

<https://doi.org/10.52645/MJHS.2026.1.03>

UDC: 616.33/.34-006.441-07-08



RESEARCH ARTICLE



Contemporary insights into diagnosis and treatment of gastrointestinal non-Hodgkin lymphomas

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ABSTRACT

Introduction. The gastrointestinal tract (GIT) is the most common site of extranodal primary non-Hodgkin lymphoma (NHL), accounting for 20% to 40% of all extranodal lymphomas. The advanced stages at diagnosis and complications remain significant issues in NHL management, imposing a substantial disease burden on patients and healthcare systems.

Material and methods. We performed a descriptive cross-sectional and cohort study of patients with gastrointestinal NHL and a narrative review of the literature in the Discussion section. This study included 50 prospective and retrospective patients with NHL treated between 2015-2024 in the Institute of Oncology in Moldova. A bibliographic search was conducted using databases such as *PubMed*, *Hinari*, *SpringerLink*, *the National Center for Biotechnology Information*, and *Medline*. The final bibliography included 18 relevant sources deemed to be representative of the literature published on the topic of this article.

Results. According to the International Clinical Classification, most patients (22, 44.0%) were diagnosed with clinical stage IV. B symptoms occurred in 38 (76.0%) patients. The overwhelming predominance of diffuse large B-cell lymphomas (46 cases - 90.2%) was observed. The complete blood count, bone marrow aspiration and biopsy of the iliac crest did not detect any specific changes in cases without bone marrow involvement, with the exception of a decrease in hemoglobin and erythrocyte counts observed in cases of posthemorrhagic anemia. The overall survival (OS) of all patients with gastrointestinal NHL was 78.1% at 1 year, 59.4% at 3 years, and 35.9% at 5 years. In patients with stage IE NHL, the 1-, 3-, and ≥5-year OS was 93.4%, 76.5%, and 69.9%, respectively. In patients with stage IIE, the OS was 91.2% at 1 year, 71.4% at 3 years, and 63.8% at ≥5 years. In patients with stage IIIE-IV, the OS was 75.1% at 1 year, 54.8% at 3 years, and 28.5% at ≥5 years with combined chemotherapy.

Conclusions. Our study demonstrated that non-Hodgkin lymphomas with primary involvement of the gastrointestinal tract exhibited distinct histopathological, clinical-evolutionary and hematological features, which influenced treatment outcomes. The aggressive histological types and the advanced stages IIIE and IV prevailed within the structure of non-Hodgkin lymphomas with primary gastrointestinal involvement, and, thus, negatively impacted the survival and prognosis.

Keywords: non-Hodgkin lymphomas, gastrointestinal tract, aggressive histological types, chemotherapy, survival.

Cite this article: Musteata L, Robu M, Musteata V, Urescu D, Cebanu I, Capanji A. Contemporary insights into diagnosis and treatment of gastrointestinal non-Hodgkin lymphomas. *Mold J Health Sci.* 2026;13(1):10-15. <https://doi.org/10.52645/MJHS.2026.1.03>.

Manuscript received: 06.08.2025

Accepted for publication: 25.01.2026

Published: 15.03.2026

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Despite the continuous improvement in outcomes for patients with non-Hodgkin lymphomas due to the increasing availability of efficient treatment options, advanced stages at diagnosis and complications remain significant issues, imposing a substantial disease burden on patients and healthcare systems. Therefore, the early diagnosis and prevention of these complications are of utmost im-

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portance for the successful management of non-Hodgkin lymphomas.

The research hypothesis

The original research and synthesis of contemporary literature will reveal a clear association among clinico-evolutionary and hematological features, histological types of non-Hodgkin lymphomas and treatment outcomes. The updated diagnostic patterns and treatment outcomes in gastrointestinal non-Hodgkin lymphomas will help to improve the management approaches.

The novelty added by the manuscript to the already published scientific literature

This article provides the updated results of a prospective study and a synthesis of recent international publications concerning the diagnostic insights and treatment approaches in gastrointestinal non-Hodgkin lymphomas. The study's findings will contribute to the improvement of diagnosis management and therapeutic options in patients with non-Hodgkin lymphomas.

