

Research Article

Primary Non-Hodgkin's Lymphoma of Stomach: To Report 54 Patients and Analysis of Major Reported Series

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Introduction. This study aimed to report the characteristics, prognostic factors, and treatment outcomes of 54 patients with primary gastric lymphoma. **Materials and Methods.** This retrospective study was carried out by reviewing the medical records of 54 adult patients diagnosed at a tertiary academic hospital. All the patients were treated with curative intent. Forty-four patients (81.5%) underwent gastrectomy followed by adjuvant chemotherapy and/or radiotherapy, whereas 10 ones (18.5%) were treated with chemotherapy alone or with radiotherapy. **Results.** The study was conducted on 25 males and 29 females with the median age of 50 years. Diffuse large B-cell lymphoma (DLCL) (67%) and Mucosa Associated Lymphoid Tissue (MALT) lymphoma (26%) were the most common histologic types. Besides, 36 (59%), 16 (30%), 5 (9%), and 1 (2%) patients were in stages I, II, III, and IV, respectively. The 5-year disease-free survival and overall survival were 64.7% and 67%, respectively. In univariate analysis for overall survival, International Prognostic Index (IPI) ($P < 0.001$), the WHO performance status ($P < 0.001$), Ann Arbor stage ($P = 0.027$), age ($P = 0.034$), and LDH serum level ($P < 0.001$) were the prognostic factors. **Conclusion.** Gastric lymphoma tends to present in early stage of the disease and has a favorable outcome.

1. Introduction

Primary gastric lymphomas are rare. Although their incidence rate is increasing, they comprise less than 10% of gastric malignancies. Despite this rarity, stomach accounts for more than two-third of all extranodal non-Hodgkin lymphomas. Because of its multiple subtypes and low prevalence, its treatment is not so clear cut. More than 30 types, with different biological and clinical characteristics, have been recognized by the WHO classification. Two main subtypes are MALT and DLCL with different behaviors and treatments. Other less frequent subtypes are follicular, mantle, and T-cell lymphoma [1–3].

Previously, the main treatment for gastric lymphomas was supposed to be surgery. Older studies pointed to

the important role of surgery in treatment of the disorder [2, 4]. However, multiple retrospective and prospective studies in late 20th century showed that extend of surgery and even performing the surgery had no roles in gastric lymphoma outcome [2, 3]. Early stage MALT lymphomas are usually treated with antibiotics. Those who are negative for or resistant to *H. pylori* are treated with radiotherapy. Chemotherapy is also an effective therapeutic option. On the other hand, gastric DLCL is treated by chemotherapy and immunotherapy. Radiotherapy could be used for localized cases. Yet, chemotherapy accompanied by cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) is the most prevalent regimen with acceptable toxicity. There is still no standard treatment and the general trend is toward less aggressive and more conservative modalities [3, 4, 30, 37, 40].

TABLE 1: Distribution of treatment schedules and histopathologic types in 54 patients with primary gastric lymphoma.

Treatment	Histopathology					Total
	DLBCL	MALT lymphoma	Follicular lymphoma	T-cell lymphoma	Mantel cell lymphoma	
Sur → RT	0	2	0	0	0	2
Sur → RT → ChT	3	2	0	0	0	5
Sur → ChT → RT	19	6	1	0	1	27
Sur → ChT → RT → ChT	1	1	0	0	0	2
Sur → ChT	5	1	0	2	0	8
ChT → RT	6	1	0	0	0	7
ChT → RT → ChT	1	1	0	0	0	2
ChT alone	1	0	0	0	0	1
Total	36	14	1	2	1	54

DLBCL: diffuse large B-cell lymphoma; Sur: surgery; RT: radiotherapy; ChT: chemotherapy.

In this study, all the patients were referred to us from surgery, gastroenterology, or hematology oncology wards, and we had no access to prior treatments, such as antibiotic therapy.

In general, the prognosis depends on multiple factors, such as patient's age and performance status, histologic subtype, treatment, lactate dehydrogenase (LDH) serum levels, and disease related factors [1, 5]. This study aims to report the characteristics, prognostic factors, and treatment outcomes of 54 patients with primary gastric lymphoma and analyze the major reported series.

