

# Prognostic Factors and Survival Outcomes in Marginal Zone Lymphoma: Real-Life Experience

## Marjinal Zon Lenfomada Prognostik Faktörler ve Sağkalım Sonuçları: Gerçek Yaşam Deneyimi

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### Abstract

**Objective:** This study evaluates the clinical and prognostic features of patients with marginal zone lymphoma (MZL) and examines the impact of key prognostic factors including lactate dehydrogenase (LDH),  $\beta$ 2-microglobulin, immunoglobulin M (IgM), and International Prognostic Index (IPI) score on survival outcomes. It also compares survival rates among extranodal, nodal, and splenic subtypes to reveal prognostic heterogeneity and provide real-world evidence for personalized treatment strategies in MZL management.

**Materials and Methods:** A total of 79 patients aged  $\geq 18$  years with pathologically confirmed MZL diagnosed between 2015 and 2025 were retrospectively analyzed. Demographic characteristics, clinical findings, laboratory results, treatment modalities, and survival data were recorded. Survival outcomes were assessed using the Kaplan-Meier method with statistical significance set at  $p < 0.05$ .

**Results:** The study included 79 patients (59.5% female; mean age:  $62 \pm 12.1$  years). Advanced-stage disease (Ann Arbor stages III-IV) was present in 81%. Extranodal MZL had the longest disease-free survival (median: 59.5 months), while nodal MZL had the poorest prognosis (median: 19 months). Elevated  $\beta$ 2-microglobulin, C-reactive protein, and IgM levels correlated with inferior survival ( $p = 0.006$ ,  $p = 0.040$ , and  $p = 0.015$ ). Patients with an IPI score of  $\geq 3$  had a 3.5-fold higher mortality risk ( $p = 0.026$ ). Complete remission occurred in 53.2% of cases and relapse in 17%.

**Conclusion:** MZL is typically an indolent malignancy, though some patients may exhibit aggressive disease. In addition to lymphocytosis, MZL should be considered in cases with lymphopenia or monoclonal gammopathy. Advanced age, elevated LDH, high IPI scores, and advanced stage have been linked to poorer survival outcomes. These findings underline the prognostic heterogeneity among MZL subtypes.

**Keywords:** Marginal zone lymphoma, Prognosis, International Prognostic Index score, Survival

### Öz

**Amaç:** Bu çalışma, marjinal zon lenfoma (MZL) hastalarının klinik ve prognostik özelliklerini retrospektif olarak değerlendirmekte ve temel prognostik faktörlerin -laktat dehidrogenaz (LDH),  $\beta$ 2-mikroglobulin, immünoglobulin M (IgM) düzeyleri ve Uluslararası Prognostik İndeks (IPI) skorunun- sağkalım sonuçları üzerindeki etkisini incelemektedir. Ayrıca, ektranodal, nodal ve splenik alt tipler arasındaki sağkalımı karşılaştırarak prognostik heterojeniteyi ortaya koymayı ve MZL yönetiminde kişiselleştirilmiş tedavi stratejilerine yönelik gerçek yaşam verileri sunmayı amaçlamaktadır.

**Gereç ve Yöntemler:** 2015-2025 yılları arasında patolojik olarak doğrulanmış MZL tanısı alan, yaşları  $\geq 18$  olan toplam 79 hasta retrospektif olarak analiz edilmiştir. Demografik özellikler, klinik bulgular, laboratuvar sonuçları, tedavi yöntemleri ve sağkalım verileri kaydedilmiştir. Sağkalım sonuçları Kaplan-Meier yöntemi kullanılarak değerlendirilmiş, istatistiksel anlamlılık düzeyi  $p < 0,05$  olarak kabul edilmiştir.

