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Primary Gastrointestinal Lymphoma: A Prospective Unicentric Study on a Romanian Cohort

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ABSTRACT

Background & Aims: Lymphomas of the gastrointestinal tract represent a rare pathology, frequently associated with a poor outcome. This study aimed to determine the prognostic factors of digestive tract lymphomas and to evaluate the role of endoscopy in the diagnosis and outcome.
Methods: Our prospective study evaluated a number of 63 patients diagnosed with digestive tract lymphomas.
Results: The mean age of the patients was 62 years ± 13.1 years. Most of the patients had B-cell lymphoma (88.8%). Localization was represented by the stomach (44.4%), followed by the small bowel (25.4%) and the oropharynx (14.2%). Diffuse large B-cell lymphoma was the most common subtype (52.3%), followed by Mantle cell lymphoma (15.8%) and MALT (14.2%). T-cell lymphoma was present in a small number of patients. Anaplastic large cell lymphoma was the most common subtype of T-cell lymphoma (6.35%) and was localized in the small bowel. One-quarter of the patients had complications such as bleeding, obstruction, or perforation. Chemotherapy alone (38.1%) was the most common treatment option, followed by surgery (28.5%). Endoscopic examination and sampling biopsy were performed on 74.6% of the patients included in the study, with a positive diagnosis for lymphoma in 58.7% of the cases. Age (p=0.208), higher ECOG values (p=0.0487), and level of albumin (p=0.0355) were independent prognostic factors for overall survival. Endoscopic monitoring impacted overall survival (p<0.0001), due to the early detection of relapse.
Conclusions: Age, high ECOG value, and low albumin levels are independent prognostic factors for overall survival. Early diagnosis of recurrent gastrointestinal tract lymphomas by endoscopy increases overall survival.

Key words: gastrointestinal lymphoma – B-cell lymphoma – T-cell lymphoma – survival –digestive endoscopy.

Abbreviations: ALCL: anaplastic large cell lymphoma; AITL: angioimmunoblastic T-cell lymphoma; BL: Burkitt lymphoma; DLBCL: diffuse large B cell lymphoma; EATL: enteropathy-associated T-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FL: follicular lymphoma; HI/H: high intermediate/high; IPI: International Prognostic Index; IPSID: immunoproliferative small intestinal disease; L/LI: low/low intermediate; LDH: lactate dehydrogenase; MALT: mucosa-associated-lymphoid tissue; MCL: Mantle cell lymphoma; NBI: narrow banding imaging; NHL: non-Hodgkin's lymphomas; Nk-T - NK-/T-cell lymphoma; PGIL: primary gastrointestinal lymphoma; WHO: World Human Organization.

INTRODUCTION

Extranodal non-Hodgkin's lymphomas (NHL) are located in approximately 40% of cases in the digestive tract. They usually affect the stomach (65%), the small intestine (20-30%), and less often the colon (10-20%) [1-4]. The ability to recognize lymphomatous lesions during endoscopic procedures and to obtain targeted biopsies has significantly improved the management, treatment and prognosis of the disease [4-8].

The type and subtype of B and T-cell lymphomas vary depending on the affected site. Only 6% of primary gastrointestinal lymphomas (PGIL) are of T-cell origin [2-4, 8-11]. Meanwhile, diffuse large B-cell lymphoma (DLBCL) is the most common subtype (30%) [2, 11-13]. Lymphomas located in the oropharynx represent 11% of all NHL cases, and patients typically present with symptoms such as dysphagia [12-14].

The etiology and pathogenesis of gastrointestinal lymphomatous lesions remain unclear, but several factors have been associated with their development, including

radiation, immunosuppressive agents, autoimmune diseases, dysbiosis (*Helicobacter pylo*ri infection), unhealthy lifestyle, or environmental pollution [1, 6, 15-17].