2. Materials and Methods

The present retrospective study was conducted on the patients with gastric lymphoma in our referral radiotherapy center between 1998 and 2010. All the patients had presented with gastrointestinal complaint, and lymphoma diagnosis was made by endoscopy biopsy first. The patients' demographic characteristic, disease factors (size, location, histology, etc.), performance status, treatment (operation, radiotherapy/chemotherapy technique, and dose), and outcome (disease-free survival and overall survival) were obtained from their records and by phone if needed. We searched "PubMed" using "gastric and lymphoma" or "stomach and lymphoma" to find the related papers.

2.1. Patients' and Disease Characteristics. This study was conducted on 54 cases with biopsy proven diagnosis of primary gastric NHL who had been treated and followed up at our ward during 1998 to 2010. The performance status (PS) was determined according to the World Health Organization (WHO) scale. Only the patients who had initially presented with gastric lymphoma were classified as gastric lymphoma, and those with secondary gastric involvement with lymphoma were excluded from the study. The patients were staged according to the Ann Arbor staging system at the time of diagnosis. All the patients had undergone endoscopy and location of tumor was mentioned at reports. However, no information was available regarding *H. pylori* status and previous treatment if performed. Tumor sizes were registered in the operation notes or imaging, pathology, or endoscopy reports. Tumors with above 5 cm maximum diameter were

defined as bulky disease. The location of the tumor at the stomach and diffuse gastric involvement were also determined.

2.2. Clinical Investigation. Clinical investigation included history, physical examination, complete blood count, erythrocyte sedimentation rate, kidney function test, liver function test, serum LDH, abdomen and pelvic ultrasonography, Computed Tomography (CT) scan, chest X ray, bone marrow aspiration, and biopsy.

2.3. Treatment. All the patients were treated with curative intent. Overall, 44 patients (81.5%) had undergone gastrectomy followed by adjuvant chemotherapy and/or radiotherapy, whereas 10 ones (18.5%) had been treated with chemotherapy alone or with radiotherapy (see Table 1). In all the patients, chemotherapy included CHOP regimen (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², prednisolone 100 mg). It should be mentioned that none of our patients, even those in the later period of the study, received rituximab. Radiotherapy consisted of external beam conventional technique with megavoltage linear accelerator or Cobalt-60 photons, and a median total dose of 31 (range 9–54) Gy was delivered.

2.4. Statistical Analysis. Disease- or progression-free survival was calculated as the duration from the date of histological diagnosis to the date of relapse or disease progression or censored at the date of the last followup. In addition, OS was calculated as the duration from the date of histological diagnosis to the date of death resulting from any cause or censored at the date of the last followup. Univariate analysis for DFS and OS rates were performed using the Kaplan–Meier method and the prognostic factors were compared using the log-rank test. Besides, multiple-covariate analysis was performed using the stepwise regression hazards regression model. The Hazard Ratio (HR) for death, with the 95% Confidence Interval (CI), was calculated for the variable groups. The stratified log-rank test was used to compare the treatment results in each variable group. A *P* value of 0.05 or less was considered as statistically significant.

