ISSN 1948-5204 (online)

# World Journal of *Gastrointestinal Oncology*

*World J Gastrointest Oncol* 2024 November 15; 16(11): 4300-4531

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

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## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGO* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

## INDEXING/ABSTRACTING

The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGO* as 2.5; JIF without journal self cites: 2.5; 5-year JIF: 2.8; JIF Rank: 71/143 in gastroenterology and hepatology; JIF Quartile: Q2; and 5-year JIF Quartile: Q2. The *WJGO*'s CiteScore for 2023 is 4.2 and Scopus CiteScore rank 2023: Gastroenterology is 80/167; Oncology is 196/404.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Gastrointestinal Oncology*

**ISSN**
ISSN 1948-5204 (online)

**LAUNCH DATE**
February 15, 2009

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Monjur Ahmed, Florin Burada

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/1948-5204/editorialboard.htm

**PUBLICATION DATE**
November 15, 2024



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*World J Gastrointest Oncol* 2024 November 15; 16(11): 4409-4423

DOI: 10.4251/wjgo.v16.i11.4409

ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Retrospective Study

# Comparison of clinical features of patients with or without severe gastrointestinal complications in aggressive gastrointestinal lymphomas

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**Specialty type:** Oncology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B

**Novelty:** Grade B

**Creativity or Innovation:** Grade B

**Scientific Significance:** Grade B

**P-Reviewer:** Frolli A

**Received:** July 17, 2024

**Revised:** August 25, 2024

**Accepted:** September 24, 2024

**Published online:** November 15, 2024

**Processing time:** 99 Days and 18.5 Hours

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## Abstract

***BACKGROUND***

Aggressive primary gastrointestinal non-Hodgkin lymphoma (PGINHL) is an uncommon and heterogeneous group of lymphoid malignancies, that differs from indolent lymphoma and has a high incidence of severe gastrointestinal complications (GICs).

***AIM***

To investigate and compare the clinicopathological characteristics, treatments and outcomes in the GICs and No-GICs group with aggressive PGINHL.

***METHODS***

This retrospective analysis was performed on aggressive PGINHL patients

between January 2013 and December 2021 at our hospital. The independent influence factors of GICs were obtained by univariate and multivariate Logistic regression analysis, the selected variables significantly related to GICs were selected as the final predictors to construct nomogram. Kaplan-Meier curves further analyzed the survival of patients in GICs and No-GICs groups. Survival analysis of GICs group was performed using Cox regression.

***RESULTS***

We focused on 124 aggressive PGINHL cases, which had a relatively high incidence 48.4% (60/124 cases) of GICs, the most common histological type in GICs group was diffuse large B-cell lymphoma (DLBCL) ($n$ = 49, 81.7%). In the GICs group, small intestine was the most common anatomic site of lesion (43.3%), followed by large intestine (31.7%), and then stomach and esophagus (25.0%). Multivariate Logistic regression analysis showed that the independent risk factors for GICs were the small intestine [odd ratio (OR) = 3.33; 95% confidence interval (CI): 1.47-9.41; $P$ = 0.009), aggressive B-cell (OR = 0.09; 95%CI: 0.01-0.83; $P$ = 0.033), maximum tumor diameter (OR = 1.25; 95%CI: 1.07-1.47; $P$ = 0.005), invaded deep serous layer (OR = 3.38; 95%CI: 1.24-9.19; $P$ = 0.017). We developed a nomogram to predict risk of GICs in aggressive PGINHL patients based on independent risk factors. The value of area under curve calculated by receiver operating characteristic curve was 0.815, and calibration curve and decision curve analysis further indicated that the prediction effect was superior. The majority of patients with GICs were given combination therapy (chemotherapy combined with surgery or radiation). Event-free survival and overall survival in GICs group were no worse than those in the No-GICs group.

***CONCLUSION***

The complication rate of GICs in patients with aggressive PGINHL was relatively high, particularly in PGI-DLBCL. The independent risk factors for GICs were the small intestine, PGI-TNKL, bulky tumor, and depth of invasion. A combination treatment, involving surgery, improved survival in the GICs group.

**Key Words:** Primary gastrointestinal; Aggressive; Non-Hodgkin lymphoma; Gastrointestinal complication; Risk factor



**Core Tip:** The characteristics of aggressive primary gastrointestinal non-Hodgkin lymphoma (PGINHL) with or without severe gastrointestinal complications (GICs) were explored in this study. The relationship between GICs and clinicopathological features of aggressive PGINHL patients, such as primary site, histological type, tumor size, depth of gastrointestinal invasion and other factors, was investigated by statistical analysis. The aim of this study was to summarize the risk factors and treatment strategies for aggressive PGINHL patients with or without GICs and to provide evidence-based evidence for clinical decision-making and individualized treatment strategies.

**Citation:** Liu XH, Chen G, Cao DD, Liu H, Ke XK, Hu YG, Tan W, Ke D, Xu XM. Comparison of clinical features of patients with or without severe gastrointestinal complications in aggressive gastrointestinal lymphomas. *World J Gastrointest Oncol* 2024; 16(11): 4409-4423

**URL:** https://www.wjgnet.com/1948-5204/full/v16/i11/4409.htm

**DOI:** https://dx.doi.org/10.4251/wjgo.v16.i11.4409

## INTRODUCTION

Primary extra-nodal lymphoma was defined as a lymphoma whose primary site was not the lymph node but originated in tissues and organs other than the lymph node[1]. The digestive system organs had relatively rich lymphatic tissue, especially the gastrointestinal tract lymphatic drainage area, so the incidence of lymphoma invading the gastrointestinal tract was relatively high. Primary gastrointestinal lymphomas were rare compared to epithelial cancers, accounting for only 1% of gastrointestinal tumors. The most commonly involved organ was the stomach, followed by the small and large intestine, while the esophagus, appendix, and rectum were rare[2]. Primary gastrointestinal lymphoma was classified into B cell and nature killer (NK)/T cell lymphoma. It also was divided into aggressive and indolent lymphoma according to the course of the disease. Indolent B-cell lymphoma such as mucosal associated lymphoid tissue (MALT) and follicular cell lymphoma (FL) had little invasive damage to the gastrointestinal tract[1,2]. The indolent T-cell and NK-cell lymphomas usually had non-destructive infiltration. Among aggressive primary gastrointestinal non-Hodgkin lymphoma (PGINHL), diffuse large B-cell lymphoma (DLBCL) was the most common pathological subtype (47.4%)[3]. Primary gastrointestinal T/NK cell lymphomas (PGI-TNKL) were also aggressive entities consisting of various subtypes with distinct clinicopathological features and prognoses[4-6]. Aggressive gastrointestinal lymphoma had a more invasive growth and a worse prognosis than indolent lymphoma. Due to aggressive lymphoma occurred in the gastrointestinal tract, aggressive behaviors such as severe gastrointestinal complications (GICs)-gastrointestinal bleeding (GIB),

gastrointestinal obstruction (GIO), and gastrointestinal perforation (GIP) were also common at the first visit, especially after chemotherapy, GIP can lead to a very high mortality rate[7-9]. Special attention should be paid to the high risk of GICs in PGINHL patients, necessitating a multidisciplinary discussion and even emergency surgical intervention.