Diagnosis is based on the World Human Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissue, updated in 2016 [4]. The Dawson criteria are used for diagnosis and include: (a) the presence of lymphomatous lesions limited to the wall of the digestive tube, without lymphadenopathies in the drainage area and invasion in adjacent organs; (b) normal white blood cell count; (b) the absence of peripheral lymphadenopathies; (c) the absence of mediastinal lymphadenopathies; (d) spleen and liver without lymphomatous infiltration [1, 4, 6, 9, 18].

This study aimed to assess the prevalence of gastrointestinal lymphomas in the Romanian population and identify specific prognostic factors for digestive tract lymphomas in a tertiary center. Additionally, the study sought to evaluate the role of the gastroenterologist and digestive endoscopy in the early diagnosis and detection of relapse in gastrointestinal, particularly given the challenges posed by undefined endoscopic aspects.

METHODS

The study was prospective, observational, and unicentric and included patients admitted to the Departments of Hematology, Internal Medicine 3, and General Surgery at the Bucharest Emergency University Hospital. Patients were enrolled and followed between February 2015 and July 2018.

The study protocol was approved by the local Ethics Committee of Bucharest Emergency University Hospital and conducted according to the Declaration of Helsinki with Protocol No. 5221/02.02.2015.

The diagnosis of PGIL was defined as the presence of any lesion at any level of the gastrointestinal tract (from the oral cavity to the anus) with histological features of lymphoma, as categorized by the WHO 2016 classification. Staging was performed based on the Ann Arbor classification [13, 17, 19-22]. Patients included in the study were admitted on an emergency or outpatient basis.

Inclusion criteria were (1) the age over 18 years, (2) the histological and immunohistochemical confirmation of lymphoma, and (3) the signed informed consent. The exclusion criteria were represented by extranodal involvement other than the digestive tract.

The data analyzed included demographic information, clinical features of digestive tract lymphomas, symptomatology B or complications, the histological subtype, disease staging, performance status, biological samples, and the International Prognostic Index (IPI). Additionally, data from endoscopic examinations, histological and immunohistochemical tests, and bone marrow biopsies were also collected.

Histological remission, according to GELA criteria, required endoscopic biopsy follow-up.

Endoscopic examinations were performed using Olympus EVIS EXERA III equipment, including a GIF-HQ190 gastroscope with dual-focus optics and narrow-banding imaging (NBI) and a CF-HQ190L/I colonoscope with dual-focus optics and NBI.

The statistical analysis included descriptive statistics (frequency, percentage) and elements of inferential statistics. The Chi-square test was applied to determine the association between qualitative variables. To investigate the effect of several variables on the time required for a specified event, we applied univariable and multivariable Cox regression for survival analysis and used Kaplan-Meier curves to estimate survival. The significance threshold chosen for the p-value was 0.05. Statistical analysis was performed using SPSS software trial version 29.0 (SPSS, Chicago, IL, USA).

RESULTS

The characteristics of the study group (63 patients) are shown in Table I. Most of the patients had B-cell lymphoma (88.89%) compared to those with T-cell lymphoma (7 patients) (Fig. 1). The mean age of the patients was 62 ± 13.1 years (table 1), and 66.67% (42 patients) were over 60 years. Older people (97.62%) had B-cell lymphoma. Meanwhile, T-cell lymphoma (6 patients) was present in younger people (p=0.014). Regarding the histologic subtype, DLBCL was the most common (52.38%), followed by Mantle cell lymphoma (MCL) (15.87%) and mucosa-associated-lymphoid tissue (MALT) (14.29%) (Fig. 2). Anaplastic large cell lymphoma (ALCL) was the most common subtype of T-cell lymphoma (6.35%) (Fig 3). In our study, the stomach was the most frequent site of lymphoma (44.44%), followed by the small bowel (25.4%) and the oropharynx (14.29%). A small number of patients had involvement of multiple sites (4.76%) (Fig. 2). Females represent the majority (52.38%) of patients, and most of them were older than 60 years (66.67%) (Table I). At the diagnosis, all patients had Eastern Cooperative Oncology Group (ECOG) evaluation, and most had a good performance status (92.06%). This parameter strongly correlated with the site of lymphoma in the disease evolution (p=0.0177) (Table I). Patients had high levels of lactate dehydrogenase (LDH) (76.19%) and low levels of albumin (74.60%). One-quarter of the patients had complications such as bleeding, obstruction, or perforation. Regarding Ann Arbor staging, most patients were diagnosed in the III or IV stage (66.67%). Also, most had gastric localization (64.29%) (Table I). Most of the patients had high intermediate and high IPI scores (65.08%). Patients with lymphoma localized in the oropharynx, stomach, small bowel, and colon had a high IPI score (Table I).

