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# Clinical features and survival in primary intestinal lymphomas: A multicentre study

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ABSTRACT

*Background:* Primary intestinal B-cell (IBCL) and T-cell (ITCL) lymphomas are rare and poorly characterized entities.
*Aim:* To compare clinical features and survival outcomes of IBCL and ITCL.
*Methods:* We conducted a multicentre, retrospective study including patients diagnosed with primary intestinal lymphoma between 2001 and 2024. Clinical and laboratory variables were analysed using univariate and multivariate logistic regression. Discriminatory accuracy was assessed through ROC analysis. Overall survival was estimated with Kaplan-Meier curves.
*Results:* Ninety-four patients (41 IBCL and 53 ITCL) were included. IBCL were more frequently diagnosed at Lugano stage I (90% vs 5.7%; $p<0.01$) and showed markedly lower lactate dehydrogenase and $\beta$2-microglobulin levels compared with ITCL ($p<0.01$). Coeliac disease (CD) was strongly associated with ITCL ($p<0.01$). In multivariable analysis, CD and biomarker levels independently differentiated IBCL from ITCL, with excellent model discrimination (AUROC 0.95). Median follow-up was 56 months for IBCL and 12 months for ITCL. IBCL demonstrated significantly greater survival (HR 0.21; log-rank $p=0.01$).
*Conclusions:* IBCL and ITCL exhibit distinct clinical and prognostic profiles, with IBCL showing more favourable clinical profile and better survival. Tailored diagnostic and therapeutic approaches that reflect the divergent behaviour of these lymphomas are urgently needed.



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## 1. Introduction

The gastrointestinal tract is the most common extranodal site involved in non-Hodgkin lymphomas. Nonetheless, primary gastrointestinal lymphomas are relatively rare [1,2] and the stomach is the most frequently affected site. Intestinal lymphomas account for only 20%-30% of primary gastrointestinal lymphomas [3], posing distinct diagnostic and therapeutic challenges.

Primary intestinal lymphomas encompass a heterogeneous group of lymphoproliferative disorders, including B-cell and T-cell histotypes, as defined in the 5$^{th}$ edition of the World Health Organization (WHO) classification of hematolymphoid tumours [4] Primary intestinal B-cell lymphomas (IBCL) are more commonly encountered [5], with diffuse large B-cell lymphoma (DLBCL) representing the most frequent subtype, followed by follicular lymphoma, marginal zone lymphoma (MZL), and mantle cell lymphoma (MCL). In contrast, primary intestinal T-cell lymphomas (ITCL) are far less prevalent, representing only 10-15% of primary intestinal lymphomas, yet they consistently show poor outcomes in most published series [6]. ITCL include enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), indolent T-cell lymphoma of the gastrointestinal tract (ITCLGT), and ITCL-not otherwise specified (NOS) [7]. Their strong association with coeliac disease (CD), particularly of EATL with refractory CD, reflects well-defined pathogenic mechanisms involving chronic mucosal inflammation and interleukin-15-driven activation of JAK/STAT and c-MYC pathways that promote clonal T-cell expansion [7]. No comparable association is described for IBCL.

Existing studies often analyse primary intestinal lymphomas collectively or concentrate on specific subtypes, leading to limited direct comparison between IBCL and ITCL [5,7–9]. To address this gap, we conducted a multicentre study directly comparing these biologically divergent entities, aiming to characterize their distinct clinical features, identify differentiating laboratory markers, and evaluate survival differences. Differences among individual B-cell and T-cell lymphoma subtypes were also assessed.

## 2. Methods

### 2.1. Study design and population

This multicentre retrospective study was conducted in seven Italian tertiary referral centres. All consecutive patients diagnosed between 2001 and 2024 with primary B-cell lymphoma and T-cell lymphoma involving the small bowel and/or the colon were screened. Inclusion criteria were: (1) age $\geq$18 years; (2) histologically confirmed primary intestinal lymphoma; and (3) sufficient clinical, laboratory, and imaging data (i.e., CT scan) to apply Dawson's criteria. Patients were excluded in case of non-primary intestinal lymphoma, failure to meet Dawson's criteria, or unavailability of diagnostic material for central pathology review. The clinical circumstances leading to diagnosis (e.g., obstruction, urgent surgery, or incidental detection) were not used as selection criteria, and all patients fulfilling the above diagnostic criteria were included.