Early identification of GICs risk factors may be beneficial to early treatment and improve the prognosis of aggressive PGINHL patients[1]. A retrospective study suggested that GICs occurred in 56.8% of 148 PGI-DLBCL patients[7]. DLBCL was the most common type of aggressive PGINHL. T-cell lymphomas were uncommon, estimated to account for 4% to 6% of GI tract lymphomas[10]. A relatively large cohort study of PGI-TNKL was performed in 38 patients from South Korea[11]. Aggressive PGI-TNKL mainly referred to as intestinal T-cell lymphoma (ITCL)[1,10]. ITCLs comprised two main entities: Enteropathy-associated T-cell lymphoma (EATL) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), plus ITCL, not specifically (NOS)[5], they were both aggressive in behavior but differ in their clinicpathological features[11]. Aggressive extranodal natural killer/T-cell lymphoma (NKTCL) was more common in Asia, gastrointestinal tract also was involved[12]. However, no studies had systematically summarized the occurrence of GICs in aggressive gastrointestinal lymphomas.

At present, there were few prospective studies on treatments. How to identify high-risk GICs in aggressive PGINHL patients, improving the therapeutic effect and overall survival time was still under discussion. In this study, we analyzed aggressive PGINHL patients in our cancer center in the past 10 years. We were the first to analyze the GICs group *vs* the No-GICs group in aggressive PGINHL, to find risk factors that predicted GICs, and establish a prediction nomogram, which was conducive to the early identification of clinicians. At the same time, we analyzed the treatment characteristics and prognosis of aggressive PGINHL with GICs, and attempted to provide evidence-based basis for treatment.

## MATERIALS AND METHODS

### *Patient Selection and evaluation criterion*

The patients included inpatient and outpatient lymphoma patients at our hospital from January 2013 to December 2021, and followed up until December 2022. Follow-up methods included in-patient review, outpatient review, and telephone follow-up. Primary gastrointestinal lymphoma was defined as predominant lesions in the alimentary tract with or without regional lymph node involvement[13,14]. All cases were diagnosed according to the World Health Organization diagnostic criteria[1]. In our cancer center, the flow chart of the selected aggressive gastrointestinal lymphomas was shown in Figure 1. The aggressive PGI-B-cell lymphomas were DLBCL and Burkitt's lymphoma (BL). ITCL patients accounted for the majority including aggressive PGI-TNKL, specifically EATL, MEITL, ITCL-NOS, and NKTCL. The exclusion criteria were defined as follows: Indolent primary PGINHL, pathological diagnosis inconsistent, infected with human immunodeficiency virus, younger than 18 years.

The clinical data of all patients at the time of initial diagnosis were collected in our cancer center, including age, gender, disease stage, eastern cooperative oncology group (ECOG) score, blood lactate dehydrogenase (LDH), hepatitis virus, Epstein-Barr virus (EBV) DNA, primary site, immunohistochemical markers, tumor size, endoscopy or endoscopic ultrasonography, imaging, bone marrow examinations, treatment methods, and outcomes. Ann Arbor staging was still the main clinical staging, referring to the modified Lugano staging[15]. This retrospective research was approved by the Medical Ethics Committee of Renmin Hospital of Wuhan University (No. WDRY2021-KS024) and conducted in accordance with the declaration of Helsinki.

### *Pathological immunophenotypic markers*

Diagnosis confirmation depended on the pathology of endoscopic biopsy or surgical specimens. The subtype of each lesion was determined using immunohistochemical analysis. According to the expression of cluster of differentiation (CD) 10, multiple myeloma oncogene 1, and human B-cell lymphoma 6 in Han's classification, patients were classified as germinal center B cells (GCB) and non-GCB. Double expression was defined as *MYC* expression ≥ 40% and *Bcl-2* expression ≥ 50%[16]. *MYC* gene rearrangement and lesion positivity for EBV-encoded small RNA were assayed by in situ hybridization.

### *Macroscopy/endoscopy and imaging findings*

Macroscopic findings regarding morphology and size were reviewed by expert endoscopists and pathologists based on the endoscopic findings and/or surgically resected specimens. Lesion morphology was classified as polypoid, ulcerative, diffuse nodular, or diffuse-infiltrating type in some literatures[14,17-20]. In our study, we divided these types into neoplasm, ulceration and other types. The neoplasm consisted of polypoid or mass without surface ulceration. Ulceration included diffuse ulceration or focal/elevated ulceration. Slightly thickened or inconspicuous luminal walls were classified as others. For later statistical analyses, the depth of tumor invasion was classified as inside or outside the serosal layer based on endoscopic ultrasonography or postoperative pathological findings in our cases.

The radiologist's first impression of imaging was classified as normal, non-specific inflammation, cancer, or lymphomain some literature[14]. In our study, imaging findings were divided into two categories: Neoplastic lesions or others (normal, non-specific inflammation). 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and maximum standardized uptake value could not be obtained before diagnosis because most patients in the GICs group were diagnosed after acute abdomen surgery.