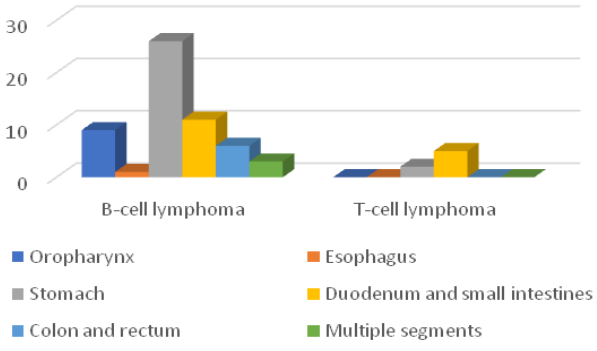

Fig. 1. Site-specific distribution of lymphoma histological types.

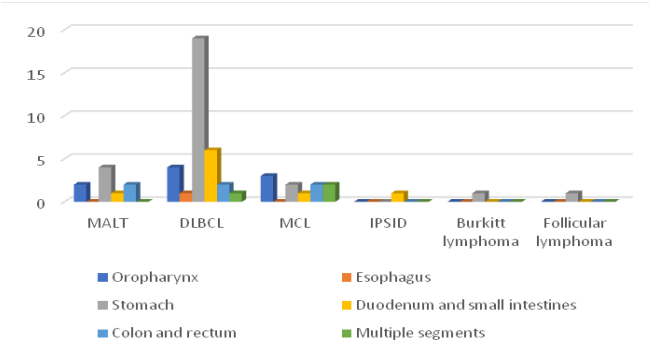

Fig. 2. Distribution of B-cell lymphoma subtypes based on localization.

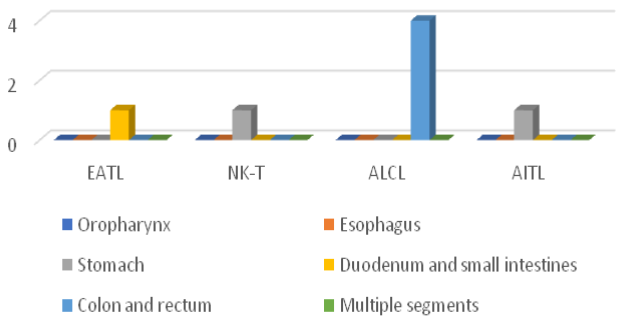

Fig. 3. Distribution of T-cell lymphoma subtypes based on localization.