The diagnosis was based on Dawson's criteria, including (1) absence of peripheral lymphadenopathy at the time of presentation; (2) lack of enlarged mediastinal lymph nodes; (3) normal total and differential white blood cell count; (4) predominance of bowel lesions at the time of laparotomy with only lymph nodes obviously affected in the immediate vicinity; and (5) no lymphomatous involvement of the liver and spleen [10]. Some patients with primary ITCL included in this study have been previously reported by our group [7,11]

The histopathological lymphoma classification followed the 5$^{th}$ edition of the WHO Classification of Hematolymphoid Tumors [4]. The final diagnosis was confirmed by two experienced hematopathologists (M.L. and M.P.) through a comprehensive review of all diagnostic slides, including H&E and immunohistochemical stains, from each participating centre. Although all cases were jointly reviewed by the two hematopathologists, independent dual scoring was not performed systematically, and therefore a kappa statistic could not be calculated.

Informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The study was approved by the Territorial Ethics Committee Lombardy 6 (CET 6 Lombardy) under protocol No. 20140003980, dated September 22, 2014.

### 2.2. Clinical data

For each patient, clinical data were retrieved, including patient age at diagnosis and sex, and lymphoma features at diagnosis, including site of involvement, presence of multiple lesions, concomitant CD, presence of B symptoms -i.e. fever, night sweats, weight loss, splenomegaly, hepatomegaly-, complications at presentation -namely, perforation, bleeding, occlusion-, and disease staging according to the Lugano classification [12]. Laboratory data at diagnosis included full blood count, lactate dehydrogenase (LDH) – normal cutoff 125-220 U/L-, and $\beta$2-microglobulin ($\beta$2MG) levels - normal cutoff 700-2530 µg/L-. Furthermore, information on first-line chemotherapy regimen administered to each patient was retrieved.

### 2.3. Follow-up

Median follow-up was calculated as the time from initial diagnosis to either last available clinical visit or death. All patients had documented clinical follow-up, and none were lost to follow-up.

### 2.4. Statistical analysis

Statistical analysis was performed using GraphPad Prism v10.3.1 (GraphPad Software, Boston, Massachusetts, USA). Continuous data were summarized as medians and interquartile ranges, while categorical data were presented as counts and percentages. Missing data were excluded from statistical calculations and the proportion of missing data for key variables is reported in Supplementary Table 1.

Univariate analysis was performed using the chi-square test for categorical variables. For continuous variables, the Mann-Whitney test was used when comparing two groups, while the Kruskal-Wallis test was applied for the comparisons involving three or more groups. Normality of distributions was assessed using the Shapiro-Wilk test. Optimal thresholds for LDH and $\beta$2MG were obtained from receiver operating characteristic (ROC) analysis using Youden's Index. Subgroup analyses were exploratory and limited by small sample sizes; therefore, no correction for multiple comparisons was applied.

Multivariate analysis was performed using logistic regression models, with odds ratios reported as the exponential of $\beta$-values. Candidate variables ($p < 0.10$ in univariate analysis) were screened, and the final model was selected based on stability and event-per-variable constraints to minimise overfitting. Model goodness-of-fit was assessed using the Hosmer-Lemeshow test. ROC curves were plotted to evaluate the discriminatory performance of variables that independently differentiated IBCL from ITCL in multivariable logistic regression. Collinearity among LDH and $\beta$2MG was assessed through variance inflation factor (VIF).

**Table 1**
Demographic and clinical features of patients with primary IBCL vs ITCL.

| | IBCL | ITCL | p value |
|---|---|---|---|
| Patients n. (%) | 41/41 (100) | 53/53 (100) | - |
| Age at diagnosis median [IQR] | 61 [50-72] | 57.5 [51-67] | 0.11 |
| M/F (ratio) | 29/12 (2.4:1) | 25/28 (0.89:1) | **0.03** |
| FEATURES AT DIAGNOSIS | | | |
| Site n. (%) | | | |
| Duodenum | 6 (14.6) | 9 (16.9) | 0.06 |
| Jejunum | 12 (29.3) | 17 (32.1) | |
| Ileum | 11 (26.8) | 19 (35.8) | |
| Colon | 16 (39) | 6 (11.3) | |
| Multifocal lesions n. (%) | 6 (14.6) | 13 (24.5) | 0.43 |
| Concomitant coeliac disease n. (%) | 3 (7.3) | 43 (81.1) | **<0.01** |
| B symptoms n.(%) | | | |
| Fever | 9 (21.9) | 14 (26) | **<0.01** |
| Night sweats | 11 (26.8) | 4 (7.5) | |
| Weight loss | 11 (26.8) | 32 (60.4) | |
| Splenomegaly | 8 (19.5) | 3 (5.7) | |
| Hepatomegaly | 4 (9.7) | 5 (9.4) | |
| Complications n. (%) | | | |
| Perforation | 2 (4.9) | 8 (15) | 0.13 |
| Bleeding | 3 (7.3) | 1 (1.9) | |
| Occlusion | 8 (19.5) | 8 (15) | |
| Lugano stage n. (%) | | | |
| I | 37 (90.2) | 3 (5.7) | **<0.01** |
| II | 1 (2.4) | 8 (15) | |
| III | 0 | 7 (13.2) | |
| IV | 2 (4.9) | 16 (30.2) | |
| Blood cell counts median [IQR] | | | |
| Hb g/dL | 11 [9-12.5] | 10.4 [9.3-12.2] | 0.49 |
| WBC x10^3/mmc | 8 [5.1-10] | 7.5 [5.4-10.4] | 0.86 |
| Neutrophils x10^3/mmc | 6.2 [3.8-8] | 5.3 [3.2-9.3] | 0.92 |
| Lymphocytes x10^3/mmc | 1.9 [1.1-3.1] | 1.5 [0.9-2.6] | 0.88 |
| PLT x10^3/mmc | 262.5 [192-396] | 257.5 [180-427] | 0.61 |
| LDH median [IQR] U/L | 176 [125-268] | 290 [230-355] | **<0.01** |
| $\beta$2MG median [IQR] mcg/L | 2300 [1945-3280] | 4470 [3300-5860] | **<0.01** |
| TREATMENT | | | |
| First line chemotherapy | | | |
| (R)-CHOP | 30 (73.2) | 22 (41.5) | **<0.01** |
| CHOEP | 0 | 9 (16.9) | |
| Other | 5 (12.2) | 6 (11.3) | |
| None | 6 (14.6) | 0 | |
| FOLLOW-UP | | | |
| Follow-up time (months) [IQR] | 56 [17-108] | 12 [8-24] | **<0.01** |
| Death n. at follow up (%) | 9 (21.9) | 41 (77.4) | **<0.01** |