Introduction

The gastrointestinal tract is the most common site of extranodal primary non-Hodgkin lymphomas, accounting for 20% to 40% of all extranodal lymphomas [1, 2]. Advanced stages at diagnosis and complications remain significant issues in non-Hodgkin lymphomas management, imposing a substantial disease burden on patients and healthcare systems. The majority of these are generalized processes secondarily involving the gastrointestinal tract. Primary gastrointestinal lymphomas are less common, accounting for approximately 10% to 15% of all non-Hodgkin lymphomas [3-5]. Most non-Hodgkin lymphomas involving the gastrointestinal tract are of B-cell lineage, of which diffuse large B-cell lymphoma is the most common type, irrespective of location [2, 6-9].

The few studies and publications on primary non-Hodgkin lymphomas affecting the gastrointestinal tract in Moldova have led to the writing of this manuscript.

Material and methods

We performed a descriptive cross-sectional and cohort study of patients with gastrointestinal non-Hodgkin lymphomas and a narrative review of the literature in the Discussion section. This study included 50 prospective and retrospective patients with non-Hodgkin lymphomas treated between 2015-2024 in the Institute of Oncology in Moldova. The diagnosis of non-Hodgkin lymphoma was confirmed by morphopathological and immunohistochemical examinations of the post-biopsy material. The type of lymphomas was classified according to the 2022 Revision of WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. Staging at diagnosis was performed according to the Ann Arbor staging system and Lugano Classification. The study included both ambulatory and hospitalized patients.

The participant inclusion criteria comprised: age over 18 years, confirmation of a non-Hodgkin lymphoma diagnosis by bone marrow examinations, histological and immunohistochemical investigations of the post-biopsy speci-

mens, patient's consent and adherence to participate in the study and the possibility of dynamic monitoring.

The exclusion criteria were as follows: patients aged <18 years, patients diagnosed with chronic lymphocytic leukemia, only cytological confirmation of diagnosis, the absence of patient's consent and adherence to participate in the study.

Descriptive statistics were used: qualitative data were presented as numbers and percentages, and quantitative data were presented as means. Overall survival was calculated according to the Kaplan-Meier estimate.

A bibliographic search was conducted using databases such as *PubMed*, *Hinari*, *SpringerLink*, *the National Center for Biotechnology Information*, and *Medline*. Articles published between 2000 and 2025 were selected using the following keywords: "non-Hodgkin lymphoma" in combination with terms such as "histologic types", "gastrointestinal", "chemotherapy" and "surgical treatment" in order to maximize search yield. Based on the established search criteria, a total of 90 full-text articles were identified. The final bibliography (References) included 20 relevant sources deemed to be representative of the literature published on the topic of this article.

The research project was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Minutes №. 3 from 17.06.2022).

Results

The clinical course, complications and treatment outcomes of non-Hodgkin lymphoma with primary involvement of the gastrointestinal tract were studied in 50 patients aged 19-78 years (mean age 57.3 years), who were treated under the supervision of hematologists during the period 1998-2023. The distribution of patients by age and sex is presented in Table 1. There were 20 males (40.0%) and 30 females (60.0%).

The diagnosis of non-Hodgkin lymphoma with primary involvement of the gastrointestinal tract was more frequent-

ly established in patients aged 50-69 (64%) years (mean age 57.3 years). The average duration from the onset of the first clinical manifestations to the confirmation of the diagnosis of non-Hodgkin lymphoma ranged from 3 to 14 months. In most patients (33 cases,66.0%) the diagnosis of the disease was established within the first 6 months. In 9 (18.0%) patients, the diagnosis of non-Hodgkin lymphoma was confirmed only after 1 year. The distribution of patients according to the duration of the disease from the first clinical signs to the establishment of the diagnosis is presented in Table 2.