Table I. Baseline patient characteristics

	Total (n=63)	Oropharinx (n=9)	Esophagus (n=1)	Stomach (n=28)	Small Bowel (n=16)	Colon and rectum (n=6)	Multiple sites (n=3)	p
Gender, n (%)								0.3973
Female	33 (52.38)	3 (33.33)	1(100)	18(64.29)	8 (50)	2 (33.33)	1 (33.33)	
Male	30 (47.62)	6 (66.67)	0 (0)	10 (35.71)	8 (50)	4 (66.67)	2 (66.67)	
Age, n (%)								0.6079
<60 years	21 (33.33)	3 (33.33)	0 (0)	10 (35.71)	7 (43.75)	1 (16.67)	0 (0.00)	
≥60 years	42 (66.67)	6 (66.67)	1 (100)	18 (64.29)	9 (56.25)	5 (83.33)	3(100.00)	
ECOG, n (%)								**0.0177**
<2	58 (92.06)	8 (88.89)	0 (0.00)	27 (96.43)	14(87.5)	6 (100)	3(100.00)	
≥2	5 (7.94	1 (11.11)	1 (100)	1 (3.57)	2 (12.5)	0 (0)	0 (0.00)	
LDH (UI/L) n (%)								0.1977
Normal	15(23.81)	1(11.11)	0 (0.00)	9 (32.14)	3 (18.75)	0 (0)	2 (66.67)	
Elevated	48(76.19)	8 (88.89)	1 (100)	19 (67.86)	13(81.25)	6 (100)	1 (33.33)	
Albumin (g/dl), n (%)								0.2684
Normal	16(25.4)	4 (44.44)	0 (0.00)	7 (25)	2 (12.5)	1 (16.67)	2 (66.67)	
Low	47(74.6)	5 (55.56)	1 (100)	21 (75)	14(87.5)	5 (83.33)	1 (33.33)	
Ann Arbor stage, n (%)								0.7227
I-II	21 (33.33)	3 (33.33)	1 (100)	10 (35.71)	5 (31.25)	1 (16.67)	1 (33.33)	
III-IV	42 (66.67)	6 (66.67)	0 (0)	18 (64.29)	11 (68.75)	5 (83.33)	2 (66.67)	
IPI score, , n (%)								0.3755
L / LI (0-2)	22 (34.92)	2 (22.22)	0 (0)	13 (46.43)	6 (37.5)	1 (16.67)	0 (0)	
HI / H (3-5)	41 (65.08)	7 (77.78)	1 (100)	15 (53.57)	10(62.5)	5 (83.33)	3(100)	
Hemoglobin, n (%)								0.3299
≤10 g/dL	32 (50.79)	2 (22.22)	1 (100)	14 (50)	10(62.5)	4 (66.67)	1 (33.33)	
>10 g/dL	31 (49.21)	7 (77.78)	0 (0)	14 (50)	6 (37.5)	2 (33.33)	2 (66.67)	
Complications, n (%)								0.3449
Absent	38 (60.32)	7 (77.78)	1 (100)	18 (64.29)	6 (37.5)	4 (66.67)	2 (66.67)	
Present	25 (39.68)	2 (22.22)	0 (0)	10 (35.71)	10(62.5)	2 (33.33)	1 (33.33)	
Histology type, n (%)								0.0944
B-cell	56 (88.89)	9 (100.00)	1 (100)	26 (92.86)	11(68.75)	6 (100)	3(100)	
T-cell	7 (11.11)	0 (0.00)	0 (0)	2 (7.14)	5 (31.25)	0 (0)	0 (0)	
Histology subtype, n (%)								
MALT	9 (14.29)	2 (22.22)	0 (0)	4 (14.29)	1 (6.25)	2 (33.33)	0 (0)	
DLBCL	33 (52.38)	4 (44.44)	1 (100)	19 (67.86)	6 (37.50)	2 (33.33)	1 (33.33)	
MCL	10 (15.87)	3 (33.33)	0 (0)	2 (7.14)	1 (6.25)	2 (33.33)	2 (66.67)	
IPSID	1 (1.59)	0 (0.00)	0 (0)	0 (0)	1 (6.25)	0 (0)	0 (0)	
BL	1 (1.59)	0 (0.00)	0 (0)	1 (3.57)	0 (0)	0 (0)	0 (0)	
FL	2 (3.17)	0 (0.00)	0 (0)	0 (0)	2 (12.5)	0 (0)	0 (0)	
EATL	1 (1.59)	0 (0.00)	0 (0)	0 (0)	1 (6.25)	0 (0)	0 (0)	
NK-T	1 (1.59)	0 (0.00)	0 (0)	1 (3.57)	0 (0)	0 (0)	0 (0)	
ALCL	4 (6.35)	0 (0.00)	0 (0)	0 (0.00)	4 (25)	0 (0)	0 (0)	
AITL	1 (1.59)	0 (0.00)	0 (0)	1 (3.57)	0 (0)	0 (0)	0 (0)	