Missing data were excluded from statistical calculations. Abbreviations: $\beta$2MG, beta2-microglobulin; CHOEP, cyclophosphamide, hydroxydaunorubicin, oncovin, etoposide, prednisone or prednisolone; F, female; GI, gastrointestinal; Hb, hemoglobin; IBCL, intestinal B-cell lymphoma; IQR, interquartile range; LDH, lactate dehydrogenase; M, male; PLT, platelet; (R)-CHOP, (Rituximab), cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone or prednisolone; WBC, white blood cell.

Kaplan-Meier survival analysis was conducted to estimate overall survival, with statistical significance determined by the log-rank test; hazard ratios and 95% confidence interval were reported. Multivariable Cox regression was not performed due to the limited number of events in several groups.

A p-value <0.05 was considered statistically significant.

## 3. Results

### 3.1. Primary IBCL versus ITCL

#### 3.1.1. Descriptive and univariate analysis

As reported in Table 1, a total of 41 patients with primary IBCL (median age at diagnosis 61 years [IQR 50–72]) and 53 primary ITCL (median age at presentation 57.5 years [IQR 51-67]) were included.

Univariate analysis was conducted to assess the differences between patients with primary IBCL and ITCL (Table 1). A significantly higher prevalence of male patients was observed in the IBCL group (M:F 2.4:1) compared to ITCL (M:F 0.9:1) (p = 0.03). Additionally, a trend towards differential anatomical involvement was noted, with a higher prevalence of IBCL in the colon (39% vs 11%) and ITCL in the ileum (36% vs 27%) (p=0.06). No significant difference was found in the prevalence of multifocal lesions at diagnosis (p=0.43). CD was strongly associated with ITCL, affecting 43 patients (81%); among these, 30 of 43 had a confirmed diagnosis of refractory CD. CD was nearly absent in IBCL (7%) (p<0.01).

Among B symptoms, night sweats and splenomegaly were more frequent in IBCL (27% vs 7.5%, and 19.5% vs 5.7%, respectively), whereas weight loss was significantly more prevalent in ITCL (60% vs 27%) (p<0.01). At diagnosis, ITCL was more aggressive, with a greater proportion presenting with Lugano stage IV disease (30.2% vs 4.9%) while IBCL was more often diagnosed at an earlier Lugano stage I (90% vs 6%) (p < 0.01). No significant difference in complication rates at presentation was observed (p=0.11).

Blood cell counts showed no difference between groups, suggesting that peripheral blood cell abnormalities do not reflect meaningful biological divergence. Nonetheless, significantly higher LDH and $\beta$2MG levels were seen in ITCL patients (p<0.01). Using ROC analysis with Youden's Index, the optimal exploratory thresh-

