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Characteristics of patients with diffuse large B-cell lymphoma of gastrointestinal tract: A single center experience

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ABSTRACT

Objectives: Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease, with approximately one-third of patients presenting with extranodal involvement. The gastrointestinal (GI) tract is the most commonly affected extranodal site. This retrospective study aimed to evaluate the clinical characteristics and treatment outcomes of patients diagnosed with GI-DLBCL at a tertiary care hospital between 2015 and 2024.

Patients and Methods: Data of patients diagnosed with GI-DLBCL were retrospectively collected from electronic medical records. Patients with lymphoma subtypes other than DLBCL were excluded from the study.

Results: A total of 35 patients were included. The median age at diagnosis was 57 years, and 48.6% were male. The most frequent histologic subtype was "DLBCL, not otherwise specified (NOS)". The stomach was the most common site of extranodal involvement. Two-thirds of the patients presented with advanced-stage disease. Rituximab-based therapies including cyclophosphamide, doxorubicin, vincristine, and prednisolone with rituximab (R-CHOP) were administered as first-line treatment in 82.9% of patients, and a complete response was achieved in 71.4%. At a median follow-up of 45 months, median progression-free survival and overall survival had not yet been reached.

Conclusion: Despite a high rate of advanced-stage disease, R-CHOP treatment achieved high response rates and durable survival. Molecular profiling may help better understand the biological heterogeneity of GI-DLBCL.

Keywords: Gastrointestinal tract, Diffuse large B cell lymphoma, Prognosis

1. INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive subtype of non-Hodgkin lymphoma (NHL). DLBCL presents with a heterogeneous clinical spectrum in terms of morphology, genetics, and clinical manifestations [1]. Both nodal and extranodal presentations are common, and approximately one-third of patients present with extranodal disease, including primary gastrointestinal (GI) tract presentation [1-3]. However, primary DLBCL of the gastrointestinal system (GIS) are relatively rare entities that account for only 1%–4% of all GI malignancies and 10%-15% of all NHL [4]. The signs and symptoms of primary GIS lymphomas are similar to those of other GI cancers, and most of these findings are non-specific, including dyspepsia, weight loss, anemia and abdominal discomfort.

Chemoimmunotherapy constitutes the cornerstone of the treatment in DLBCL. The most preferred therapy is rituximab-based therapies including cyclophosphamide, doxorubicin, vincristine, and prednisolone with rituximab (R-CHOP). Since GIS-DLBCLs including gastric lymphomas share a similar cell of origin with thyroid, craniofacial, and localized bone lymphomas; they also respond well to chemoimmunotherapy [3, 5, 6] and R-CHOP therapy is preferred as the first line therapy for primary GIS-DLBCLs. But the role of radiotherapy remains unclear especially in early stage and non – bulky diseases and surgery is reserved only for managing complications and establishing a diagnosis. In the literature, approximately one-third of the patients had radiotherapy in combination with chemoimmunotherapy, but its role in survival and response rates was unclear.

In the light of these findings, the optimal treatment for GIS-DLBCL remains unclear. Therefore, we performed a retrospective analysis of 35 patients with GIS-DLBCL who were treated at a tertiary academic hospital between 2015 and 2024.

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2. PATIENTS and METHODS

A total of 48 patients were evaluated, and 35 patients were included in the analysis. Thirteen patients were excluded from the study. Eight patients were excluded due to missing follow-up data, three patients were under the age of 18 at the time of initial diagnosis, and in two patients, a definitive diagnosis of primary GI-DLBCL could not be established.

As a final analysis, we retrospectively analyzed 35 patients diagnosed with GIS-DLBCL between January 2015 and December 2024. Ethics Committee approval was obtained from the Ethics Committee. Data of the patients (age, sex, time of diagnosis, signs and symptoms at diagnosis, stages, treatments, responses to treatments, international prognostic indices, and follow-up periods) were retrieved from the archives and medical records of the Hematology Department.

Patients diagnosed with lymphomas other than DLBCL, those without GIS involvement at diagnosis, those younger than 18 years of age at diagnosis, and patients with lacking follow-up data were excluded. The diagnosis was confirmed in all patients with endoscopic biopsy.