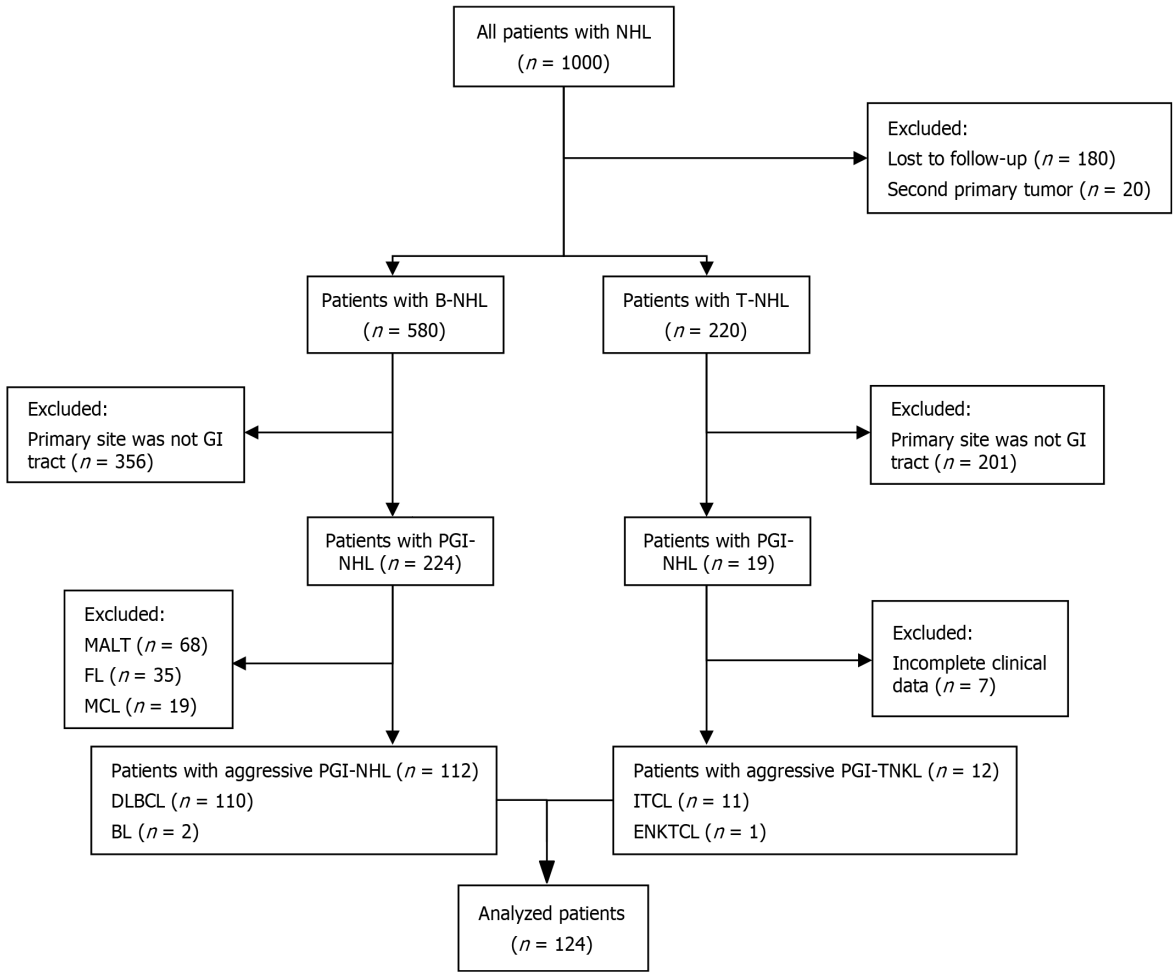


**Figure 1 Screening flowchart for aggressive gastrointestinal non-Hodgkin lymphoma.** NHL: Non-Hodgkin lymphoma; PGI: Primary gastrointestinal; GI: Gastrointestinal; MALT: Mucosal associated lymphoid tissue; FL: Follicular cell lymphoma; MCL: Mantle cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; BL: Burkitt's lymphoma; PGI-TNKL: Primary gastrointestinal T/NK cell lymphomas; ITCL: Intestinal T-cell lymphoma; ENKTCL: Extranodal natural killer T cell lymphoma.

### *Evaluation outcome criteria*

GICs were confirmed by clinical symptoms, laboratory tests, imaging, and /or surgery. GIO, including partial and complete obstruction, was considered to be the absence of passage of flatus or feces[21]. GIP was defined as the presence of free air under the diaphragm on abdominal imaging, or intestinal perforation during laparotomy[22]. GIB was defined as overt bleeding (hematemesis, bloody stools) and drop in hemoglobin of ≥ 2 g/dL[23]. All the above GICs were confirmed using imaging or surgery. During the course of the disease, it was possible to develop two or more complications. Patients with GICs required surgery, we also included those who suffered from GICs but could not undergo surgery due to their poor general condition.

Revised response criteria, known as the 2014 Lugano criteria, was divided into imaging remission and metabolic remission using FDG-PET scans[15]. The response was categorized as complete remission, partial remission, stable disease and relapsed disease or progressive disease. Event-free survival (EFS) was defined as the time from the diagnosis to disease progression, recurrence, death or last follow-up. The overall survival (OS) duration was measured from the time of diagnosis to the time of death or last follow-up.

### *Statistical analysis*

After data collection, frequency (%) was used as a descriptive statistic. Quantitative variables were expressed as mean ± SD or median (quartile range). The differences in clinical parameters were compared using $\chi^2$ test or Fisher's exact for categorical variables, or one-way analysis of variance for continuous variables. $P$ values < 0.05 at both sides were considered statistically significant. The GICs risk nomogram was constructed with the most significant factors associated with GICs using Logistic regression analysis. The receiver operating characteristic (ROC) curve was used to evaluate the accuracy of nomogram in predicting the risk of GICs. Then, calibration curves were generated for the comparison between the actual outcomes and nomogram-predicted outcomes. Finally, decision curve analysis (DCA) was conducted by measuring the net benefits for a group of threshold probabilities to measure clinical utility[24]. EFS and OS were evaluated using Kaplan Meier analysis with a log rank comparison. Cox regression univariate and multivariate analyses were used to assess predictors of survival. Statistical analyses were performed using statistical product and service

solutions (SPSS) software (version 25.0) for Windows (SPSS Inc., Chicago, IL, United States), R software (version 3.3.0) (http://www.r-project.org/).

## RESULTS

### *Clinicopathologic characteristics of GICs group with aggressive PGINHL*

Among approximately 224 PGINHL cases diagnosed from 2013 to 2021, more than 60 indolent gastrointestinal lymphomas (MALT, FL) were excluded, ten cases of mantle cell lymphoma (MCL) with small B-cell lymphoma were also excluded, leaving 124 patients with aggressive PGINHL. Among them, aggressive PGI-B cell lymphomas accounted for 90.3% (110 cases of DLBCL and 2 cases of BL), aggressive PGI-TNKLs only accounted for 9.7% (11 cases of ITCL and 1 case of NKTCL). The final follow-up period was December 2022 (Figure 1).