Table I (continued)

Treatment options, n (%)							0.1083
Chemotherapy alone	24 (38.1)	7 (77.78)	1 (100)	7 (25%)	5 (31.25)	3 (50)	1 (33.33)
Chemotherapy and surgery	18 (28.57)	1 (11.11)	0 (0)	7 (25%)	8 (50.00)	1 (16.67)	1 (33.33)
Other	21 (33.33)	1 (11.11)	0 (0)	14 (50%)	3 (18.75)	2 (33.33)	1 (33.33)

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; IPI score: International Prognostic Index; L/LI: low/low intermediate; HI/H: high intermediate/high; MALT: mucosa-associated-lymphoid tissue; DLBCL: diffuse large B cell lymphoma; MCL: Mantle cell lymphoma; IPSID: immunoproliferative small intestinal disease; BL: Burkitt lymphoma; FL: follicular lymphoma; EATL: enteropathy-associated T-cell lymphoma; Nk-T: NK-/T-cell lymphoma; ALCL: anaplastic large cell lymphoma; AITL: angioimmunoblastic T-cell lymphoma.

Regarding treatment, chemotherapy alone (38.10%) was the most common treatment option, followed by surgery (28.57%). Other treatment options included surgery alone, a combination of chemotherapy with surgery and radiotherapy, or chemotherapy with *Helicobacter pylori* eradication ± radiotherapy or surgery.

The follow-up period was defined as the time from diagnosis until death or at the end of the study. The average follow-up period from the diagnosis was 19 months.

Endoscopic examination and sampling biopsy were performed on 74.6% of the patients included in the study, with a positive diagnosis for lymphoma in 58.73% of the cases. Endoscopic features varied, the most frequent being the ulceration pattern (35.14%), followed by the exophytic and the mixed patterns (Fig. 4).

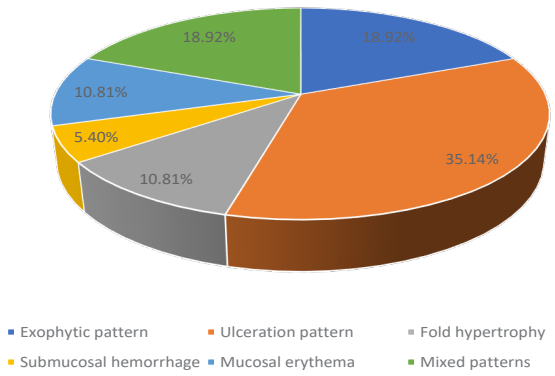

Fig. 4. Endoscopic patterns of the study group.

Univariate statistical analysis revealed that survival of the patients was influenced by age over 60 years (p=0.0208) and higher ECOG values (≥2) (p=0.04) (Table II). Biologic parameters such as LDH, hemoglobin, or albumin level were not strongly associated with survival (Table II).

Multivariate analysis revealed that older patients (≥60 years) had a higher mortality (p=0.208) and males had an increased risk for lower survival rate compared to females (HR=1.512; 95%CI: 0.658-3.475) but without statistical significance (p=0.3306). Reduced time of survival was associated with high values of ECOG ≥2 (p=0.0487) and low levels of albumin (p=0.0355) (Table II).