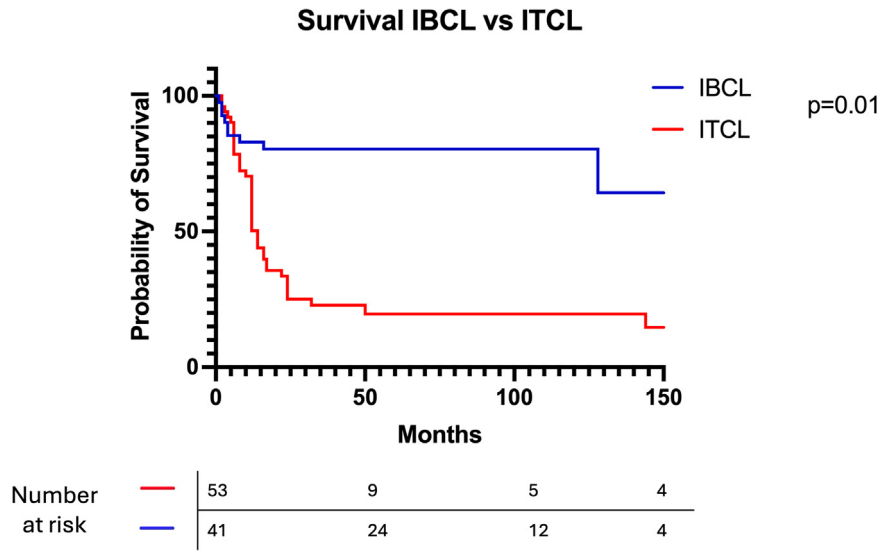


**Fig. 1. Kaplan–Meier survival curves comparing patients with B-cell (IBCL) and T-cell (ITCL) primary intestinal lymphomas.** Patients with IBCL (blue line) demonstrated significantly better overall survival compared to those with ITCL (red line) (HR 0.21; 95%CI, 0.12-0.38; p = 0.01). Median survival was 56 months for IBCL and 12 months for ITCL.

**Table 2**
Multivariate analysis for factors differentiating primary IBCL vs ITCL.

| | Coefficient ($\beta$) | Odds ratio | 95% CI | p |
|---|---|---|---|---|
| Female Sex | -1.38 | 0.25 | 0.03 to 1.49 | 0.15 |
| Coeliac disease | -2.4 | 0.09 | 0.01 to 0.51 | **0.01** |
| B symptoms | -1.3 | 0.27 | 0.02 to 2.08 | 0.23 |
| LDH | -1.1 | 0.34* | 0.11 to 0.83 | 0.03 |
| $\beta$2MG | -0.1 | 0.90* | 0.83 to 0.96 | **< 0.01** |

Dependent variable (outcome) B-cell lymphoma; ITCL used as reference group. *Odd ratios for LDH and $\beta$2MG calculated per 100-unit increase. Hosmer-Lemeshow p=0.94 (good fit). *Abbreviations: $\beta$2MG, beta2-microglobulin; LDH, lactate dehydrogenase*

olds of LDH for distinguishing ITCL from IBCL was 210 U/L, yielding a sensitivity of 96.4% (95% CI - 82.3%-99.8%) and specificity of 69.2% (95% CI – 53.4%-81.4%) (Supplementary Figure 1). The optimal exploratory thresholds for $\beta$2MG was 2733 µg/L, with 100% sensitivity (95% CI 87.9%-100%) and 64.1% specificity (95% CI - 48.4-77.2%) (Supplementary Figure 2).

Regarding therapeutic regimens, the (R)-CHOP [cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone or prednisolone, with or without rituximab] was more frequently administered in IBCL (p<0.01), although data on the initial therapeutic regimen were unavailable for 16 ITCL patients.

Follow-up time was longer for IBCL, with a median follow-up of 56 months [IQR 17-108] compared to 12 months [8–24] in ITCL (p < 0.01). This difference reflects the markedly higher mortality in the ITCL group (77% vs 22%; p<0.01). Consistently, survival analysis confirmed a significantly better survival probability for IBCL (HR 0.21, 95% CI 0.12-0.38; p=0.01; Fig. 1). Median overall survival was 14 months for ITCL, whereas the median was not reached for IBCL since more than half of patients were still alive at last follow-up.

### 3.1.2. Multivariate analysis

In the multivariate analysis, three factors significantly differentiated primary IBCL from ITCL, namely lower association with CD (OR 0.09, 95% CI, 0.01–0.51, p=0.01), lower LDH levels (OR 0.34, 95% CI, 0.11–0.83, p=0.03), and lower $\beta$2MG levels (OR 0.90, 95% CI, 0.83-0.96, p<0.01) (Table 2). The model demonstrated a good fit based on to the Hosmer-Lemeshow test (p=0.94) and excellent discriminatory ability with an AUROC of 0.95 (95% CI, 0.91–1.00, p<0.01; Supplementary Figure 3). LDH and $\beta$2MG showed no collinearity (VIF =1.13).