In our study of 124 cases of aggressive PGINHL, GICs occurred in 48.4% (60/124), including 36 cases of GIO, 9 cases of GIP, 12 cases of GIB, and 3 cases of GIO and GIB. In the subgroup that combined GICs, the median age was 61 years (range: 28 to 89 years), and the male to female ratio was 1.73:1. The most common histological type in the GICs group was DLBCL ($n$ = 49, 81.7%), followed by ITCL ($n$ = 10, 16.7%), NKTCL ($n$ = 1, 1.6%). The most frequently affected anatomic location in GICs group was the small intestine (43.3%), followed by large intestine (31.7%), stomach and esophagus (25.0%), and tumor maximum diameter was 7.03 cm ± 3.7 cm. Compared with the No-GICs group (8/37 cases), the GIC group had a significantly higher proportion of serosal layer and outside (29/37 cases). No matter in No-GICs group or GICs group, in terms of the macroscopic appearance of gastrointestinal tract growth (through endoscopy or surgery), lymphoma was mainly neoplasm, followed by an ulcerative type. In terms of imaging findings, radiologists often considered neoplastic lesions, but they could not further indicate cancer or lymphoma (Table 1). Supplementary Figure 1 showed an endoscopic picture of inflammatory changes in a patient with primary small intestinal TNKL, and another endoscopic picture of a large ulcer in a patient with primary ileocecal junction DLBCL was shown in Supplementary Figure 2.

### *Risk factors associated with GICs in aggressive PGINHL patients*

Results of univariate analysis [odds ratio (OR); 95% confidence interval (CI); $P$ value] were as follows: Primary site (small intestine OR = 6.55; 95%CI: 2.61-16.40; $P$ < 0.001; colon OR = 5.60; 95%CI: 2.15-14.61; $P$ < 0.001), aggressive B cell lymphomas (OR = 0.09; 95%CI: 0.01-0.83; $P$ = 0.033), max tumor diameter (OR = 1.30; 95%CI: 1.13-1.48; $P$ < 0.001), invasive depth (serosal layer and outside OR = 6.55; 95%CI: 2.67-16.06; $P$ < 0.001), ECOG ≥ 2 (OR = 3.35; 95%CI: 1.02-11.05; $P$ = 0.047), and double expression (OR = 0.40; 95%CI: 0.16-0.97; $P$ = 0.044) were risk factors for GICs.

Multivariate analysis revealed that primary site (small intestine OR = 3.33; 95%CI: 1.47-9.41; $P$ = 0.009; colon OR = 2.50; 95%CI: 1.17-7.15; $P$ = 0.023), aggressive B cell lymphomas (OR = 0.09; 95%CI: 0.01-0.83; $P$ = 0.033), max tumor diameter (OR = 1.25; 95%CI: 1.07-1.47; $P$ = 0.005), invasive depth (serosal layer and outside OR = 3.38; 95%CI: 1.24-9.19; $P$ = 0.017) were independent indicators for GICs (Table 2).

### *Development of GICs risk predictive nomogram*

Based on univariate and multivariate analyses, four parameters (primary tumor site, histopathological type, depth of tumor invasion, and max tumor diameter) were identified as independent risk factors. Hence, based on these four significant variables, a nomogram was created to predict risk of GICs in aggressive PGINHL patients (Figure 2). Add up the corresponding scores for each item and find the corresponding percentage on the GICs risk score.

Then, DCA showed that if the threshold probability was over 0.5, the nomogram for GICs prediction added more benefit than all or none, indicating that our nomogram provided a better clinical net benefit (Figure 3). As depicted in Figure 4, ROC analysis revealed that the nomogram exhibited favorable predictive performance for GICs. ROC curves were generated to further evaluate the predictive performance (area under curve = 0.815). Additionally, the calibration curves for the GICs probability exhibited optimal agreement (Figure 5).

### *Treatment characteristics and prognosis of patients with GICs in aggressive PGINHL*

Patients with aggressive PGINHL in the GICs group were treated differently from those in the No-GICs group (Table 3). In the former group, emergency surgery was performed because of GICs accounting for 88.3% in the GICs group, while in the No-GICs group, 3 patients underwent surgery because the tumors were not detected by endoscopy but were highly suspected by imaging. The rate of chemotherapy (71.7%) and radiotherapy (8.3%) in the GICs group were lower than those in the No-GICs group, probably because some patients could not tolerate chemotherapy because of poor ECOG for GICs, some patients improved after surgical resection of bulky masses and did not require radiotherapy. In conclusion, the patients with GICs were mainly given combination therapy (chemotherapy combined with surgery or radiotherapy). EFS and OS of GICs group were close to those in the No-GICs group ($P$ > 0.05). At the end of follow-up, 26 patients (43.3%) died in the GIC group, and 20 patients (31.3%) died in the No-GIC group, there was no significant difference between the two groups ($P$ > 0.05) (Figure 6).

Analysis of prognostic factors in patients with aggressive PGINHL with GICs: Univariate analysis suggested that histopathology, LDH, stage, ECOG, non-GCB, chemotherapy combined with surgery or radiotherapy were related to OS ($P$ < 0.05). Multivariate analysis suggested that histopathology, LDH, stage, ECOG, chemotherapy combined with surgery or radiotherapy were independent factors ($P$ < 0.001, $P$ = 0.005, $P$ = 0.007, $P$ < 0.001, $P$ < 0.001 respectively) (Table 4).

**Table 1 Clinicopathologic characteristics of 124 cases of aggressive primary gastrointestinal non-Hodgkin lymphoma, *n* (%)**

| Characteristics | No-GICs (*n* = 64) | GICs (*n* = 60) | *P* value |
|---|---|---|---|
| Age, mean ± SD | 59.8 ± 12.5 | 60.0 ± 14.2 | 0.932 |
| ≥ 60 | 32 (50.0) | 34 (56.7) | 0.573 |
| < 60 | 32 (50.0) | 26 (43.3) | |
| Gender | | | 0.427 |
| Male | 35 (54.7) | 38 (63.3) | |
| Female | 29 (45.3) | 22 (36.7) | |
| Stage | | | 0.875 |
| I/II | 29 (45.3) | 29 (48.3) | |
| III/IV | 35 (54.7) | 31 (51.7) | |
| LDH | | | 0.406 |
| Elevated | 27 (42.2) | 20 (33.3) | |
| Normal | 37 (57.8) | 40 (66.7) | |
| Virus | | | 0.876 |
| Yes | 8 (12.5) | 6 (10.0) | |
| No | 56 (87.5) | 54 (90.0) | |
| ECOG | | | 0.139 |
| 0-1 | 59 (92.2) | 49 (41.7) | |
| ≥ 2 | 5 (7.8) | 11 (18.3) | |
| Depth | | | < 0.001 |
| Inside serous membrane | 54 (87.5) | 31 (51.7) | |
| Serosal layer and outside | 8 (12.5) | 29 (48.3) | |
| Diameter, mean ± SD | 4.65 ± 2.4 | 7.03 ± 3.7 | < 0.001 |
| Primary site | | | < 0.001 |
| Esophagus or stomach | 40 (62.5) | 15 (25.0) | |
| Small intestine | 12 (18.8) | 26 (43.3) | |
| Colon | 12 (18.8) | 19 (31.7) | |
| Histopathology | | | < 0.001 |
| DLBCL + BL | 63 (98.4) | 49 (81.7) | |
| ITCL + NKTCL | 1 (1.6) | 11 (18.3) | |
| N-GCB | 39 (60.9) | 43 (71.7) | 0.284 |
| CD5 + | 13 (20.3) | 7 (11.7) | 0.287 |
| CD30 + | 5 (7.8) | 7 (11.7) | 0.673 |
| Double expression | 18 (28.1) | 9 (15.0) | 0.121 |
| Ki 67 ≥ 70% | 39 (60.9) | 40 (66.7) | 0.634 |
| Macroscopic findings | | | 0.858 |
| Neoplasm | 29 (45.3) | 30 (50.0) | |
| Ulceration | 31 (48.4) | 27 (45.0) | |
| Others | 4 (6.2) | 3 (5.0) | |
| Imaging findings | | | 0.205 |
| Neoplasticlesions | 53 (82.8) | 43 (71.7) | |
| Others | 11 (17.2) | 17 (28.3) | |