The Ann Arbor Staging System (stage I–IV) was used for staging of the patients at the time of diagnosis. The early stage was defined as stage I/IIA [6]. Performance status of the patients was recorded according to Eastern Cooperative Oncology Group (ECOG) performance status. The response to treatment was evaluated according to International Workshop Criteria (IWC) [6]. Complete response (CR) was defined as the disappearance of all lesions and radiological or biological abnormalities observed at the time of diagnosis and absence of new lesions. Partial response (PR) was defined as regression of all measurable lesions by >50%, disappearance of nonmeasurable lesions, and absence of new lesions. Progressive disease (PD) was defined as the appearance of new lesions, growth of the initial lesions by >25%, or growth of any measurable lesion that had regressed during treatment by >50% at its smallest dimension. Stable disease (SD) was neither PR nor PD.

Progression-free survival (PFS) was calculated from the date of diagnosis to the date of documented disease relapse/progression or the date of death whichever occurred first. Overall survival (OS) was calculated from the date of diagnosis to the date of death as a result of any cause, or in surviving patients, censored at the last known alive visit.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to assess the assumption of normality. Continuous variables were presented depending on normal distribution with either mean±standard deviation or (in case of no normal distribution) median (25th-75th percentile). Categorical variables were summarized as counts (percentages). Comparisons of continuous variables between groups were carried out using Mann-Whitney U test and Kruskal-Wallis test since normality assumption did not hold. Kaplan Meier method was used for the survival analysis. Associations between continuous variables were determined by Spearman correlation analysis and the association between two categorical variables was examined by Chi-square test. All statistical analyses were carried out with 5% significance, and a two-sided p-value<0.05 was considered statistically significant.

3. RESULTS

We retrospectively analyzed 35 patients diagnosed with GIS-DLBCL between January 2015 and December 2024. The clinical characteristics are summarized in Table I. The median age at diagnosis was 57 years (range 22–81), and 48.6% were male. 26% of the cases were diagnosed during the COVID-19 pandemic and nineteen patients had primary gastric lymphoma, while 16 had non-gastric GI involvement. B symptoms were present in 80% of patients. The predominant histologic subtype was DLBCL, not otherwise specified (NOS) according to World Health Organization (WHO) classification. Rare subtypes included DLBCL coexistent with extranodal marginal zone lymphoma, Epstein-Barr virus (EBV)-positive DLBCL, and T-cell-rich B-cell lymphoma. The stomach was the most common site of extranodal involvement. Other sites included the liver, pancreas, and small intestine. Two-thirds of patients presented with advanced-stage disease, with gastric-DLBCL cases being more localized compared to non-gastric cases. Gastric-DLBCL was more often of germinal center B-cell (GCB) origin.

Most patients (82.9%) received first-line therapy, predominantly R-CHOP. A CR was achieved in 71.4% of patients, with higher rates observed in the gastric-DLBCL group. Radiotherapy was used in four patients (two from each group) as first line therapy (Table II). Patients who did not achieve remission after first line therapy, were treated with second line chemotherapy and autologous stem cell therapy in eligible patients.

At a median follow-up of 45 months, the median PFS and OS had not been reached. The 1-year and 5-year PFS rates were 88.6% and 74.3%, respectively. The 1-year and 5-year OS rates were 94.2% and 82.8%. There was no significant difference in survival outcomes between gastric and non-gastric DLBCL groups (Figure 1a-b). We either could not document a statistically significant survival difference between GCB and non-GCB subgroups.

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Table I. *Demographic and clinical characteristics of the patients*

Characteristics	Gastric (n (n=19)	Non-Gastric (n=16)	Total (n=35)
Age, median (range), year	57 (41-81)	56 (22-70)	57 (22-81)
Sex (male), n (%)	10 (52.6)	7 (43.8)	17 (48.6)
Histologic subtype*, n (%)			
DLBCL, NOS	18 (94.7)	14 (87.5)	32 (91.4)
DLBCL coexistent with gastric EMZL	0 (0)	1 (6.3)	1 (2.9)
EBV + DLBCL NOS	0 (0)	1 (6.3)	1 (2.9)
T cell rich BCL	1 (5.3)	0 (0)	1 (2.9)
B symptoms, n (%)	12 (63.1)	16 (100)	28 (80)
Spleen involvement, n (%)	3 (15.8)	3 (18.8)	6 (17.1)
Extranodal involvement, n (%)			
Stomach	19 (100)	0 (0)	19 (54.3)
Liver	0 (0)	8 (50)	8 (22.8)
Pancreas	2 (10.5)	2 (12.5)	4 (11.4)
Small intestine	0 (0)	3 (18.7)	3 (8.6)
Bone	2 (10.5)	1 (6.3)	3 (8.6)
Tongue	0 (0)	2 (12.5)	2 (5.7)
Tiroid	0 (0)	1 (6.3)	1 (2.9)
Testis	1 (5.3)	0 (0)	1 (2.9)
Pericardium	1 (5.3)	0 (0)	1 (2.9)
Colorectal	0 (0)	1 (6.3)	1 (2.9)
Diaphragm	0 (0)	1 (6.3)	1 (2.9)
Kidney	0 (0)	1 (6.3)	1 (2.9)
ECOG-PS 2≤, n (%)[n]	0 (0)	1 (5.9)	1 (2.9)
Ann-Arbor advanced stage, n (%)	13 (68.4)	11 (68.8)	24 (68.6)
LDH elevation (≥ 250 U/L), n (%)	10 (52.6)	11 (68.8)	21 (60)
IPI score[a] 3≤ , (n, %)	8 (42.1)	6 (37.5)	14 (40)
Cell of origin[b], n (%)			
GCB	7 (36.8)	8 (50)	15 (42.9)
Non-GCB	6 (31.6)	4 (25)	10 (28.6)
Unclassified	6 (31.6)	4 (25)	10 (28.6)