### 3.2. Primary IBCL histological subtypes

Among the 41 cases of primary IBCL (Supplementary Table 2), the most frequent histological subtype was the DLBCL, accounting for 18 patients (43.9%). This was followed by follicular lymphoma (11 patients, 26.8%), MZL (6 patients, 14.6%), and MCL (3 patients, 7.3%). The remaining 3 cases (7.3%) were diagnosed with rare aggressive entities: plasmablastic lymphoma (n=2) and high-grade B-cell lymphoma NOS (n=1). Representative histological images of duodenal-type follicular lymphoma, the most typical indolent B-cell lymphoma of the small intestine, are shown in Fig. 2A–F.

Although limited by the small sample size, particularly for less common subtypes, no statistically significant differences were observed across IBCL histotypes in terms of clinical presentation, laboratory findings, or Lugano staging (p>0.05 for all comparisons). Notably, the vast majority of patients (90.2%) presented with localized disease (Lugano stage I), which may have influenced overall prognostic comparability.

Despite the lack of statistically significant differences in survival across histotypes (log-rank p=0.34; Supplementary Figure 4), trends in outcomes reflected known biological behaviour. Patients with DLBCL, plasmablastic lymphoma, and high-grade B-cell lymphoma NOS experienced the worst survival probabilities and the highest mortality rates: 27.8% in DLBCL and 66.7% in plasmablastic and high-grade B-cell lymphoma cases.

### 3.3. Primary ITCL histological subtypes

A total of 53 patients with primary ITCL were included, comprising 42 EATL (79.2%), 5 MEITL (9.4%), 3 ITCL-NOS (5.7%) and 3 ITCLGT (5.7%) (Supplementary Table 3). Representative histological

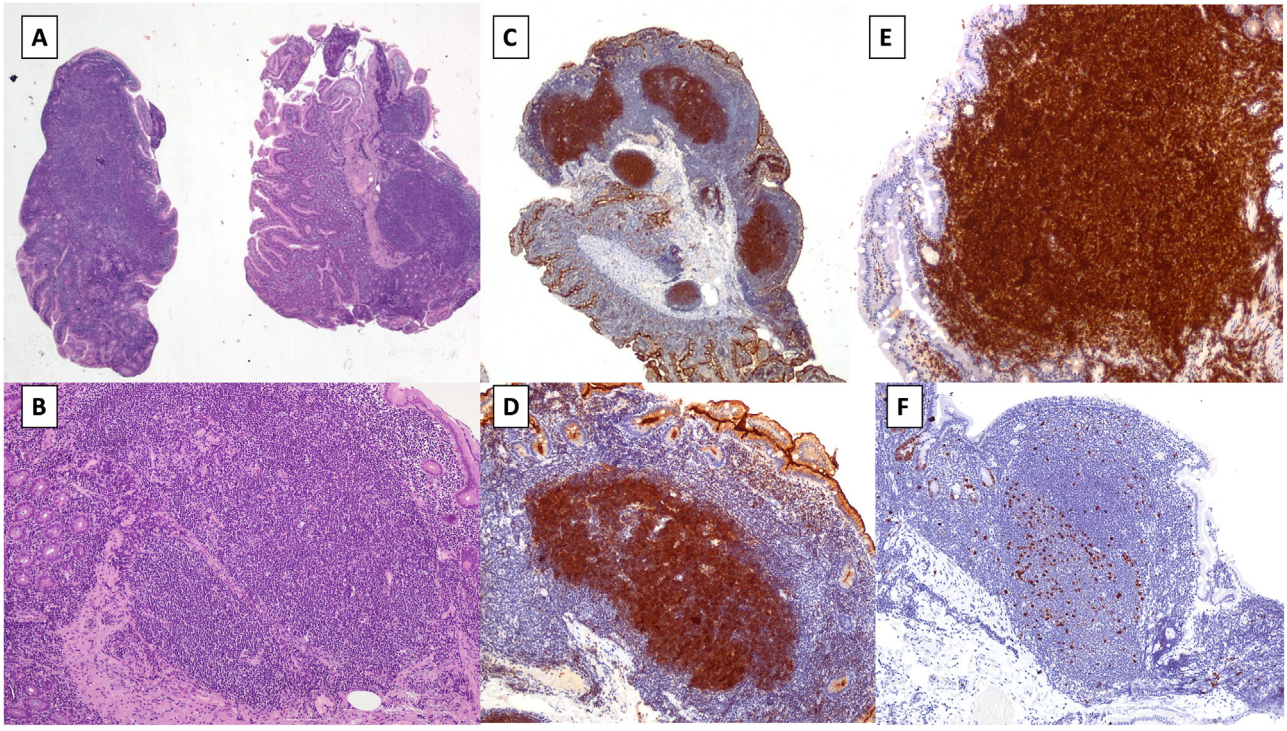


**Fig. 2. Duodenal-type follicular lymphoma representative images.** A) Biopsy samples revealing intense lymphoid infiltrate in the lamina propria, with abnormal follicles (HE, 2X). B) Follicles mainly consist of a monomorphic population of small lymphocytes, with no admixed macrophages (HE, 10X). C) CD10 immunostaining highlights follicular growth pattern (IHC, 2X). D) Strong CD10 expression in follicle centre cells (IHC, 10x). E) Strong BCL-2 expression in neoplastic follicles (IHC 20x). F) Immunostaining for Ki-67 shows low proliferation rate (IHC 10x).

images of EATL, the prototypical T-cell lymphoma of the small intestine, are shown in Fig. 3A–D.

