501	0.83 (0.32–2.18)[a] p=0.707	0.53 (0.24–1.15) p=0.106	0.61 (0.28–1.32)[a] p=0.208
R-CHOP vs. CHOP[d]	0.37 (0.11–1.20) p=0.099	0.40 (0.12–1.29)[a] p=0.125	0.51 (0.20–1.29) p=0.152	0.58 (0.23–1.48)[a] p=0.252
Diagnosis ≥2007 vs. <2007	0.64 (0.21–1.95) p=0.433	0.65 (0.21–2.00)[a] p=0.457	0.89 (0.37–2.14) p=0.793	0.93 (0.39–2.24)[a] p=0.870
Non-responder vs. responder[e]	7.16 (1.69–30.33) p=0.008	7.04 (1.65–29.95)[a] p=0.008	5.74 (1.97–16.71) p=0.001	5.20 (1.77–15.26)[a] p=0.003

OS analyses included 58 patients (18 deaths) and PFS analyses 59 patients (26 events) unless otherwise indicated. [a] Adjusted for IPI risk group (low vs. low-intermediate or higher). [b] ECOG performance status and stage entered together in the same model. [c] High-risk IPI (n=2) was combined with the intermediate groups because a separate HR could not be estimated. [d] Patients treated with CHOP or R-CHOP (OS: n=43, 13 deaths; PFS: n=44, 19 events). [e] Patients with evaluable response (OS: n=35, 8 deaths; PFS: n=36, 15 events); response is a post-treatment variable. – Not adjusted because age and LDH are IPI components. CI: Confidence interval; DLBCL: Diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; OS: Overall survival; PFS: Progression-free survival.

p=0.003) after adjustment for IPI. Female sex was not significantly associated with OS in Cox regression (HR 0.25, 95% CI: 0.06–1.10; p=0.066).

Exploratory Subgroup Analyses

Survival did not differ significantly between DLBCL and non-DLBCL histology (OS: HR 0.64, 95% CI: 0.25–1.62; p=0.348). Among patients treated with CHOP or R-CHOP (n=43), R-CHOP was associated with a numerically lower risk of death that did not reach statistical significance (2-year OS 81% vs. 55%; HR 0.37, 95% CI: 0.11–1.20; p=0.099). A similar non-significant trend was observed within the DLBCL subgroup (n=28; HR 0.49, 95% CI: 0.11–2.21; p=0.357). Survival did not differ between patients diagnosed before 2007 and from 2007 onward (OS: HR 0.64, 95% CI: 0.21–1.95; p=0.433).

Discussion

In this multicenter retrospective study, we evaluated 68 patients with primary intestinal lymphoma diagnosed between 2000 and 2013 across five tertiary oncology centers. Given the rarity of primary intestinal lymphoma, large prospective datasets are limited, and most available evidence is derived from retrospective series. In this context, our study aimed to characterize the clinical presentation, histopathological distribution, and survival outcomes of this heterogeneous disease entity.

Although gastrointestinal involvement is common in extranodal non-Hodgkin lymphomas[3], primary intestinal NHL represents a relatively rare entity. Compared with other gastrointestinal lymphomas, primary intestinal lymphomas have been reported to present at a younger age, with more aggressive histological subtypes and distinct clinical characteristics.[4] Primary gastrointestinal lymphomas represent a distinct group of malignancies, differing from both other lymphomas and gastrointestinal cancers in terms of diagnostic evaluation, clinical management, and prognostic outcomes. Several studies have attempted

to identify factors influencing prognosis in these tumors. Among these, the anatomical site of involvement, histological subtype, immunophenotypic profile, and disease stage are key determinants of treatment strategy.[5,9] It has also been suggested that primary intestinal lymphoma may be associated with poorer survival compared with gastric lymphoma, although optimal management strategies remain unclear.[11]The clinical presentation of intestinal lymphoma varies according to histological subtype; nevertheless, abdominal pain is consistently reported as the most common presenting symptom.[5,9] According to the World Health Organization (WHO) classification and available epidemiological data, diffuse large B-cell lymphoma represents the most common histological subtype of primary intestinal lymphoma, accounting for approximately 50–70% of cases, followed by mucosa-associated lymphoid tissue (MALT) lymphoma and follicular lymphoma in most reported series.[6,7,12-15]Most studies have demonstrated a male predominance in primary intestinal and gastrointestinal lymphomas. Although sex distribution may vary across histological subtypes, with female predominance reported in certain subtypes such as follicular lymphoma and some T-cell lymphomas.[5–9,13–16] In terms of age distribution, previous studies have reported that the median age of patients with primary gastrointestinal and intestinal lymphomas generally falls within the sixth and seventh decades of life, although this may vary according to geographic region and histological subtype. In several large Western and Japanese series, the reported median age has been in the mid-60s, whereas studies from some Asian countries have described relatively younger patient populations.[5-9,13-16]In our study, the median age was 45 years, indicating a relatively younger patient population compared with many Western cohorts. This difference may reflect regional demographic characteristics, referral patterns to tertiary centers, or potential biological variations across populations. A male predominance was observed, consistent with previously published series. Diffuse large B-cell lymphoma was the most frequent histological subtype in our cohort, in accordance with the distribution reported in the literature. The remaining patients had biologically distinct subtypes, including mantle cell lymphoma, PTCL, MALT lymphoma, and Burkitt lymphoma, whose clinical behavior and treatment differ substantially. Survival did not differ significantly between DLBCL and non-DLBCL cases in our exploratory analysis, but the small size of the non-DLBCL group precluded meaningful subtype-specific comparisons, and pooled estimates should be interpreted with this heterogeneity in mind. Most patients were diagnosed at an early stage (I–II), which may be related to earlier clinical evaluation prompted by symptomatic presentation. Abdominal pain was the most common presenting symptom, consistent with previous reports describing similar clinical patterns in primary intestinal lymphoma.