Table 1. Distribution of patients with gastrointestinal non-Hodgkin lymphomas according to the age and sex

Age groups, years	Number of patients, abs. (%)	Sex	
		Males, abs. (%)	females, abs. (%)
20-39	5 (10.0)	3 (15.0)	2 (6.7)
40-49	8 (16.0)	4 (20.0)	4 (13.3)
50-59	18 (36.0)	7 (20.0)	11 (36.7)
60-69	14 (28.0)	4 (30.0)	10 (33.3)
70-79	5 (10.0)	2 (10.0)	3 (10.0)
Total:	50 (100.0)	20 (40.0)	30 (60.0)

Note: Descriptive statistics were used: qualitative data were presented as numbers and percentages, and quantitative data were presented as means.

Table 3. Distribution of patients with gastrointestinal non-Hodgkin lymphomas according to the stage of the disease

Primary site location	Number of patients, abs. (%)	Number of patients, abs. (%)			
		Stage IE	Stage IIE	Stage IIIIE	Stage IV
Stomach	40 (80.0)	10 (25.0)	13 (32.5)	2 (5.0)	15 (37.5)
Small intestine	6 (12.0)	2 (33.3)	-	-	4 (66.7)
Large intestine	4 (8.0)	-	1 (25.0)	-	3 (75.0)
Total:	50 (100.0)	12 (24.0)	14 (28.0)	2 (4.0)	22 (44.0)

Note: Descriptive statistics were used: qualitative data were presented as numbers and percentages, and quantitative data were presented as means. Staging was performed according to the Ann Arbor staging system and Lugano Classification.

By distributing patients with non-Hodgkin lymphoma with primary involvement of the gastrointestinal tract according to the histological type of the tumor, we revealed the overwhelming predominance of diffuse large B-cell lymphomas (46, 90.2%). The small lymphocytic (2, 4.9%) and lymphoplasmacytic (2, 4.9%) types were rarely encountered.

The study of the clinical picture of non-Hodgkin lymphoma with primary involvement of the gastrointestinal tract showed that patients with primary localization of the tumor site in the stomach most often presented with pain in the epigastric region (36, 90%), weight loss (31, 62%), anorexia (18, 45%), nausea and vomiting (17, 42.5%). Vomiting with coffee grounds content occurred in 2 (5%) patients, and dysphagia and the feeling of a tumor formation in the abdomen occurred in 1 (2.5%) case. Fever occurred in 5 (10.0%) patients, and profuse night sweats – in 38 (76.0%).

Patients with primary small intestine involvement had abdominal pain (4, 66.0%) and vomiting (2, 33.0%). Patients with non-Hodgkin lymphoma with primary colon involvement had abdominal pain in 4 (100.0%) cases, anorexia in 2 (50.0%) cases.

The complete blood count, bone marrow aspiration and biopsy of the iliac crest did not detect any specific changes

Table 2. Distribution of patients with gastrointestinal non-Hodgkin lymphomas according to the duration of the disease from the onset to diagnosis

Number of patients	Distribution of patients according to the duration of the disease (months)		
	3-6, abs. (%)	7-12, abs. (%)	≥13, abs. (%)
50	33 (66.0)	8 (16.0)	9 (18.0)

Note: Descriptive statistics were used: qualitative data were presented as numbers and percentages, and quantitative data were presented as means.

The study of the location of the primary focus in patients with non-Hodgkin lymphoma with primary involvement of the gastrointestinal tract showed that in 40 (80.0%) patients the stomach was affected, in 6 (12.0%) – the small intestine and in 4 (8%) – the large intestine (Table 3).

According to the International Clinical Classification, most patients (22, 44.0%) were diagnosed with clinical stage IV (Table 3). Stage IE was established in 12 (24.0%) cases and stage IIE in 14 (28.0%) cases. Stage IIIIE was diagnosed in 2 (4.0%) patients. B symptoms occurred in 38 (76.0%) patients, mainly in stage IV disease (17, 34.0%).

in cases without bone marrow involvement, with the exception of a decrease in hemoglobin and erythrocyte counts observed in cases of posthemorrhagic anemia.

In 20 patients in local stages (IE and IIE), the diagnosis of non-Hodgkin lymphoma was confirmed by surgical intervention with morphopathological and immunohistochemical examinations of the removed sector of the gastrointestinal tract, in the other cases, it was confirmed by endoscopic examination of the affected site with tumor biopsy and investigation of the removed material.