When stratified by histotype, EATL and MEITL predominantly involved the small bowel (35.7% jejunum and 30.9% ileum for EATL and 40% jejunum and 60% ileum for MEITL). ITCL-NOS consistently involved the ileum (100%) and the colon (66.7%), while ITCLGT exclusively involved the duodenum ($p=0.01$). Multifocal lesions were significantly more frequent in ITCL-NOS and ITCLGT ($p<0.01$). As expected, CD was strongly associated with EATL (92.9%) and MEITL (60%) ($p<0.01$). No additional significant differences were observed in clinical, laboratory, therapeutic, or follow-up characteristics. Larger cohorts will be needed to resolve potential phenotypic distinctions.

Survival analysis demonstrated a significant difference in overall survival across subtypes (log-rank $p=0.01$; Supplementary Figure 5). ITCLGT showed the most favourable prognosis, followed by EATL and MEITL, while ITCL-NOS had the poorest outcome.

## 4. Discussion

This multicentre retrospective study offers a comprehensive clinical and prognostic comparison between primary IBCL and ITCL, based on a cohort of 94 patients diagnosed across seven Italian tertiary referral centres. While previous studies have described primary intestinal lymphomas, mainly in single-centre cohorts, our multicentre study directly compared these two biologically distinct entities. It further offers a detailed analysis of differences among histological subtypes within each group. Notably, the ITCL cohort included in this study is the largest reported to date, offering novel insights into the heterogeneity and clinical behaviour of these rare and aggressive neoplasms. Although primary IBCL is more frequent than ITCL [2], the higher representation of ITCL in our cohort likely reflects a selection bias inherent to the retrospective, referral-based nature of the study. As such, no conclusions can be drawn regarding the relative prevalence or incidence of these lymphoma subtypes.

Our findings showed that IBCL is associated with significantly better overall survival, whereas ITCL is more frequently linked to CD and elevated levels of LDH and $\beta$2MG. Although differences in anatomical site involvement between IBCL and ITCL did not reach statistical significance, the observed trend toward colonic involvement in IBCL and ileal involvement in ITCL is consistent with previously reported biological patterns.

Additionally, no significant differences in clinical features and survival were observed among IBCL subtypes. In contrast, ITCL subtypes showed distinct anatomical distributions, multifocal involvement, association with CD, and divergent prognoses.

Previous studies have consistently shown better outcomes for intestinal B-cell lymphomas compared to T-cell lymphoma [3,9], as confirmed by our comparison analysis. Kaplan–Meier survival curves demonstrated significantly lower survival probabilities for T-cell lymphomas, with B-cell lymphomas showing better overall survival and fewer deaths. Although numerically higher complication rates were observed in ITCL, the absence of statistical significance may reflect limited statistical power for infrequent events rather than true similarity between groups. These differences reflect both the distinct biological behaviours of these neoplasms and differences in stage at diagnosis. Indeed, T-cell lymphomas are more aggressive at presentation and, in our cohort, most ITCL cases in our cohort presented at an advanced stage (stage IV), while the majority of B-cell lymphomas diagnosed at an early stage (stage I), contributing to the observed survival disparity. This stage imbalance may reflect challenges in early recognition of ITCL, where nonspecific symptoms and overlap with refractory CD may delay diagnostic workup. By contrast, IBCL lesions may produce localised findings that prompt early diagnosis.

Associated with that, treatment options also play a critical role. While chemotherapy is the main choices for both neoplasms [13–