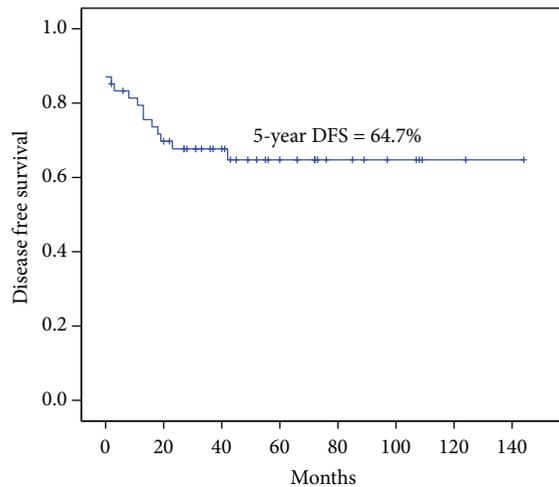


FIGURE 1

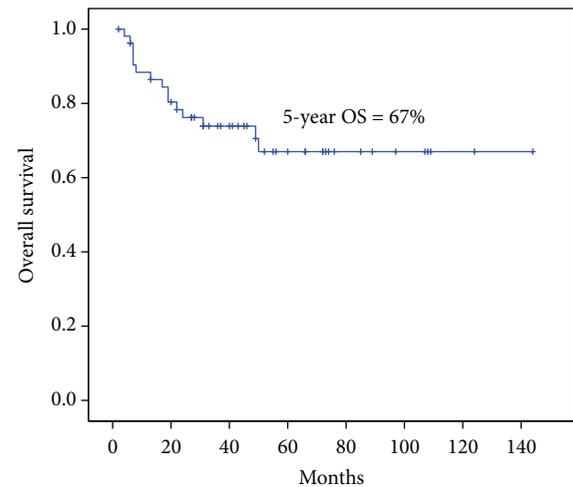


FIGURE 2

3. Results

3.1. Patients and Clinical Characteristics. A total of 54 patients with primary gastric lymphoma were reviewed. The patients' median age was 50 (17–75) years, and 28 patients (51%) were 50 years old or younger. Besides, the peak age was during the sixth decade of life in both sexes. The WHO performance status was 0 or 1 in approximately 83% of the patients, while 2 or 3 in 13%. Epigastric pain and discomfort (83%), anorexia and weight loss (41%), and postprandial vomiting (28%) were the most common presenting signs and symptoms. B symptoms occurred in 33% of the patients. In addition, bulky disease (primary tumor size more than 10 cm in the greatest diameter) was documented in 20 patients (37%). According to the pathologic, imaging, and clinical findings, 36 (59%), 16 (30%), 5 (9%), and 1 (2%) patients were in stages I, II, III, and IV, respectively. Diffuse large B-cell lymphoma (67%) and Mucosa Associated Lymphoid Tissue (MALT) lymphoma (26%) were the most common histological types. Table 1 represents the distribution of the treatment schedules and histopathological subtypes. Most patients, including 19 patients with DLCL and 6 ones with MALT lymphoma, were treated with surgery and followed by chemotherapy and radiotherapy. Most patients were referred to us from gastrointestinal ward or hematology ward, and we had no information on prior antibiotic treatment if it has been done. The total 5-year disease-free survival and overall survival were 64.7% and 67%, respectively (Figures 1 and 2).

3.2. Prognostic Factors. All the potential prognostic variables, including the WHO performance status, age, sex, Ann Arbor stage of disease, primary tumor size and location, B symptoms, histologic grade, serum LDH level, treatment modality, dose of radiation, and International Prognostic Index (IPI), were analyzed to find out their impacts on disease-free survival and overall survival of the patients with gastric lymphoma (Table 2). A modified IPI including four prognostic factors (performance status, age, stage, and serum LDH level) was considered in this study. In univariate analysis for

overall survival in all patients, IPI ($P < 0.001$), WHO performance status ($P < 0.001$), Ann Arbor stage ($P = 0.027$), age ($P = 0.034$), and LDH serum level ($P < 0.001$) were the prognostic factors (Table 2). These factors were also separately analyzed in DLCL and MALT lymphoma by stratified log-rank test (Table 3). However, in multivariate analysis using the stepwise logistic regression model, only modified IPI ($P = 0.001$, HR = 7.53, and 95% CI = 1.619–35.065) and the WHO performance status ($P = 0.01$, HR = 3.00, and 95% CI = 1.599–5.630) were independent prognostic factors for overall survival.

4. Discussion

This retrospective study has been conducted at the Nemazee hospital, the referral center in south of Iran. This study is the first report on GL in Iran. In this study multiple factors, including gender, age, grade, surgery, and LDH level (Table 4), have been proposed as prognostic factors. Some of these prognostic factors are disease related and some are patient related. Some authors believe that prognostic factors are more important than the treatment schedule for survival [5].

Mean age in our study was 50 (17–75) years. As seen in Table 5, other studies showed similar results. Although in some studies age was a prognostic factor, we found no relation between it and outcome [6–8]. Most of our patients were females. Results in other studies are inhomogenous. Although it was a prognostic factor in 1 study, others including the present study revealed no relation [7].

Extranodal lymphoma consists of 25–40% of all lymphomas. The most common location for extranodal lymphoma is the gastrointestinal tract which consists of 30–40% of the extranodal lymphoma [2, 37]. Gastric Lymphoma (GL) consists of 1–7% of stomach malignancies and is an older population disease [1, 3]. Primary GL is not so common, but the stomach is the most common site for extranodal lymphoma, and its incidence is increasing [3, 6, 37].

TABLE 2: Univariate analysis of prognostic factors for clinical outcome.