The study group had a median overall survival time of 28.739 months (95%CI: 28.739–34.072). Patients with B-cell lymphoma had a median survival time of 28.870 months (95%CI: 23.266–34.474). Meanwhile, those with T-cell lymphoma had a longer median survival time of 42.429 months (95%CI: 9.813–39.044) (Fig. 5). Among the B-cell lymphoma subtypes, the longest mean survival time was observed in Burkitt lymphoma (33 months), followed by MALT lymphoma (23 months) and MCL (22 months). In contrast, patients diagnosed with DLBCL, and follicular lymphoma had the lowest mean survival time at 12 months (Fig 6). Regarding T-cell lymphoma subtypes, the longest median survival time was observed in NK-T lymphoma (44 months), followed by EATL and T-helper lymphoma (12 months). Despite most patients with T-cell lymphoma being diagnosed with anaplastic lymphoma, this group had the shortest median survival time, at 3.5 months, with a maximum survival time of 24 months (Fig. 7).

Also, we observed in our study group that those with endoscopy and those without relapse had a higher mean value

Table II. Univariate and multivariate of overall survival

Variable	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
Age (≥60 years vs. <60 years)	2.834	1.076-7.461	0.0349	4.003	1.234-12.981	0.0208
Gender (male vs. female)	1.316	0.640-2.706	0.4553	1.512	0.658-3.475	0.3306
ECOG PS (≥2 vs. <2)	5.384	1.930-15.023	0.0013	3.061	1.006-9.308	0.0487
LDH (elevated vs. normal)	2.165	0.816-5.744	0.1208	1.615	0.539-4.842	0.3922
Hemoglobin (≤10 g/dL vs. >10 g/dL)	0.950	0.461-1.954	0.8882	1.526	0.598-3.895	0.3771
Albumin (low vs normal)	2.295	0.876-6.017	0.0910	3.186	1.081-9.387	0.0355
Complication (present vs. absent)	0.669	0.313-1.432	0.3010	0.598	0.216-1.660	0.3238
Histology type (T-cell vs B-cell)	1.109	0.335-3.674	0.8652	2.114	0.491-9.115	0.3151
Treatment (chemotherapy and surgery vs chemotherapy alone vs. other)	0.745	0.473-1.173	0.2035	-	-	-
Treatment (chemotherapy alone vs. other)	1.182	0.564-2.479	0.6574	0.672	0.225-2.007	0.4765
Relapse	1.008	0.970-1.048	0.6765	1.032	0.975-1.092	0.2783

for survival (44.06 months). In comparison, those without endoscopy and relapse had the lowest value (7.45 months) (Fig 8). There is a statistically significant difference between the survival distribution (p<0.0001).

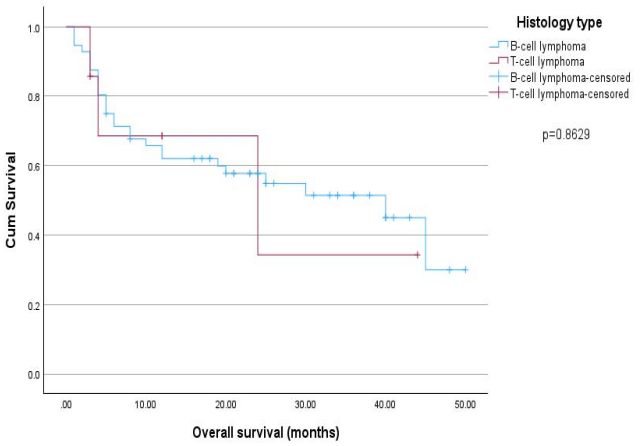

Fig. 5. Overall survival according to lymphoma histological classification.

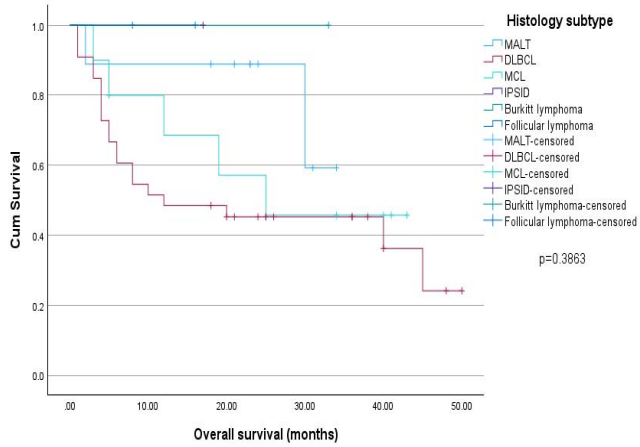

Fig. 6. Survival outcomes based on B-cell lymphoma subtypes.