Patients with localized clinical stages (IE and IIE) underwent surgical treatment (gastrectomy), followed by 2-3 cycles of standard CHOP, R-COP and R-CHOP combined chemotherapy, subsequent radiotherapy with a total dose of 36-38 Gy to the involved sites, and then 3-4 additional cycles of combined chemotherapy using the aforementioned regimens. For patients in stages IIIIE and IV, only the aforementioned combined chemotherapy was administered in 6-8 cycles.

The short-term responses to treatment in patients with non-Hodgkin lymphoma with primary involvement of the gastrointestinal tract were studied (Table 4).

The treatment proved to be effective in 41 (82%) of 50 patients. Complete responses were achieved in 24 (48.0%)

patients and partial responses in 17 (34.0%) patients. In stage IE, complete responses occurred in all 12 (100%) patients, in stage IIE – in 42.85%, and in stages IIIIE and IV only in 25.0% of patients.

The long-term results of treatment of patients with primary involvement of the gastrointestinal tract are presented in Table 5.

Table 4. Short-term results of treatment in patients with gastrointestinal non-Hodgkin lymphomas according to the stage of the disease

Clinical stage	Number of patients, abs. (%)	Total response, abs. (%)	Type of responses, abs. (%)		Response failure, abs. (%)
			Complete	Partial	
IE	12 (24.0)	12 (100.0)	12 (100.0)	-	-
IIE	14 (28.0)	12 (85.7)	6 (42.85)	6 (42.85)	2 (14.3)
IIIIE – IV	24 (48.0)	17 (70.8)	6 (25.0)	11 (45.8)	7 (29.2)
Total:	50 (100.0)	41 (82.0)	24 (48.0)	17 (34.0)	9 (18.0)

Note: Descriptive statistics were used: qualitative data were presented as numbers and percentages, and quantitative data were presented as means. Staging was performed according to the Ann Arbor staging system and Lugano Classification.

Table 5. Overall survival of patients with gastrointestinal non-Hodgkin lymphomas according to the stage of the disease

Clinical stage	Number of patients	Overall survival (%)		
		1 year	3 years	≥5 years
IE	12	93.4	76.5	69.9
IIE	14	91.2	71.4	63.8
IIIIE – IV	24	75.1	34.8	28.5
Total:	50	78.1	59.4	35.9

Note: Overall survival was calculated according to the Kaplan-Meier estimate. Staging was performed according to the Ann Arbor staging system and Lugano Classification.

The overall survival of all patients with gastrointestinal NHL was 78.1% at 1 year, 59.4% at 3 years, and 35.9% at 5 years. In patients with stage IE NHL, the 1-, 3-, and ≥5-year overall survival was 93.4%, 76.5%, and 69.9%, respectively. In patients with stage IIE, the overall survival was 91.2% at 1 year, 71.4% at 3 years, and 63.8% at ≥5 years. In patients with stage IIIIE-IV, the overall survival was 75.1% at 1 year, 54.8% at 3 years, and 28.5% at ≥5 years under the combined chemotherapy, and thus significantly lower ($p < 0.05$).

Adverse events were evaluated in patients with primary gastrointestinal involvement following treatment. The most common adverse event, observed in 34 (68.0%) patients, was leukopenia, which did not interfere with the planned treatment schedule. Peripheral neuropathy occurred in 28 (56.0%) patients with non-Hodgkin lymphomas and primary gastrointestinal involvement. The administration of appropriate medications allowed continuation of both chemotherapy and radiotherapy in standard doses and regimens.