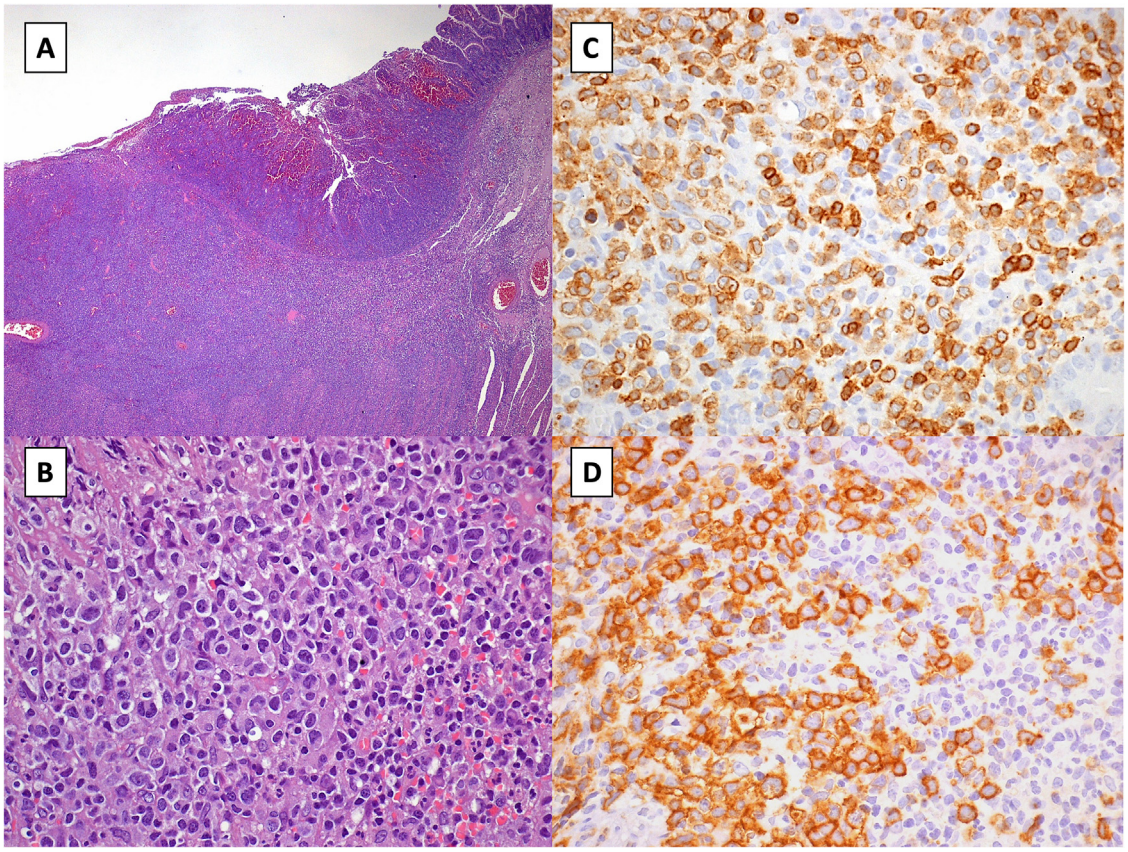


**Fig. 3. EATL representative histological images.** A) Lymphoma infiltrate involving the whole ileal wall, with mucosal ulceration (HE2,5x). B) Lymphoma infiltrate consists of pleomorphic large cells (HE 20X). C) CD3 immunostaining shows intense positivity on lymphoma cells (40X). D) CD30 expression may be documented in most cases (40x).

15], B-cell lymphomas are typically more amenable to prompt initiation of therapy [16]. In our cohort, 73% of B-cell lymphoma patients received (R)-CHOP, while this regimen was applicable to only a minority of ITCL patients. This evidence highlights the need for early diagnosis and timely intervention in this population. The development of novel targeted therapies remains a critical priority, particularly for ITCL, where current treatment options are limited [17,18]

Surprisingly, when stratified by subtype, no significant survival differences were observed among B-cell lymphomas. This contrasts with existing literature, which suggests that aggressive subtypes, such as DLBCL and plasmablastic lymphoma, typically have worse outcomes than indolent forms, like follicular lymphoma or MZL [3]. Nonetheless, it is worth noting that in our cohort aggressive subtypes (DLBCL, plasmablastic lymphoma, and high-grade B-cell lymphoma NOS) still exhibited lower survival probabilities and higher mortality rates. The absence of statistical significance likely reflects insufficient power to detect modest inter-group differences rather than true clinical equivalence across distinct disease entities. Moreover, the predominance of early-stage disease at diagnosis may have potentially attenuated differences in long-term outcomes. Conversely, among T-cell lymphomas, our findings aligned with existing literature and previous data from our centre [7]. We confirmed that ITCLGT is associated with the most favourable prognosis, while ITCL-NOS continues to represent the subtype with the poorest outcomes. These differences reflect distinct immunophenotypic and molecular features. ITCLGT reflects antigen-driven, gluten-dependent lymphoproliferation with a less cytotoxic phenotype; EATL and MEITL are characterized by cytotoxic T-cell biology with EATL often arising in inflammatory CD30-positive settings and MEITL displaying $\gamma\delta$ T-cell signatures with SETD2 pathway alterations; whereas ITCL-NOS encompasses heterogeneous cytotoxic and molecularly undefined lymphomas, consistent with its poorer prognosis [19,20]