PGINHL: Primary gastrointestinal non-Hodgkin lymphomas; GICs: Gastrointestinal complications; LDH: Lactate dehydrogenase, ECOG: Eastern cooperative oncology group; DLBCL: Diffuse large B-cell lymphoma; BL: Burkitt lymphoma; ITCL: Intestinal T-cell lymphoma; NKTCL: Natural killer/T-cell lymphoma; N-GCB: Non-germinal center B cells; CD: Cluster of differentiation; Ki: Kiel proliferation index.

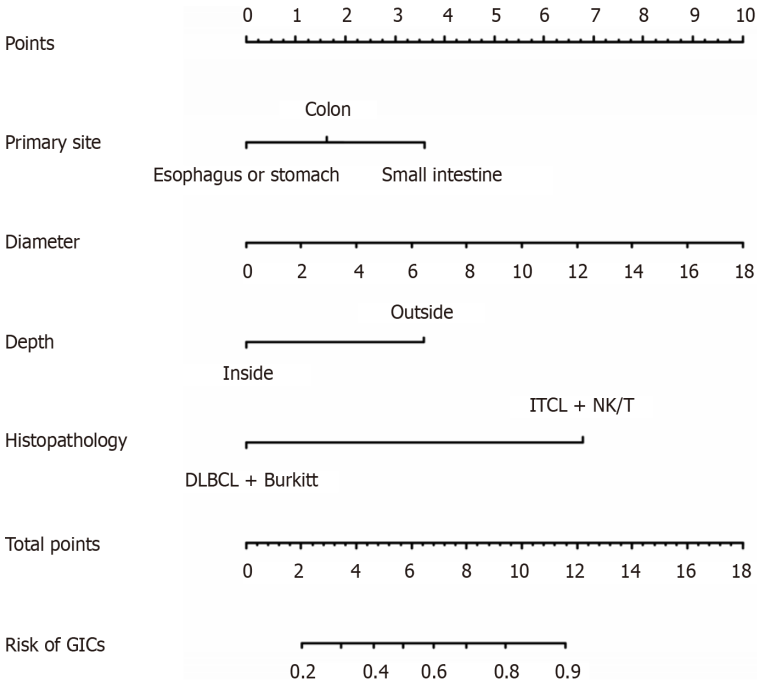


**Figure 2 Nomogram for predicting the risk of gastrointestinal complications in aggressive gastrointestinal non-Hodgkin lymphoma.** GICs: Gastrointestinal complications; ITCL: Intestinal T-cell lymphoma; NK: Nature killer; DLBCL: Diffuse large B-cell lymphoma.

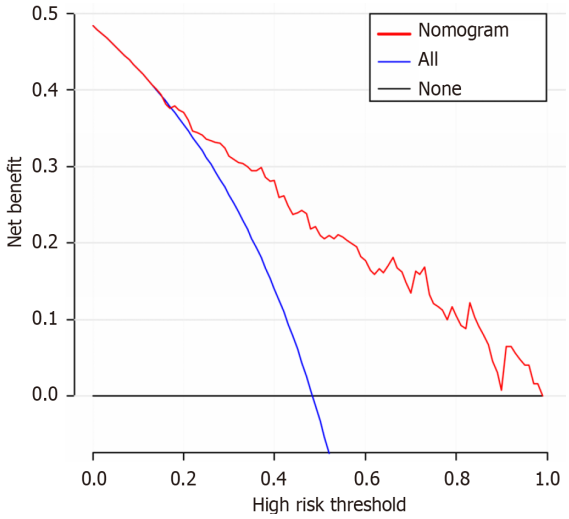


**Figure 3 Decision curves analysis for the risk nomogram of gastrointestinal complications in aggressive gastrointestinal non-Hodgkin lymphoma.**

## DISCUSSION

Primary gastrointestinal lymphoma can occur in any part of the digestive tract, most commonly in the stomach, followed by the small intestine, colon and rectum, rarely in the esophagus[25,26]. The most common pathological type of PGINHL was DLBCL, followed by MALT, MCL, rare types included ITCL, BL, NKTCL, *etc.*[27]. More attention should be paid to aggressive gastrointestinal lymphomas such as DLBCL, BL, ITCL, and NKTCL. Owing to the rapid progression of the aggressive lymphomas, the enlargement and invasive characteristics of the mass were easy to cause GICs, the management of GICs remained a clinical challenge[22]. In our study of aggressive gastrointestinal lymphoma cohort, GICs occurred in 48.4% of patients. The most common histological type in GICs group was DLBCL (81.7%). The most