**Bulgular:** Çalışmaya 79 hasta (%59,5 kadın; ortalama yaş:  $62 \pm 12,1$  yıl) dahil edilmiştir. Hastaların %81'inde ileri evre hastalık (Ann Arbor III-IV) mevcuttu. Ektranodal MZL en uzun hastalısız sağkalımı göstermiştir (medyan: 59,5 ay), buna karşın nodal MZL en kötü prognoza sahipti (medyan: 19 ay). Yüksek  $\beta$ 2-mikroglobulin, C-reaktif protein ve IgM düzeyleri daha kötü sağkalımla ilişkili bulunmuştur ( $p = 0,006$ ;  $0,040$ ;  $0,015$ ). IPI skoru  $\geq 3$  olan hastalarda mortalite riski 3,5 kat daha yüksek saptanmıştır ( $p = 0,026$ ). Hastaların %53,2'sinde tam remisyona elde edilirken, %17'sinde nüks gelişmiştir.

**Sonuç:** MZL genellikle indolen seyirli bir malignite olmakla birlikte, bazı hastalarda agresif hastalık özellikleri gösterebilmektedir. Lenfositozun yanı sıra, lenfopeni veya monoklonal gammopati saptanan olgularda da MZL olasılığı göz önünde bulundurulmalıdır. İleri yaş, yüksek LDH düzeyleri, yüksek IPI skorları ve ileri evre hastalık, daha kötü sağkalım sonuçları ile ilişkili bulunmuştur. Bu bulgular, MZL alt tipleri arasındaki prognostik heterojenitenin altını çizmektedir.

**Anahtar Sözcükler:** Marjinal zon lenfoma, Prognoz, Uluslararası Prognostik İndeks skoru, Sağkalım



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## Introduction

Marginal zone lymphomas (MZLs) are indolent malignancies derived from B lymphocytes, accounting for approximately 10% of all non-Hodgkin lymphomas. MZL arises from memory B-cells located in the marginal zone of secondary lymphoid follicles, which are found in the spleen, mucosa-associated lymphoid tissues, and, more rarely, lymph nodes [1]. In addition to these, the most frequent site of involvement is the stomach, followed by the eyes, salivary glands, skin, and lungs [2]. Primary bone and lacrimal gland involvement, excluding the breast and thyroid, has also been reported in the literature, albeit rarely [3,4]. The median age at diagnosis is 67 years and the disease is observed more frequently in women [5]. Infections caused by certain microorganisms have been implicated in the pathogenesis of MZL; however, MZL may also develop as a result of chronic autoimmune inflammation leading to persistent exposure to autoantigens. Based on sites of involvement and molecular characteristics, the World Health Organization classifies MZL into four subtypes, each with distinct epidemiology, clinical presentation, and treatment options: extranodal MZL (EMZL), nodal MZL (NMZL), splenic MZL (SMZL), and primary cutaneous MZL [6].

In our clinic, we sought to contribute to the medical literature with real-world data by evaluating the long-term follow-up results of patients with MZL, a group rarely encountered among non-Hodgkin lymphoma cases.

## Materials and Methods

This study included 79 patients aged  $\geq 18$  years who were pathologically diagnosed with MZL and admitted between 2015 and 2025. The study was conducted in accordance with institutional guidelines for retrospective studies. MZL was classified into the nodal, splenic, and extranodal subtypes, and due to the limited number of patients, primary cutaneous MZL cases were included in the EMZL group. The following patient data were recorded: age, sex, Eastern Cooperative Oncology Group performance status, International Prognostic Index (IPI) score, laboratory tests, bone marrow involvement at diagnosis, and treatment protocols. Extranodal disease was defined as “bulky” for masses with largest diameter of  $\geq 7$  cm.

The study was approved by the Health Sciences Research Ethics Committee (decision no: 2024/86, dated 10 July 2024).

## Statistical Analysis

The data of patients diagnosed with MZL between 2015 and 2025 were retrospectively reviewed. For survival analysis, the Kaplan-Meier method was applied, and complementary statistical analyses were performed with IBM SPSS Statistics 25.0. Values of  $p < 0.05$  were considered statistically significant. For descriptive statistics, mean, standard deviation, median, minimum,

maximum, frequency, and percentage values were calculated. The distribution of variables was assessed using the Kolmogorov-Smirnov test. For the analysis of quantitative independent data, the independent-samples t-test and Mann-Whitney U test were applied. For qualitative independent data, the chi-square test was used.