**DLBCL, NOS: Diffuse large B-cell lymphoma, not otherwise specified, EMZL: extranodal marginal zone lymphoma, EBV: Ebstein Barr Virus, BCL: B cell lymphoma LDH: Lactate dehydrogenase.*

[n] ECOG-PS: Eastern Cooperative Oncology Group Performance Score

[a] IPI score: International Prognostic Index [b] GCB: germinal center B cell

Table II. *Treatments and response status*

Variable	Gastric (n=19)	Non-Gastric (n=16)	Total (n=35)
First line treatment regimen, n (%)			
R-CHOP	18 (94.7)	15 (93.7)	33 (94.3)
R-CEOP	1 (5.3)	0 (0)	1 (2.9)
R-DA-EPOCH	0 (0)	1 (6.3)	1 (2.9)
Median number of cycles (range)	6 (3-8)	6 (3-8)	6 (3-8)
Second-line treatment regimen, n (%)			
R-ICE	2 (50)	2 (100)	4 (66.6)
R-DHAP	2 (50)	0 (0)	2 (33.3)
Median number of treatment-line (range)	1 (1-5)	1 (1-3)	1 (1-5)
1, n (%)	15 (78.9)	14 (87.4)	29 (82.9)
2, n (%)	3 (15.8)	1 (6.3)	4 (11.4)
>2, n (%)	1 (5.3)	1 (6.3)	2 (5.7)
Radiotherapy	2 (10.5)	2 (12.5)	4 (11.4)
Response of first line therapy			
CR	14 (73.7)	11 (68.8)	25 (71.4)
PR	3 (15.8)	4 (25)	7 (20)
SD	0 (0)	0 (0)	0 (0)
PD	1 (5.3)	1 (6.2)	2 (5.7)
N/E	1 (5.3)	0 (0)	1 (2.9)

R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine sulphate and methylprednisolone, R-CEOP: rituximab, cyclophosphamide, etoposide, vincristine sulphate and prednisone, R-DA-EPOCH: dose adjusted rituximab, etoposide, prednisolone, vincristine sulphate, cyclophosphamide, doxorubicin, R-ICE: rituximab, ifosfomide, carboplatin, etoposide, R-DHAP: rituximab, dexamethasone, cisplatin, cytarabine, CR: complete remission, PR: partial remission, SD: stable disease, PD: progressive disease, N/E: not evaluable (death/discontinue treatment).