**Table 2 Univariate and multivariate analyses of factors associated with gastrointestinal complications in aggressive Primary gastrointestinal non-Hodgkin lymphomas patients**

| Characteristics | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Age | | | | |
| ≥ 60 | 1.21 (0.60-2.45) | 0.597 | | |
| < 60 | Ref. | - | | |
| Gender | | | | |
| Male | 1.48 (0.72-3.03) | 0.289 | | |
| Female | Ref. | - | | |
| Primary site | | | | |
| Esophagus or stomach | Ref. | - | Ref. | |
| Small intestine | 6.55 (2.61-16.40) | < 0.001 | 3.33 (1.47-9.41) | 0.009 |
| Colon | 5.60 (2.15-14.61) | < 0.001 | 2.50 (1.17-7.15) | 0.023 |
| Histopathology | | | | |
| DLBCL + BL | 0.08 (0.01-0.63) | 0.017 | 0.09 (0.01-0.83) | 0.033 |
| ITCL + NK/T | Ref. | - | Ref. | - |
| Max tumor diameter | 1.30 (1.13-1.48) | < 0.001 | 1.25 (1.07-1.47) | 0.005 |
| Invasive depth | | | | |
| Inside serous membrane | Ref. | - | Ref. | |
| Serosal layer and outside | 6.55 (2.67-16.06) | < 0.001 | 3.38 (1.24-9.19) | 0.017 |
| LDH | | | | |
| Elevated | 0.67 (0.33-1.40) | 0.287 | | |
| Normal | Ref. | - | | |
| Virus | | | | |
| Yes | 0.70 (0.23-2.14) | 0.529 | | |
| No | Ref. | - | | |
| Stage | | | | |
| I/II | Ref. | - | | |
| III/IV | 0.82 (0.40-1.66) | 0.581 | | |
| ECOG | | | | |
| 0-1 | Ref. | - | Ref. | - |
| ≥ 2 | 3.35 (1.02-11.05) | 0.047 | 1.02 (0.24-4.39) | 0.974 |
| N-GCB | 0.62 (0.29-1.31) | 0.207 | | |
| CD5 + | 0.46 (0.17-1.25) | 0.128 | | |
| CD30 + | 1.40 (0.42-4.68) | 0.584 | | |
| Double expression | | | | |
| Yes | 0.40 (0.16-0.97) | 0.044 | 0.51 (0.17-1.52) | 0.227 |
| No | Ref. | - | Ref. | - |
| Ki 67 ≥ 70% | | | | |
| Yes | 1.13 (0.54-2.25) | 0.747 | | |
| No | Ref. | - | | |
| Macroscopic findings | | | | |

| | | |
|---|---|---|
| Neoplasm | 0.59 (0.12-2.88) | 0.515 |
| Ulceration | 0.69 (0.33-1.42) | 0.311 |
| Others | Ref. | - |
| Imaging findings | | |
| Neoplasticlesions | 0.49 (0.21-1.17) | 0.109 |
| Others | Ref. | - |

LDH: Lactate dehydrogenase, ECOG: Eastern cooperative oncology group; DLBCL: Diffuse large B-cell lymphoma; BL: Burkitt lymphoma; ITCL: Intestinal T-cell lymphoma; NKTCL: Natural killer/T-cell lymphoma; N-GCB: Non-germinal center B cells; CD: Cluster of differentiation; Ki: Kiel proliferation index; CI: Confidence interval; NK: Nature killer.

**Table 3 Treatments and outcomes of patients in the No-gastrointestinal complications *vs* gastrointestinal complications groups of aggressive primary gastrointestinal non-Hodgkin lymphomas**

| Characteristics | No-GICs (*n* = 64) | GICs (*n* = 60) | *P* value |
|---|---|---|---|
| Chemotherapy, *n* (%) | | | 0.000 |
| No | 3 (4.7) | 17 (28.3) | |
| Yes | 61 (95.3) | 43 (71.7) | |
| Radiotherapy, *n* (%) | | | 0.022 |
| No | 49 (76.6) | 55 (91.7) | |
| Yes | 15 (23.4) | 5 (8.3) | |
| Surgery, *n* (%) | | | 0.000 |
| No | 61 (95.3) | 5 (11.7) | |
| Yes | 3 (4.7) | 53 (88.3) | |
| Treatment, *n* (%) | | | |
| Without CT | 3 (4.7) | 17 (28.3) | 0.000 |
| CT alone | 43 (67.2) | 4 (6.7) | |
| CT + Sur/RT | 18 (28.1) | 39 (65.0) | |
| EFS time, M (IQR) | 21.0 (11.0, 36.0) | 17.0 (5.5, 36.0) | 0.580 |
| OS time, M (IQR) | 28.5 (14.5, 45.0) | 24.5 (6.5, 47.5) | 0.335 |
| Death toll, *n* (%) | 20 (31.3) | 26 (43.3) | 0.164 |

GICs: Gastrointestinal complications; CT: Chemotherapy; RT: Radiotherapy; Sur: Surgery; EFS: Event-free survival; OS: Overall survival; IQR: Interquartile range.

common anatomical site in the GICs group was the small intestine (43.3%). Some studies suggested that primary small intestinal DLBCL was indeed more likely to develop intestinal obstruction or perforation[28]. In our GICs group, bulky lymphoma accounted for a relatively high proportion, the maximum tumor diameter in this group was approximately 7.03 cm ± 3.7 cm, which was also a factor that leaded to more GIO in this group. In our study, GICs occurred in 11 cases (91.7%) of 12 patients with PGI-TNKL, while 49 patients (43.8%) of the 112 patients with PGI-B cell lymphoma developed GICs, which including 36 cases of GIO, 9 cases of GIP, 12 cases of GIB, and 3 cases of GIP and GIB. ITCL was more prone to perforation than intestinal B-cell lymphoma[14,29].

Multivariate Logistic regression analysis showed that the four independent risk factors for GICs were the primary site of small intestine, pathological type PGI-NKTL, large tumor diameter, invasion of the serosal layer and beyond. First, regarding the discussion of the most common primary site, a study suggested that the small intestine was the most common site, accounting for 59%[22]. In the single-center study on intestinal lymphoma complicated with perforation, 55% (51/92) of the cases occurred after chemotherapy[30]. Most patients had GIO before chemotherapy, accounting for 60% (36/60), and there were 20% (12/60) cases with intestinal perforation before or after chemotherapy. In our study, the highest occurrence site of GICs was also in the small intestine, accounting for 43.3%. The decrease in perforation rate in our study may be related to our early surgical intervention. Second, regarding the most common histopathological types, a study suggested that aggressive B-cell lymphoma had a higher risk of perforation than indolent B-cell lymphoma, particularly DLBCL[22]. In addition, although the incidence of enteric T-cell lymphoma was lower, GIP was higher in