Discussion

Non-Hodgkin lymphomas develop and disseminate at different rates, being divided according to histopathological and clinical-evolutionary characteristics into indolent and aggressive [10]. Tumors originating in extranodal tissue are identified as primary extranodal lymphomas, while he-

matogenous and lymphogenous spread of the disease from lymph nodes to the extranodal sites is termed secondary extranodal lymphoma [11]. The most common diagnoses are diffuse large B-cell lymphoma and marginal zone lymphoma (MALT), but many other lymphomas may be found in the gastrointestinal tract [2]. The most frequent sites of occurrence are the stomach, followed by the small intestine and ileocecal region. In the last 2 decades, there has been a rapid development in the diagnosis, staging and management of gastrointestinal lymphomas, but some of these lymphomas, especially T-cell ones, constitute a therapeutic challenge. Globally, non-Hodgkin lymphomas caused 6.8 million DALYs (disability-adjusted life-years) in 2016 [12]. Despite the development of new antineoplastic agents, the short- and long-term results of treatment of the aggressive non-Hodgkin lymphomas remain modest, with frequent relapses and primary refractory forms [13]. Patients' survival differs depending on the stage and histological type of malignant lymphomas at diagnosis, the presence of signs of intoxication, the age, and concomitant pathologies [14]. According to the study conducted in the United Kingdom between 2004 and 2016, 60 out of 100 patients with diffuse large B-cell lymphomas survived 5 years or more after diagnosis, while 55 out of 100 patients with Burkitt lymphoma survived 5 years, and only 35 out of 100 patients with T-cell lymphomas survived 5 years after diagnosis [14].

The incidence of extranodal lymphomas has been continuously increasing in recent years. There are numerous factors that “favor” this increase: HIV/AIDS infection, the expanded use of immunosuppressive therapy, chronic inflammatory diseases and indolent viral infections (EBV, CMV, HCV) [15]. Primary gastric diffuse large B-cell lymphoma is commonly associated with HIV/AIDS, and MALT lymphoma is associated with *Helicobacter pylori* [16]. *Helicobacter pylori* eradication, thus, is recommended in cases of MALT lymphoma. More than 70% of the patients obtain remission following eradication of *Helicobacter pylori* using triple or quadruple therapy [16].

The increase in morbidity and disability in the working-age population, the high rate of late diagnosis of non-Hodgkin lymphomas and the modest results of treatment of the aggressive histopathological types [5, 17-19] remain an actual problem for clinical medicine and public health, requiring additional management and financial resources. According to the MarketScan® Commercial Claims and Encounters and Health and Productivity Management Databases, patients with non-Hodgkin lymphomas suffered more significant losses of productivity at work (31.99 days; 95% CI: 25.24 days, 38.73 days; $p < 0.001$) as compared to the control group [18]. In aggressive non-Hodgkin lymphomas, the average monthly costs of induction treatment (\$10,970) and palliative care (\$9,836) exceeded those associated with secondary treatment (\$3,302). The average cost of treatment failure in respective histopathological types was \$14,174 per month and \$85,934 over the entire study period [20]. Therefore, it is important to recognize different lymphoid and solid tumors within the gastrointestinal tract

in conjunction with the clinical and endoscopic features as gastrointestinal biopsies are among the most common specimens in academic and private pathology practices [8]. The recognition of these lymphomas' morphology, immunophenotype, and genetic/molecular patterns ensures an efficient and reliable clinical management and treatment.

Conclusions

Our study demonstrated that non-Hodgkin lymphomas with primary involvement of the gastrointestinal tract exhibited distinct histopathological, clinical-evolutionary and hematological features, which influenced treatment outcomes. The aggressive histological types and the advanced stages IIIIE and IV prevailed within the structure of non-Hodgkin lymphomas with primary gastrointestinal involvement, and, thus, negatively impacted survival and prognosis. The response rates and overall survival of patients with gastrointestinal non-Hodgkin lymphomas are consistent with the short- and long-term outcomes observed in the cases of other localizations of aggressive malignant lymphomas and necessitate additional management and financial resources in order to improve life expectancy and quality of life.

Competing interests

None declared.

Authors' contributions

LM conceived the study, participated in study design and drafted the manuscript. MR revised the methodology and draft of the article. VM participated in the study design, performed the statistical analysis and helped drafting the manuscript. DU, IC and AC collected research data, summarized and systematized data from the published studies and revised the draft of the manuscript. All the authors reviewed the work critically and approved the final version of the manuscript.

Ethics approval

The research project was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Minutes №. 3 from 17.06.2022).

Patient consent

The informed consent was obtained from all identifiable study participants.

Acknowledgements and funding

No external funding.

Provenance and peer review

Not commissioned, externally peer reviewed.

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