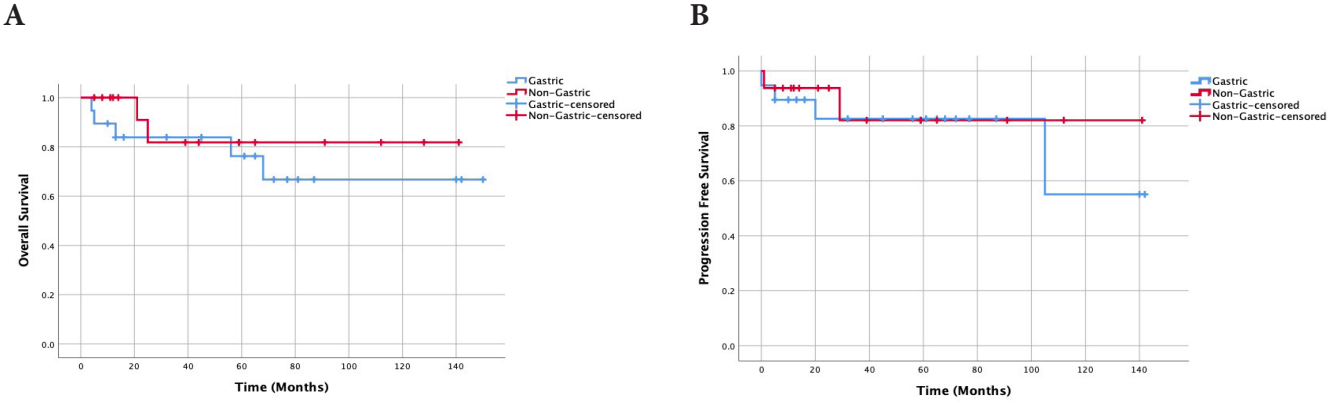

Figure 1. a: *Overall survival and b: Progression free survival in gastric and non – gastric B cell lymphoma patients.*

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4. DISCUSSION

In this retrospective single-center study, we aimed to investigate the clinical characteristics, treatment outcomes, and survival data of patients diagnosed with GI-DLBCL over a nearly decade-long period. Our results contribute to the expanding body of evidence on GI-DLBCL, an entity recognized for its aggressive nature but also for its relatively favorable outcomes when appropriately treated [3].

The median age of our cohort was 57 years, and there was a slight male predominance similar to a prospective cohort of primary GI-DLBCL reported by Suresh et al. [4]. The median age in the literature had a range of 48 – 75 years [5-8]. In a study from Japan, the cohort was older (median age: 74 years old) [5] when compared to studies by MD Anderson group (median age 63 years) [6, 7]. Similarly, the median age also differs according to the involved organ and type of the lymphoma. Koch et al., also reported an older median age in patients with NHL [8] and a younger age when the lymphomas were localized to ileocecal area. It should be noted that their cohort included all NHLs besides DLBCL. Hellenic Cooperative Oncology Group (HeCOG) also reported median age of 62 years in a cohort of GIS lymphomas in which 44.5 % of patients had DLBCL [9]. A retrospective article from Türkiye also reported a younger cohort of primary GIS lymphomas with a median age of 47 years [10] similar to our results but DLBCL constituted 86.4 % of their total cohort. These demographic findings align with previous epidemiological studies that describe DLBCL as a disease predominantly affecting middle-aged to older adults.

Notably, approximately two-thirds of our patients presented with advanced-stage disease according to the Ann-Arbor classification, which underscores the aggressive nature and often late diagnosis of GI-DLBCL. Suresh et al., reported a rate of 23% stage IV patients, but the number of patients with stage III was not mentioned [4]. The lack of patients with advanced stage in the Japanese study was also remarkable, but the stage of 2 patients were unknown [5]. Similarly, MD Anderson cohort exhibited more localized disease with 61.3% of patients having early stages disease. German group also reported lower prevalence of advanced stage in total GI-NHL cohort [8]. HeCOG reported a slightly higher number of advanced-stage cases, but it was also lower than our cohort [9]. Yıldırım et al., reported only stage IV patients with a rate of 22.7% [10]. One explanation to this difference can be the timing of studies. All of the aforementioned studies were performed before the COVID-19 pandemic, but 26% our cohort diagnosed during or after the pandemic that resulted in diagnostic delays in particular conditions.

The stomach remained the most commonly involved site, accounting for 54.3% of all cases, which is in line with the well-documented predilection of DLBCL for gastric involvement when arising in the extranodal regions [1-4, 6-10]. Involvement of other GI sites such as the liver, pancreas, and small intestine was observed with varying frequencies. Non-gastric involvement, particularly liver and small intestine localization, was associated with a higher rate of B symptoms, suggesting a possibly more systemic and symptomatic or complicated disease course compared to gastric DLBCL [11].

Histopathological analysis revealed that the majority of patients were classified as having DLBCL, NOS. A minority of cases represented rarer subtypes, including EBV-positive DLBCL and T-cell-rich B-cell lymphoma. These findings are noteworthy because EBV positivity in DLBCL is often associated with poorer prognosis, although the limited number of cases in our cohort precluded meaningful statistical analysis [11, 12].