Several studies have evaluated survival outcomes and prognostic factors in primary intestinal lymphoma. A large population-based SEER analysis including more than 9,000 patients reported a median overall survival of approximately 111 months, with advanced age, higher disease stage, and T-cell histology identified as adverse prognostic factors. Similarly, cohort studies from Thailand and Korea reported 5-year overall survival rates of approximately 64–67%. These studies consistently highlighted the prognostic importance of clinical factors such as performance status, elevated LDH levels, advanced stage, and histological subtype. In addition, progression-free survival data reported in the Korean multicenter CISL study showed a median PFS of 88 months, further supporting the role of disease stage, immunophenotype, and patient-related factors in determining clinical outcomes.[5,6,9,13]In our study, the median progression-free survival was 50 months, while the median overall survival was not reached, with estimated 2-year PFS and OS rates of 61% and 66%, respectively. Consistent with previous reports, disease stage, ECOG performance status, and IPI score were significantly associated with survival outcomes. Patients with early-stage disease (stage I–II) demonstrated markedly longer progression-free survival compared with those with advanced disease, and poor performance status (ECOG 3–4) was strongly associated with inferior PFS and OS. Similarly, higher IPI scores and lack of treatment response were associated with worse survival outcomes. In contrast, age, tumor localization, B symptoms, and laboratory parameters were not significantly associated with survival in our cohort.

In the study by Wang et al.[16], overall survival appeared to be better in female patients; however, the difference did not reach statistical significance. In our study, female sex was associated with improved overall survival in univariate analysis (p=0.034), although median OS was not reached in either group. This association did not reach statistical significance in Cox regression, was based on only two deaths among female patients, and should therefore be interpreted cautiously.

Serum lactate dehydrogenase (LDH) has been reported as an important prognostic marker in primary intestinal lymphoma. Kim et al.[13] demonstrated that elevated LDH levels were independently associated with worse overall survival. Similarly, Tran et al.[8] reported significantly lower 5-year survival rates in patients with high LDH levels compared with those with normal LDH values. In addition, Aronico et al.[9] observed that LDH levels were significantly higher

in intestinal T-cell lymphomas, which are known to have a more aggressive clinical course. In contrast to these findings, serum LDH levels were not significantly associated with progression-free or overall survival in our cohort. This discrepancy may be related to the relatively small sample size and the retrospective design of our study.

Previous studies have evaluated the role of surgical intervention in primary intestinal lymphoma. In a retrospective analysis from India including 27 patients, Khosla et al.[17] reported improved survival outcomes in patients treated with surgery followed by chemotherapy compared with those receiving non-surgical treatment. The authors concluded that combined modality treatment was associated with better long-term survival in selected patients.

In our study, surgery was associated with longer PFS in the log-rank analysis, but this association was not statistically significant in Cox regression or after adjustment for IPI, and no OS benefit was observed. Surgery was not allocated by protocol; it was performed for diagnosis, for complications such as obstruction or perforation, or as elective resection of localized disease. Patients selected for surgery may therefore have had more localized disease or better performance status, and this finding should be regarded as exploratory and hypothesis-generating rather than as evidence of a therapeutic benefit.