Our study showed an almost exclusive correlation between T-cell lymphoma and CD, especially for EATL, aligning with previous results and established physiopathology of this neoplasm [21]. Notably, we have also reported additional evidence supporting a potential association between CD and MEITL, a link that has been rarely described [23]. While B-cell lymphomagenesis is primarily driven by genetic events, such as immunoglobulin gene translocations, and is often associated with infections [22], T-cell lymphomas arise through distinct pathogenic pathways. In particular, ITCL frequently harbour mutations in the JAK/STAT signalling pathway and c-MYC regulatory circuits [7,23]. These pathways are activated mainly via interleukin-15 in patients with refractory CD, contributing to uncontrolled T-cell proliferation and lymphomagenesis [24–27] In our cohort, most ITCL patients exhibited refractory CD, diagnosed through the evidence of aberrant intraepithelial lymphocytes and clonal T-cell receptor gamma chain rearrangements.

No differences in peripheral blood cell counts were observed between IBCL and ITCL, suggesting that routine haematological parameters may have limited value in distinguishing these entities at presentation. Intriguingly, two routine blood tests, namely LDH and $\beta$2MG, demonstrated discriminatory ability, with significantly higher levels observed in ITCL. Although these biomarkers may reflect the greater biological aggressiveness, systemic inflammatory activity, and proliferative kinetics of ITCL, their elevation may also partly result from a more advanced disease stage or higher tumour burden at presentation. LDH is already incorporated into the International Prognostic Index for lymphomas, and $\beta$2MG has been consistently identified in prior studies as a strong independent prognostic marker in malignant lymphomas [28]. Furthermore, our previous work confirmed that elevated $\beta$2MG levels were associ-

ated with refractoriness to a gluten-free diet and could predict progression to overt lymphoma [29]. Although LDH and $\beta$2MG are not novel biomarkers, their established utility and availability make them valuable tools in clinical decision-making. However, given the retrospective nature of our study and the absence of external validation, these findings should be regarded as exploratory and require validation in larger prospective cohorts. The development of novel diagnostic and prognostic indices remains an unmet clinical need.

This study has some limitations. First, referral bias may have affected the composition of our cohort, as tertiary centres are more likely to receive complex or severe cases, potentially limiting the generalisability of these findings. Missing clinical information restricts the interpretability of statistical analyses and may introduce residual confounding. For instance, chemotherapy information was unavailable for 16 ITCL patients, which limits the interpretation of survival analyses and may contribute to residual confounding. The retrospective design further contributes to potential case-selection and documentation biases. The long study period may also introduce heterogeneity in diagnostic criteria, imaging modalities, pathological classification, and treatment strategies, even though patients were analysed according to current classifications. Systematic assessment of treatment response and adverse events was not feasible and these data could not be reliably analysed. Furthermore, molecular and immunophenotypic profiling was not uniformly available across the cohort, limiting mechanistic interpretation and preventing integration of genomic data into subtype comparisons. The sample size for certain rare subtypes was very limited, which may reduce the statistical reliability of subgroup comparisons. These analyses should therefore be considered exploratory. Finally, multivariable Cox regression was not feasible since the number of events within several groups was insufficient to support a stable adjusted model.

Looking ahead, prospective multicentre studies with larger cohorts are needed to validate and further develop our findings. Nonetheless, the clinical patterns emerging from this study may already inform diagnostic and therapeutic pathways [30]. For example, the consistent association between ITCL and CD underscores the need for structured surveillance of refractory CD, including routine assessment of LDH and $\beta$2MG and appropriate imaging, which could support earlier recognition of malignant transformation. In the diagnostic setting, integrating immunophenotypic and – where available - molecular profiling into standard histopathological workflows would allow more reliable differentiation of lymphoma subtypes, enabling more precise prognostication. Therapeutically, our data reinforce the importance of timely diagnosis and rapid treatment initiation in ITCL, in contrast to IBCL where early-stage presentation and response rates are more favourable. Standardised treatment algorithms—particularly for ITCL—could facilitate more uniform clinical management and permit clearer comparative assessment of outcomes across centres.

## Authors' contributions

conceptualization: NA, GS, ADS; investigation: NA, GS, ML, MVL, PIB, DB, AV, GN, CC, FZ, UV, LE, SM, RER; data curation: NA, GS; formal analysis: GS; writing – original draft: NA, GS; writing – review and editing: GS, MVL, ADS; supervision: ML, MVL, AV, GRC, LA, MP, ADS.

## Ethic statement

Approval of the research protocol by Territorial Ethics Committee Lombardy 6 (CET 6 Lombardy); Protocol No. 20140003980, dated September 22, 2014.

## Informed consent statement

Informed consent was obtained from all subjects involved in the study.

## Financial support

None to report.

## Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

## Disclosures

nothing to disclose.

## Declaration of competing interest

The authors declare that they have no conflicts of interest relevant to this manuscript.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.12.029.

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