Prognostic factors	Patients' number	5-year DFS (%)	P value	5-year OS (%)	P value
WHO performance score					
0-1	45	73.9		76.2	
2	5	00.0	<0.001	00.0	<0.001
3	4	00.0		00.0	
Sex					
Female	29	61.8	0.742	66.8	0.923
Male	25	68.1		67.3	
Age					
≤50 years	28	73.9	0.097	79.6	0.034
>50 years	26	55.2		49.1	
Ann Arbor stage					
I	33	73.2		75.1	
II	15	59.5	0.071	70.1	0.027
III	5	40.0		25.0	
IV	1	00.0		00.0	
Histology					
DLBC	36	61.2		59.5	
MALT	14	71.4	0.645	77.9	0.405
Others	4	100.0		100.0	
Primary tumor size					
1-5 cm	13	61.5		75.0	
6-9 cm	21	72.8	0.412	75.9	0.182
≥10 cm	20	58.9		50.5	
B symptoms					
No	36	78.8	0.001	77.8	0.013
Yes	18	36.4		40.6	
Serum LDH level					
Normal	34	93.1	<0.001	92.6	<0.001
Elevated	20	28.7		34.0	
Histological grade					
I	27	64.0		66.4	
II	13	69.2	0.977	76.2	0.951
III	14	64.3		61.9	
Treatment modality					
Surgery + CT ± RT	44	61.5	0.387	64.7	0.606
CT and/or RT	10	80.0		80.0	
Radiation dose					
No RT	7	34.3		41.7	
<30 Gy	11	61.4	0.236	47.7	0.169
30-40 Gy	26	75.4		80.7	
>40 Gy	10	60.0		60.0	
IPI					
0-1 risk factor	35	84.4		89.2	
2 risk factor	6	33.3	<0.001	25.0	<0.001
≥3 risk factor	13	16.2		13.6	
Location					
Proximal	27	67.3		72.1	
Distal	24	61.4	0.791	61.7	0.623
Diffuse involvement	3	66.7		66.7	
All patients	54	64.7		67.0	—

DFS: disease-free survival; OS: overall survival; CT: chemotherapy; RT: radiotherapy; IPI: International Prognostic Index.

TABLE 3: The stratified log-rank test analysis of prognostic factors for histologic subtypes.

Prognostic factors	Patients' number	5-year OS (%)		P value
		DLBC	MALT	
WHO performance score				
0-1	45	67.0	90.9	<0.001
2	5	00.0	00.0	
3	4	00.0	50.0	
Sex				
Female	29	59.8	72.9	0.985
Male	25	58.6	83.3	
Age				
≤50 years	28	74.9	88.9	0.021
>50 years	26	36.2	60.0	
Ann Arbor stage				
I	33	64.7	90.0	0.039
II	15	73.3	50.0	
III-IV	6	00.0	50.0	
Primary tumor size				
1-5 cm	13	57.1	—	0.107
6-9 cm	21	72.1	—	
≥10 cm	20	63.6	57.1	
B symptoms				
No	36	73.2	81.8	0.025
Yes	18	35.4	66.7	
Serum LDH level				
Normal	34	94.7	87.5	<0.001
Elevated	20	21.4	66.7	
Treatment modality				
Surgery + CT ± RT	44	53.8	82.5	0.502
CT and/or RT	10	87.5	50.0	
IPI				
0-1 risk factor	35	87.0	90.9	<0.001
2 risk factor	6	20.0	—	
≥3 risk factor	13	00.0	33.3	
All patients	54	59.5	77.9	0.405

DFS: disease-free survival; OS: overall survival; CT: chemotherapy; RT: radiotherapy; IPI: International Prognostic Index.

In general, GL more frequently involves antrum, corpus, and cardia [3]. In our study, most of the patients (50%) had primary lesion in the proximal half and tumor location was not related to the outcome. Most of lesions in our study were larger than 5 cm. Tumor sizes were not associated with better or worse outcomes, but Economopoulos showed that there may be a relation [9]. Staging in our study was performed according to the Ann Arbor system. Most of our cases were in stages I and II (65% and 28%, resp.), and only 1 patient was in stage IV. As shown in Table 4 stage was a significant prognostic factor in multiple studies [8, 10–14]. But we found a relation in univariate analysis not in multivariate analysis.