Treatment strategies for primary intestinal lymphoma are largely determined by histological subtype and disease stage. Rituximab-containing regimens, particularly R-CHOP, are currently accepted as the standard first-line treatment for diffuse large B-cell lymphoma.[18] Treatment modality has been reported as an important prognostic factor in primary intestinal lymphoma. Rituximab-containing immunochemotherapy has been shown to significantly improve overall survival.[5] Combined treatment with surgery and chemotherapy has been associated with better survival outcomes compared with single-modality approaches.[6,13] In addition, achieving complete response after chemotherapy has been reported as an important determinant of prognosis.[8] In contrast, in selected patients with indolent subtypes such as follicular lymphoma and MALT lymphoma, a watch-and-wait strategy may represent an acceptable management approach.[14]In the present study, the majority of patients received CHOP- or R-CHOP-based chemotherapy. Because the study period spanned from 2000 to 2013, treatment approaches changed over time, and access to rituximab may not have been uniform across centers. In our exploratory analysis, R-CHOP was associated with a numerically lower risk of death than CHOP (2-year OS 81% vs. 55%), but the difference did not reach statistical significance, including within the DLBCL subgroup, and survival did not differ between patients diagnosed before and after 2007. These comparisons were limited by small group sizes and few events, and the absence of a significant difference should not be read as evidence against the benefit of rituximab, which has been established in randomized trials.[18] Treatment era and rituximab use should therefore be considered as potential sources of heterogeneity when interpreting our survival estimates.

Treatment response was strongly associated with survival outcomes. Responders had markedly longer PFS than non-responders (median 130 months vs. 5 months, p=0.001), and non-response remained associated with worse OS and PFS after adjustment for IPI. This observation likely reflects the biological aggressiveness of refractory disease and the impact of treatment effectiveness on long-term disease control. However, treatment response is a post-treatment variable and cannot be used for risk stratification at diagnosis. Patients had to survive long enough to be evaluated, which may introduce guarantee-time bias, and response data were available for only about half of the cohort. This association should therefore be regarded as descriptive rather than as evidence of an independent baseline prognostic factor.

The International Prognostic Index (IPI), which incorporates age, ECOG performance status, serum LDH level, disease stage, and the number of extranodal sites, remains a widely used tool for risk stratification in non-Hodgkin lymphomas.[19] Previous studies have confirmed its prognostic value in primary intestinal lymphoma. Kim et al.[13] demonstrated a strong association between higher IPI scores and worse overall survival, while Tran et al.[8] and Aronico et al.[9] highlighted that key IPI components, particularly elevated LDH levels and poor ECOG performance status, were significantly associated with inferior outcomes. Consistent with these findings, higher IPI scores in our cohort were significantly associated with shorter progression-free and overall survival, with patients in the low-risk group demonstrating substantially better outcomes than those in intermediate- and high-risk categories. In two-variable Cox models, poor ECOG performance status remained associated with inferior OS and PFS after adjustment for stage, whereas stage did not retain statistical significance. Because the limited number of events allowed only two covariates per model, these results cannot establish the independent contribution of each factor and should be confirmed in larger cohorts.

Overall, our findings are consistent with the prognostic importance of established clinical parameters in primary intestinal lymphoma. As most associations were derived from univariate analyses with few events, they should be

viewed as exploratory real-world observations rather than definitive prognostic estimates.

Limitations

The findings of this study should be interpreted within the context of certain methodological considerations. First, the retrospective design reflects real-world clinical practice across multiple institutions; however, treatment allocation, response assessment, and follow-up strategies were not protocol-driven and may have varied between centers. Ten patients lacked valid follow-up dates and were excluded from the survival analyses, and treatment response was not documented for a substantial proportion of patients.

Second, the study period (2000–2013) represents a transitional era in lymphoma management, during which rituximab-containing regimens were gradually incorporated into routine practice. The number of patients treated with CHOP or R-CHOP was too small to reliably assess the effect of rituximab. Consequently, the results provide insight into outcomes during an evolving therapeutic landscape, and direct extrapolation to current treatment paradigms should be undertaken with caution.

Third, the limited sample size and number of events (18 deaths and 26 PFS events) restricted the statistical analysis. Cox models were limited to two covariates, so the independent prognostic value of individual factors could not be definitively established, and subgroup estimates were imprecise. Treatment response, a post-treatment variable, did not fully meet the proportional hazards assumption for OS, and its association with survival may be affected by guarantee-time bias.

Furthermore, the inclusion of multiple histopathological subtypes reflects the biological heterogeneity of primary intestinal lymphoma and may have contributed to variability in clinical outcomes; the non-DLBCL subtypes were too few for subtype-specific analyses. Finally, surgical intervention was not standardized and was likely influenced by clinical presentation, including emergency indications, which may limit direct comparisons between surgical and non-surgical groups.

Conclusion

Primary intestinal lymphoma remains a rare and clinically heterogeneous malignancy with variable outcomes. In this multicenter retrospective study, survival outcomes were significantly associated with established clinical risk parameters, including disease stage, performance status, and IPI score, in univariate analyses; in limited two-variable Cox models, poor performance status remained associated with inferior survival. These findings are consistent with previously reported data and support the continued use of conventional risk stratification approaches in clinical practice.

As treatment strategies evolved during the study period, this analysis provides contextual insight into survival outcomes during a transitional therapeutic era. Given the small number of events, these results should be regarded as exploratory real-world observations. Larger prospective and histology-specific studies are warranted to better define outcome patterns and inform optimal management strategies.

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