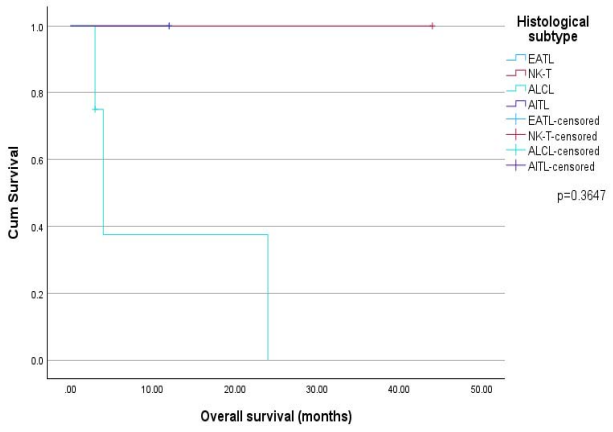

Fig. 7. Survival outcomes based on T-cell lymphoma subtypes.

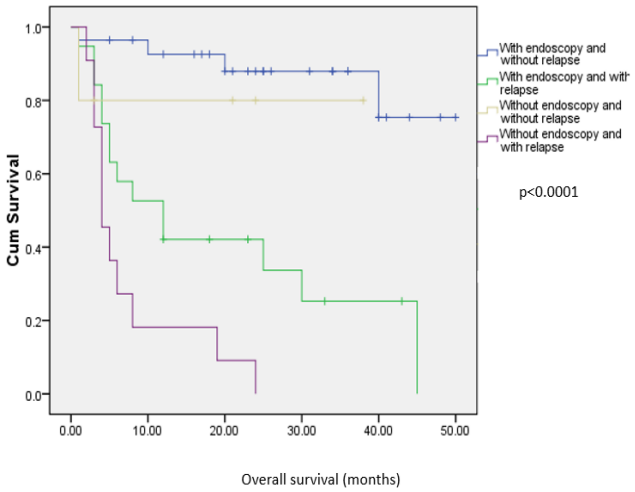

Fig. 8. Overall survival for patients with and without endoscopy and relapse.

DISCUSSION

This study aimed to identify prognostic factors for PGIL in a Romanian cohort. In Romania, we did not have data regarding the prevalence of PGI. We have data from clinical cases published in the literature.

In our study group, most of the patients were diagnosed with B-cell lymphomas, data that are similar to those from the literature [10]. B-cell lymphomas usually affect older people compared to T-cell lymphomas that are present in younger people [10].

The distribution of B-cell lymphoma localizations in our study group mirrored that of existing literature; the stomach was the most common site (46.42%), followed by the small bowel (19.64%) [2-4, 8, 10]. Regarding the subtype, DLBCL was the most frequent subtype of lymphomas (52.38%), followed by MCL (15.88%) and MALT (14.29%). According to literature data, DLBCL represents the most common primary gastric lymphoma, which is also confirmed in our study. This lymphoma subtype usually develops from MALT lymphoma associated with *Helicobacter pylor*i infection [23]. Our study also revealed a limited presence of gastric MALT lymphoma. This subtype was also present in the oropharynx and colon (2 cases each).

Mantle cell lymphoma is rare, but in our study, it represents the third most common subtype, B-cell lymphoma. Regarding distribution on the digestive tract, the most common site was the oropharynx (3 patients), followed by gastric and colon. In two cases, we had multiple sites involved, as it was recorded in the literature was recorded [24].