**Table 4 Univariate and multivariate analyses of factors associated with overall survival in aggressive primary gastrointestinal non-Hodgkin lymphoma patients with gastrointestinal complications**

| Characteristics | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95%CI) | *P* value | HR (95%CI) | *P* value |
| Age | | | | |
| ≥ 60 | 1.29 (0.58-2.84) | 0.535 | | |
| < 60 | Ref. | - | | |
| Gender | | | | |
| Male | 1.83 (0.77-4.36) | 0.174 | | |
| Female | Ref. | - | | |
| Primary site | | | | |
| Esophagus or stomach | Ref. | - | | |
| Small intestine | 1.53 (0.55-4.31) | 0.417 | | |
| Colon | 1.25 (0.41-3.82) | 0.697 | | |
| Histopathology | | | | |
| ITCL + NKTCL | 5.58 (2.40-13.00) | < 0.001 | 8.75 (2.87-26.71) | < 0.001 |
| DLBCL + BL | Ref. | - | Ref. | - |
| Max tumor diameter | 1.03 (0.93-1.14) | 0.598 | | |
| Invasive depth | | | | |
| Inside serous membrane | Ref. | - | | |
| Serosal layer and outside | 1.15 (0.53-2.49) | 0.728 | | |
| LDH | | | | |
| Elevated | 3.33 (1.51-7.33) | 0.003 | 3.90 (1.50-10.12) | 0.005 |
| Normal | Ref. | - | Ref. | - |
| Virus | | | | |
| Yes | 2.13 (0.73-6.23) | 0.169 | | |
| No | Ref. | - | | |
| Stage | | | | |
| I/II | Ref. | - | Ref. | - |
| III/IV | 6.29 (2.35-16.82) | < 0.001 | 5.49 (1.58-19.09) | 0.007 |
| ECOG | | | | |
| 0-1 | Ref. | - | Ref. | - |
| ≥ 2 | 13.40 (5.39-33.35) | < 0.001 | 24.14 (6.28-92.70) | < 0.001 |
| N-GCB | 0.28 (0.09-0.94) | 0.040 | | |
| CD5 + | 1.47 (0.51-4.28) | 0.479 | | |
| CD30 + | 1.58 (0.57-4.92) | 0.347 | | |
| Double expression | | | | |
| Yes | 1.55 (0.58-4.12) | 0.380 | | |
| No | Ref. | - | | |
| KI 67 ≥ 70% | | | | |
| Yes | 0.95 (0.42-2.12) | 0.891 | | |
| No | Ref. | - | | |
| Treatment | | | | |

| | | | | |
|---|---|---|---|---|
| Without CT | Ref. | - | Ref. | - |
| CT alone | 0.85 (0.24-2.97) | 0.800 | 1.82 (0.44-7.50) | 0.407 |
| CT + Sur/RT | 0.07 (0.03-0.19) | < 0.001 | 0.07 (0.02-0.24) | < 0.001 |

LDH: Lactate dehydrogenase, ECOG: Eastern cooperative oncology group; DLBCL: Diffuse large B-cell lymphoma; BL: Burkitt lymphoma; ITCL: Intestinal T-cell lymphoma; NKTCL: Natural killer/T-cell lymphoma; N-GCB: Non-germinal center B cells; CD: Cluster of differentiation; Ki: Kiel proliferation index; CI: Confidence interval; NK: Nature killer; CT: Chemotherapy; RT: Radiotherapy; Sur: Surgery; HR: Hazard ratio.

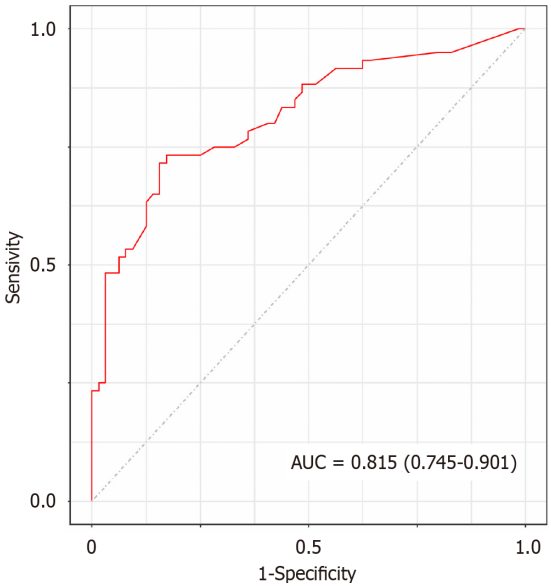


**Figure 4 The predictive performance of the risk nomogram for predicting gastrointestinal complications in aggressive gastrointestinal non-Hodgkin lymphoma.** Receiver operating characteristic curves displayed that this nomogram discriminated well. AUC: Area under the curve.

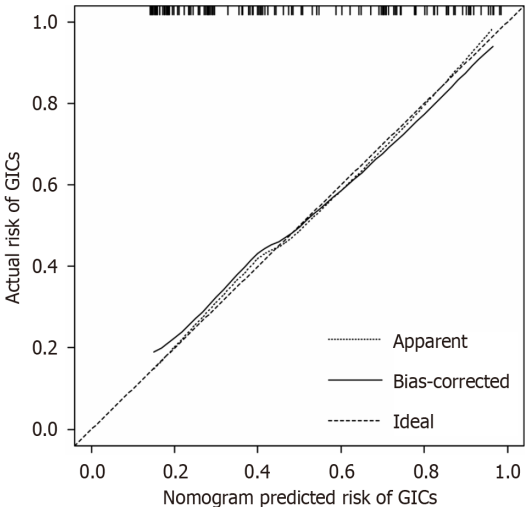


**Figure 5 The calibration curve of risk nomogram of gastrointestinal complications in aggressive gastrointestinal non-Hodgkin lymphoma.** GICs: Gastrointestinal complications.

aggressive T-cell lymphoma[31]. In our study, the most common histological type of GICs group was DLBCL (81.7%), followed by ITCL (16.7%), and NKTCL (1.6%). However, GICs occurred in 11 of the 12 patients with PGI-TNKL, especially intestinal perforation, required emergency surgery. At the end of our follow-up, only one patient in PGI-TNKL survived, and the others died within a year.