In terms of cell of origin, GCB like phenotype was slightly more common among non-gastric DLBCL patients. The prognostic implications of cell of origin have been well established, particularly with inferior outcomes reported in activated B-cell-like (ABC) subtypes. The frequency of ABC/non-GCB-like DLBCL varied in the literature and was 42–73% in the stomach, 40% in the duodenum, 6–14% in the small intestine, and 57% in the large intestine [12-14]. Our study did not observe a statistically significant survival difference between GCB and non-GCB subgroups, likely due to the limited sample size.

The standard immunochemotherapy regimen, R-CHOP, was utilized as the first-line treatment in most of the patients, resulting in a high overall CR rate of 71.4%. Gastric-DLBCL patients exhibited slightly higher CR rates compared to non-gastric DLBCL patients, although the difference was not statistically significant. This observation may be attributed to the more localized nature of gastric involvement compared to the often multifocal presentation of non-gastric lymphomas. Suresh et al., reported a lower rate of CR even in patients with localized disease, but most of their patients received CHOP chemotherapy without rituximab [4]. MD Anderson group reported better CR rates similar to our cohort with rituximab containing systemic chemotherapy or combined treatment modality [6].

A population-based retrospective study showed poorer survival in patients with advanced stage in extranodal DLBCL [15]. Importantly, the survival outcomes in our cohort were favorable. The 1-year and 5-year PFS rates were 88.6% and 74.3%, respectively, while the corresponding OS rates were 94.2% and 82.8% which were compatible with another study by Soyer et al., from Türkiye [16]. Although MD Anderson group reported higher survival rates, it should be noted that their cohort included more localized disease which was associated with prolonged OS and PFS compared to advanced stages [16]. These findings highlight the effectiveness of current chemoimmunotherapy protocols in achieving durable remissions in patients with GI-DLBCL. Interestingly, non-gastric DLBCL patients demonstrated numerically higher PFS and OS rates compared to their gastric counterparts; however, the differences were not statistically significant. This may reflect the relatively small cohort size or selection bias, where patients with better performance status were more likely to complete therapy.

Several limitations must be acknowledged in the interpretation of our findings. First and foremost, the retrospective design of the study introduces inherent biases, including selection and information bias. Secondly, the relatively small sample size limited the statistical power to detect subtle differences

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between subgroups and prevented more robust multivariable analyses. Moreover, detailed molecular characterization, such as MYC, BCL2, and BCL6 rearrangements, was not routinely available, precluding deeper biological insights into the disease heterogeneity. Treatment decisions, including the use of radiotherapy or second-line regimens, were not standardized but were based on clinician discretion, which may introduce variability in outcomes. Finally, the single-center nature of the study limits the generalizability of our results to broader, more diverse patient populations.

Future research should aim to address these limitations by conducting multicenter, prospective studies with larger and more diverse patient cohorts. Integrating comprehensive molecular profiling—including gene expression analysis and next-generation sequencing—would enable a better understanding of the biological heterogeneity of GI-DLBCL and potentially identify novel prognostic biomarkers or therapeutic targets. Additionally, randomized controlled trials comparing treatment strategies, such as R-CHOP versus intensified regimens or the role of consolidative radiotherapy, could refine therapeutic approaches. Long-term follow-up studies evaluating late relapses and therapy-related toxicities are also warranted to optimize survivorship care in this patient population.

Conclusion

In conclusion, GI-DLBCL represents a distinct clinical entity characterized by aggressive behavior but favorable responses to standard chemoimmunotherapy. High proportion of patients presenting with advanced-stage disease, treatment with R-CHOP resulted in excellent CR rates and durable PFS and OS outcomes. No significant differences in survival were observed between gastric and non-gastric lymphomas. However, the heterogeneous clinical presentations highlight the need for individualized patient management strategies. Future prospective, multicenter studies incorporating detailed molecular characterization are essential to further refine risk stratification and optimize therapeutic interventions for this diverse and complex group of patients.

Compliance with Ethical Standards

Ethical approval: Ethical approval for this research was obtained from the Marmara University, School of Medicine, Non-Interventional Ethics Committee (approval number : 03.12.2021.1371, date: 02.12.2021). This study was performed in line with the principles of the Declaration of Helsinki.

Conflict of interest: The authors declare that there is no conflict of interest.

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Author contributions: MUM : Conception, data collection, data analysis, writing, revision, AFY : Conception, supervision,data analysis, writing,revision, CG : Data collection, data analysis, writing, FT : Data collection, analysis, FA, SS, AB, RBO and SO: Data collection, revision, TT and IA: Supervision, English editing. All authors approved the final version of the manuscript.

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