Gastric Burkitt lymphoma is a rare, aggressive tumor with a poor prognosis [25]. In our study, one case was included. Another finding in our study was follicular lymphoma; we included two cases with small bowel involvement. This type of lymphoma rarely occurs in the gastrointestinal tract but more often affects the duodenum and the ampulla of Vater [26, 27]. Immunoproliferative small intestinal disease (IPSID) was

also present in our study. This type of lymphoma is a variant of B-cell lymphoma of MALT related to *Campylobacter jej*uni infection and is common in Africa and Southeast Asia [28, 29]. In our case, we could not identify the presence of infection with *Campylobacter jejuni* [12, 30-32].

For T-cell lymphomas, the most frequent localization was the small bowel (5 patients), followed by gastric localization (2 patients), which aligns with findings from the literature [10, 33].

Anaplastic large cell lymphoma was the most common subtype of T-cell lymphoma (6.35%) (Fig 3). This is a rare type of lymphoma and usually involves the small bowel, which was also recorded in our study.

Each type of lymphoma behaves differently in terms of its clinical and endoscopic manifestations, therapeutic management, evolution and prognosis. Each variant has unique characteristics that require personalized attention and treatment, which is crucial. Comprehensive evaluation and analysis of each type of lymphoma is indispensable to ensure accurate diagnoses and effective treatment strategies to optimize patient outcomes and improve their long-term prognosis. In the last years different prognostic factors for every type of lymphoma were cited. Univariate statistical analysis in our study identified age and ECOG as prognostic factors. Meanwhile, multivariate analysis revealed that age, ECOG, and low albumin levels are independent prognostic factors for overall survival. Low albumin levels were associated with lymphoma localization in the small bowel, a region crucial for nutrient absorption. In the literature, albumin has been cited as a prognostic factor for patients diagnosed with DLBCL [34, 35].

Digestive endoscopy plays a key role in the early diagnosis of this condition, enabling rapid initiation of specific treatment and better outcomes. Furthermore, endoscopic follow-up of these patients is essential for early relapse detection, reducing the time to specific therapy initiation, and ultimately enhancing survival [36]. Endoscopic examination contributed to the diagnosis of more than 50% of patients enrolled in our study.

Given the non-specific endoscopic appearance, which can mimic a variety of diseases, there is an increasing need for a multidisciplinary team, including a dedicated gastroenterologist, who can accurately diagnose and monitor patients with PGIL [33, 36].

Endoscopy is also crucial for managing complications, such as digestive hemorrhage or strictures. Furthermore, it plays a key role in tumor resection through techniques such as endoscopic mucosal resection (EMR) or endoscopic mucosal dissection (ESD). These methods help reduce the need for surgery and its associated complications, ultimately contributing to improved survival [33, 37].

However, our study had several limitations. It was a single-center study with a relatively short duration and a small sample size, so we could not identify etiologic factors. During the study period, our unit lacked advanced endoscopic techniques such as endoscopic ultrasound, double-balloon endoscopy, or capsule endoscopy, which could have enhanced early diagnosis and relapse detection. Future randomized, prospective, multicentric studies involving larger patient cohorts are required to explore potential etiologies and prognostic factors in our country. Moreover, obtaining such data would provide valuable insights for establishing optimal management strategies for patients diagnosed with primary gastrointestinal lymphomas.

CONCLUSIONS

Independent prognostic factors, including age, ECOG, and albumin levels, significantly influence the outcomes of patients diagnosed with primary gastrointestinal lymphomas. Endoscopic examination plays a crucial role in the early diagnosis and detection of disease recurrence, thereby contributing to improved overall survival.

Conflicts of interest: None to declare.

Authors' contribution: P.V.F. conceived the study. P.V.F and A.M.V. designed the methodology. All the authors contributed to the management of the patients. P.V.F and A.T collected the data. D.C analyzed the data. P.V.F and N.T drafted the manuscript. A.T. revised the manuscript. C.S.P and L.S.D. supervised the study. All authors have read and agreed with the published version of the manuscript.

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