Third, the depth of tumor invasion of the tube wall was related to the occurrence of GICs. Studies have suggested that patients with gastrointestinal cancer were prone to perforation once the tumor encroached on the serosal layer[32]. Microscopic findings showed that alterations in gastrointestinal lymphoma began in the submucosal layer where they

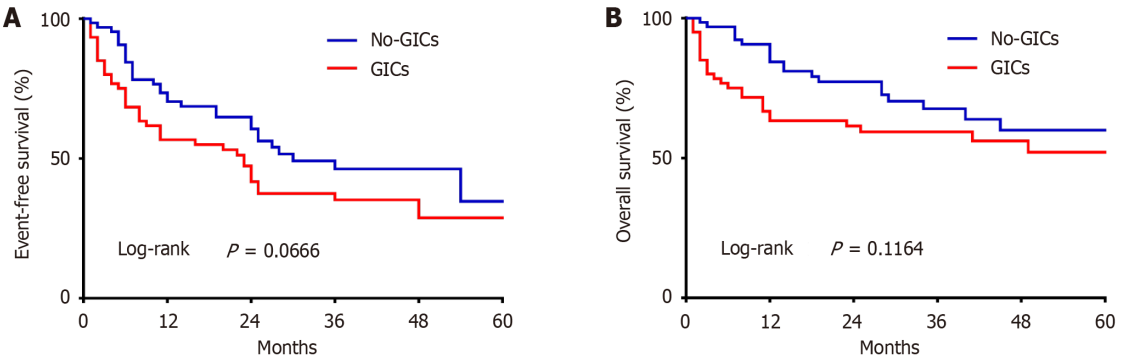


**Figure 6 Survival analysis of the gastrointestinal complications and No-gastrointestinal complications groups in primary gastrointestinal non-Hodgkin lymphomas.** A: Event-free survival curves for the comparison between gastrointestinal complications (GICs) and No-GICs group; B: Overall survival curves for the comparison between GICs and No-GICs group ($P > 0.05$). GICs: Gastrointestinal complications.

were most extensive, rarely spread to the muscular layer, and serosal layer[33]. Fourth, regarding the correlation between the maximum tumor diameter and the risk of GICs, the main reason was digestive tract obstruction caused by bulky mass. In a retrospective study of DLBCL, patients with tumor mass ≥ 10 cm, or intestinal involvement had significantly higher risk of severe GICs as initial manifestations[7].

Summarizing our study and previous clinical studies, these four factors did have GICs correlation, and we developed a nomogram to predict risk of GICs in aggressive PGINHL patients based on independent risk factors. The higher the total scores of the corresponding nomogram, the greater the risk of GICs. The high risk of GICs suggested that clinicians needed to take emergency measures such as surgical intervention and postponing chemotherapy. DCA mapping showed that our predictive model provided better clinical benefits. The ROC and calibration curves for the GICs probability exhibited an optimal agreement. Currently, there were no predictive GICs risk models for aggressive intestinal lymphoma. A small sample study proposed a risk scoring system that included indolent PGI lymphoma patients to predict severe GICs events, patients with high scores were candidates for elective surgery to prevent GIC events[34]. Our predictive GICs risk nomogram covered a more susceptible population than the few previously reported, with a relatively many predictors. Regarding prognostic markers for large B-cell lymphoma (Double expression, CD5, no-GCB), these markers did not hold up in multivariate analyses in this study population and it may be worthwhile to look specifically at their role in patients with large B-cell lymphoma. The limitation of this study was that there was a certain bias in the study data because it was retrospective. Also, it was the absence of external validation. In the future, multi-center and prospective studies are needed to verify and improve these results.

Unlike the patients with nodal or other primary extra nodal lymphomas, PGINHL patients with GICs required immediate intervention. because GICs were life-threatening acute abdomens such as GIO, GIB, and GIP. In particular, the perforation rate of small intestine was more than 50%, and the mortality rate was high[30]. How to adjust the treatments of those patients? Priority surgery, delayed surgery, or reduced-dose chemotherapy? In the GICs cohort we studied emergency surgery was performed, accounting for 88.3%. In the No-GICs group, three patients underwent surgery because the tumors were not detected by endoscopy but highly suspected by imaging. The majority of patients with GICs were given combination therapy. Due to identification of emergency and timely treatment of GICs, local surgery can prevent spontaneous perforation and/or bleeding during chemotherapy or radiotherapy and provide opportunities for subsequent systemic treatment. Patients with good recovery after total resection were treated with immunochemo-therapy. Adjuvant radiotherapy was given to bulky patients who could not be totally resected. For inoperable patients, attention should be paid to the initial chemotherapy starting from a low dose and gradually increasing to a standard dose. The tumor regression should be closely observed. Lymphoma was sensitive to immunochemotherapy and retreated rapidly; and normal tissue could not be repaired because of bulky or deep invasion lesions in the gastrointestinal tract. Thus, GICs caused by tumor regression after high-dose chemotherapy should be avoided as much as possible. Even if they undergo emergency surgery, faced severe myelosuppression after chemotherapy and had a poor prognosis. Therefore, we need to summarize the characteristics of patients with aggressive PGINHL and expand the sample size to avoid small sample bias.

Our survival analysis in GICs group, suggested that histopathology, LDH, stage, ECOG, chemotherapy combined with surgery or radiotherapy were independent factor. It had been reported that high LDH, advanced stage, and high ECOG in the international prognostic index scoring system were associated with poor OS of NHL[35,36]. In our study, ten cases of PGI-TNKL died of intestinal perforation and bleeding, the prognosis were poor. A multi-center prospective study in Asia suggested that PGI-TNKL showed aggressive behavior and poor OS[37]. Aggressive clinicopathological features of PGI-TNKL were different from indolent T-cell lymphoproliferative disorder[4]. Microscopic examination showed a diffuse transmural lymphoid infiltrate with accompanying mucosal ulceration[38]. Therefore, both clinicians and pathologists must be aware of the distinct characteristics of these lesions to ensure that appropriate care was provided. In our study, combination therapy did improve survival of the patients with GICs, EFS and OS were close to those in the No-GICs group. However, Surgery was controversial in GI lymphoma[39-41], we should grasp the surgical indications and avoid meaningless invasive surgery in low-risk populations.

## CONCLUSION

The complication rate of GICs in patients with aggressive PGINHL was relatively high, especially in those with PGI-DLBCL. The independent risk factors for GICs were the small intestine, PGI-TNKL, bulky tumor, and depth of invasion. A preliminary risk model for predicting GICs was established. We analyzed therapeutic interventions for patients with a high incidence of GICs. Comprehensive treatment including surgery improved the OS of patients with GICs. We hope to further validate the nomogram with larger samples in the future.

## FOOTNOTES

**Author contributions:** Liu XH and Liu H designed the study and interpreted the data; Chen G, Ke XK, Ke D, Tan W and Cao DD contributed to the acquisition of the clinical samples and data; Hu YG, Cao DD, Liu XH and Xu XM performed the analytic calculations and wrote the manuscript; All authors have read and approved the final manuscript.

**Institutional review board statement:** The study was approved by the Medical Ethics Committee of Renmin Hospital of Wuhan University, No. WDRY2021-KS024.

**Informed consent statement:** Patient consent was waived by the IRB because all patient data was de-identified.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Data sharing statement:** Pathology data and the statistical analyses for the current study are available from the corresponding author upon reasonable request.



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**S-Editor:** Fan M
**L-Editor:** A
**P-Editor:** Zhao S

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