Rise in LDH level, BM involvement, and B symptoms are less frequent in GL [34, 37]. In our series, 34 patients had normal LDH levels and their 5-year disease-free survival and overall survival were significantly improved (P value < 0.001). Although some studies have shown no relationships between

LDH level and survival, abnormally elevated LDH level was a prognostic factor in our study [5, 11, 15, 16, 35].

IPI consists of some prognostic factors, such as age > 60 years, stage > II2, high LDH level, ECOG PS > 2, and more than one Extranodal Site (EN) of disease. Our study results indicated a significant relationship between IPI and survival. IPI has been proposed as the strongest prognostic factor [15, 38]; however, some studies have reported this factor not to have any effects on survival [7, 35].

The most common subtype in our study was DLCL followed by MALT. T-cell, mantle, and follicular lymphomas totally were detected in 4 cases. Survivals in different subtypes were not statistically different. Up to now, over 30 subtypes of GL with various prognoses have been recognized by the WHO classification, and the disease treatment is guided by the subtype [1, 3]. Different studies have reported MALT and DLCL as the most common types [2, 17, 39]. In our study as

TABLE 4: Survival rates and prognostic factors in patients with primary gastric lymphoma in the literature.

Author [ref]	Patients' number	5-year DFS (%)	3-year OS (%)	5-year OS (%)	Prognostic factor
Medina-Franco et al. [5]	41	52.5	—	71.2	LDH serum level, PS
Danzon et al. [6]	361	—	63	61	Age
Park et al. [7]	214	—	—	—	Age, LDH serum level, gender, ascites
Bani-Hani et al. [8]	19	—	—	48.2	Age, stage
Economopoulos et al. [9]	29	—	—	58	Stage, size
Tanaka et al. [10]	95	—	81.7	—	Stage, LDH serum level
Huang et al. [11]	83	52	—	59	PS, stage, modified IPI
Muller et al. [12]	45	—	—	40	Grade, stage
Mäkelä et al. [13]	32	—	—	56	Stage, radical surgery, age
Xue et al. [14]	83	—	—	77.8	Lymph node involvement and clinical stage
Brincker and D'Amore [15]	106	—	—	67	LDH serum level, fever
Luo et al. [16]	68	75.7	78.2	75.7	Surgery
Barreda et al. [17]	169	—	61.34	—	IPI, HDL, remission, treatment, location
Durr et al. [18]	35	90	—	—	Grade
Shaw et al. [19]	62	—	—	—	Weight loss, invasion of adjacent organs, nonsurgical treatment
Al-Bahrani et al. [20]	32	—	—	—	Stage, resectability
Salvagno et al. [21]	525	—	—	65.4	Surgery
Jaser et al. [22]	66	—	—	—	Stage
Present study	54	64.7	—	67	IPI, LDH serum level

TABLE 5: Characteristics of some major reported series of primary gastric lymphoma in the literature.

Author [ref]	Country	Year	Patients' number	Median age (range)	Male/female ratio	Most frequent histological type
Medina-Franco et al. [5]	Mexico	1990–2000	41	52.6	0.86	Large cell lymphoma
Danzon et al. [6]	France	1989–1997	361	—	1.24	High grade
Park et al. [7]	Republic of Korea	1990–2004	214	55 (21–81)	1.27	Only high grade
Bani-Hani et al. [8]	Jordan	1991–2002	19	—	—	DLCL
Economopoulos et al. [9]	Greece	1977–1983	29	55 (21–74)	2.2	Diffuse histiocytic
Huang et al. [11]	China	2001–2008	83	52 (15–81)	1.18	DLCL
Muller et al. [12]	UK	1973–1992	45	65 (25–84)	1.5	High grade
Luo et al. [16]	China	1990–2003	68	50 (25–82)	1.93	—
Barreda et al. [17]	Peru	1995–2000	169	—	0.83	DLCL
Durr et al. [18]	USA	1975–1991	35	63	—	DLCL
Lybeert et al. [23]	The Netherlands	1982–1992	81	69.7 (30–88)	—	Intermediate grade
Parvez et al. [24]	Saudi Arabia	1990–1998	22	—	—	DLCL
Schmidt et al. [25]	Germany	1985–2000	92	60 (29–85)	—	DLCL
Shaw et al. [19]	New Zealand	1969–1987	62	—	0.87	—
Takahashi et al. [26]	Japan	1974–1996	85	60.5	1.07	—
Aoyagi et al. [27]	Japan	1980–1994	25	59.6 (26–89)	0.92	—
Waisberg et al. [28]	Brazil	1973–2001	16	62.8 (40–83)	3	Low grade
Koch et al. [29]	Germany	1996–2004	398	63.2 (20–83)	1.2	DLCL
Al-Bahrani et al. [20]	Iraq	1965–1978	32	42.6 (12–70)	2.5	PDLL
Present study	Iran	1998–2012	54	50 (17–75)	0.86	DLBCL