## Results

Of the 79 patients included in this study, 47 were female (59.5%) and 32 were male (40.5%). The mean age at diagnosis was  $62 \pm 12.1$  years. A chronic comorbidity was present in 75.9% of cases, and more than half of these patients had two or more comorbidities (40.5%). Bulky disease was detected in 13.9% and splenomegaly in 41.8%. Ann Arbor stage III-IV disease was observed in 81% of the patients. Four patients had hepatitis B virus infection and two had hepatitis C virus infection, with both polymerase chain reaction and antibody tests yielding positive results. Antiviral therapy was initiated for these patients even if they were asymptomatic. *Helicobacter pylori* infection was detected in 15 patients (23.7%) (Table 1).

There were 32 patients in the EMZL subgroup. Their mean age was  $60 \pm 13.6$  years and 56.3% were female. B symptoms were observed in 34.4% of cases. Bone marrow involvement was detected in 25% of these patients, with a statistically significant difference between subgroups ( $p < 0.001$ ). Advanced-stage disease (Ann Arbor Stage III-IV) was present in 87.5% of cases. Elevated lactate dehydrogenase (LDH) was observed in 15.6%, while elevated  $\beta 2$ -microglobulin was found in 56.3%. Monoclonality was detected in 28.6% of patients. Those with a low IPI score (0-2) accounted for 53.1% of this subgroup, while the higher-risk group accounted for 46.9% (Table 1). The demographic characteristics of the patients in the NMZL and SMZL subgroups are presented in Table 1.

In patients with bulky disease, survival time was shorter (mean: 53 months, median: 25 months), whereas those without bulky disease had longer survival (mean: 66 months, median: 62.5 months), suggesting an effect on overall survival (OS) ( $p = 0.372$ ).

The bone marrow was the most commonly involved site at diagnosis, accounting for 30.4% of cases. In the EMZL subgroup, the sites of involvement included the stomach, the lung, the pleura, the skin, the breast, the eye, and the thyroid.

When the blood parameters of the patients were examined, lymphopenia was observed in 6.3%, while lymphocytosis was present in 45.6%. The mean lymphocyte count was  $8460/\text{mm}^3$  (range:  $1320/\text{mm}^3$  to  $193,000/\text{mm}^3$ ). By MZL subtype, lymphopenia was most common in EMZL (12.5%), whereas lymphocytosis was most frequent in SMZL (66.7%). Increases in  $\beta 2$ -microglobulin ( $p = 0.006$ ), C-reactive protein ( $p = 0.040$ ), and immunoglobulin M (IgM) ( $p = 0.015$ ) were all associated

with reduced survival (Table 2). Anemia was detected in 12.5% of patients. Higher hemoglobin levels were associated with improved survival ( $p=0.030$ ). Two patients had iron deficiency anemia, while 8 patients had anemia secondary to bone marrow involvement.

Elevated LDH levels were present in approximately one-third of the overall patient group. In Cox regression analysis evaluating the effect of elevated LDH on OS, the risk of death was 1.185 times higher in patients with elevated LDH than in those without (hazard ratio [HR]: 1.185; 95% confidence interval [CI]: 0.506-2.774;  $p=0.696$ ). Patients with elevated LDH had an approximately 2.25-fold higher risk of relapse (HR: 2.253; 95% CI: 0.919-5.523;  $p=0.076$ ). This finding suggests that LDH levels may have prognostic relevance.

According to the flow cytometry results, kappa monoclonality was present in 20.3% ( $n=16$ ) and lambda monoclonality was present in 10.1% ( $n=8$ ). Kappa and lambda light chain analyses were not available for the remaining patients. While elevated IgG levels were detected in 3.7% ( $n=3$ ) of the patients, elevated

IgM levels were more frequently observed, being reported in 15.1% ( $n=12$ ) of the cases. The mean IgM level in patients with monoclonality was 2230.8 mg/dL (HR: 1.045; 95% CI: 0.336-3.249;  $p=0.940$ ).