DLCL: diffuse large cell lymphoma; DLBCL: diffuse large B-cell lymphoma; PDLL: poorly differentiated lymphocytic lymphoma; DFS: disease-free survival; OS: overall survival; LDH: lactic dehydrogenase.

TABLE 6: Major reports on gastric MALT.

Author	Country	Stage	Years	Number	Median age (range)	M/F	Survival
Andriani et al. [30]	Italy	I-II	1993–2006	60	60 (23–80)	1.2	94.7 (74.6)% 5 y
Gisbert et al. [31]	Spain	I-IV	1991–2005	37	61	1.63	NM
Park et al. [32]	Republic of Korea	I	1998–2002	11	55.7 (36–73)	0.83	NM
Stathis et al. [33]	Italy	I-II	1990–2006	105	64 (20–94)	1.05	92%
Present study	Iran	I-IV	1998–2010	14	47.50 (17–75)	0.75	77.9 5 Y DFS

NM: not mentioned.

TABLE 7: Major reports on gastric DLCL.

Author	Country	Stage	Years	Number	Median age (range)	M/F	Survival
Tanaka et al. [10]	Japan	I-IV	1995–2009	95	68 (32–86)	1.11	—
Leopardo et al. [34]	Italy	I-IV	2000–2007	30	58	1.5	100% 5 y DFS 73.3%
Ibrahim et al. [35]	Saudi Arabia	I-IV	1982–1998	185	54 (17–94)	1.34	68% 5 y OS
Spectre et al. [36]	Israel	I-IV	1990–2005	73	57 (20–80)	1.28	62% 3OS
Present study	Iran	I-IV	1998–2010	36	49 (17–74)	1.0	59.5 5 Y DFS

in others, most common subtypes were MALT and DLCL, Table 1. Subtype in some studies was a prognostic factor, however, our study findings revealed no difference among the subtypes regarding the survival rate (Table 3). Some studies have evaluated MALT or DLCL alone and are mentioned in Tables 6 and 7.

GL treatment is not so clear and multiple strategies have been proposed in this regard; however, it is not known which one is more beneficial [5]. As Table 1 depicts, most of our patients were operated on and received chemotherapy and radiotherapy afterwards. Chemotherapy in our study included CHOP without rituximab. Rituximab is recently covered by the insurance system. However, none of our 54 patients could afford this agent. In the previous decades, surgical tumor removal and surgical abdominal staging were important parts of the treatment [37]. Surgery was supposed to be necessary, but several studies showed that surgery might not have an essential role and conservative treatment had the same cure rate with fewer side effects [4, 41]. Most of our patients (44 cases or 81%) had undergone surgery before referral to our ward. These patients were those who had received treatment in the early years of this study. These patients had a shorter survival (61.5 months versus 80.0 months).

Rituximab is a monoclonal antibody against CD20 on B-cell lymphoma. It is widely used and is effective in overall survival as well as disease-free survival in nodal lymphoma. Studies on the effectiveness of rituximab in gastric DLCL have revealed improvement in the response rate and survival [10, 34]. This agent is also effective in gastric MALT lymphoma [42]. On the other hand, Aviles in a retrospective study on 42 patients who were affected by stages IE-IIIE GL reported the 5-year disease-free survival and overall survival as 95%. In that study, CHOP and rituximab were administered for 6 cycles and comparing to historical reports, no survival benefit was observed [43]. In this study, none of the patients was treated with rituximab.

5. Conclusion

GL is a diverse category according to its subtypes and associated prognostic factors. Thus, further prospective studies according to each subtype may open the horizons.

Acknowledgments

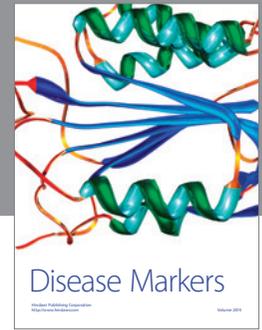
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