When disease-free survival (DFS) was evaluated by MZL subtype, the highest cumulative survival was observed in patients with EMZL, making it the subtype with the best prognosis in our study. The median DFS values were 59.5 months in EMZL, 19 months in NMZL, and 48 months in SMZL (Figure 1).

For patients with EMZL, OS was 71.5 months, with survival rates reaching up to 60% even at 10 years. In NMZL, OS was 51 months, while in SMZL, OS was 68.5 months (Figure 2).

The number of patients with an IPI score of  $\geq 3$  was 30, accounting for 38%. In patients with an IPI score of  $< 3$ , OS was 73 months, whereas in those with an IPI score of  $\geq 3$ , OS was 31 months. An increase of 1 unit in the IPI score raised the risk of death by 2.2 times, and having an IPI score of  $\geq 3$  increased the risk by 3.5 times ( $p=0.026$ ) (Figure 3A). When IPI scores were analyzed

**Table 1. Patients' baseline characteristics.**

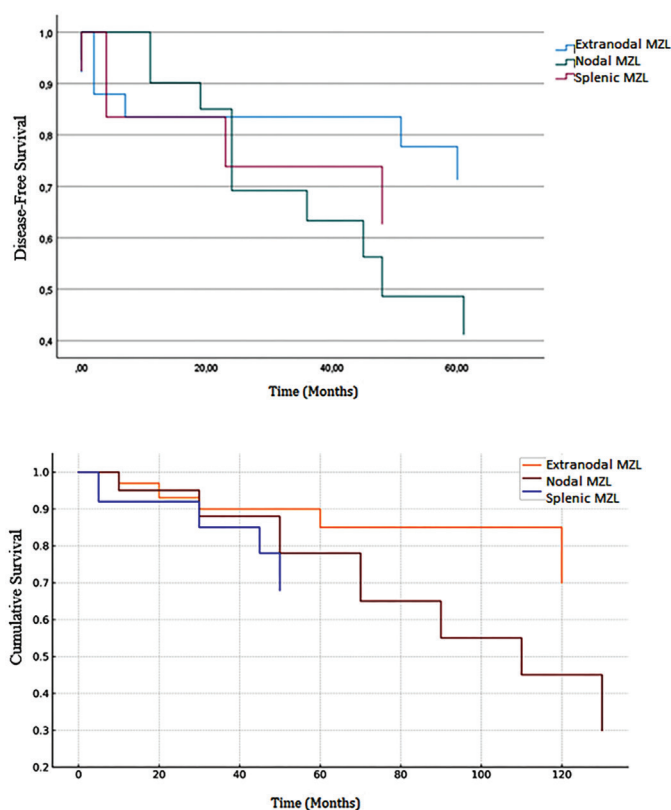
Characteristic	Overall n=79	EMZL n=32	NMZL n=35	SMZL n=12	p
Female	47 (59.5%)	18 (56.3%)	24 (68.6%)	5 (41.7%)	0.237
Age, years	62±12.1	60±13.6	62±11	57±11.3	0.200
<b>ECOG PS</b>					
0-1	76 (96.0%)	30 (93.8%)	35 (100%)	11 (91.7%)	0.359
2-4	3 (4.0%)	2 (6.3%)	0 (0.0%)	1 (8.3%)	
B symptoms	37 (46.8%)	11 (34.4%)	20 (57.1%)	6 (50.0%)	0.174
Bulky mass (>7 cm)	11 (13.9%)	4 (12.5%)	6 (17.1%)	1 (8.3%)	0.719
Splenomegaly	33 (41.8%)	6 (18.8%)	16 (45.7%)	11 (91.7%)	<b>0.020</b>
Bone marrow involvement	40 (50.6%)	8 (25.0%)	24 (68.6%)	8 (66.7%)	<b>&lt;0.001</b>
Extranodal involvement	32 (40.5%)	32 (100%)	0 (0.0%)	0 (0.0%)	<b>&lt;0.001</b>
Nodal involvement	60 (75.9%)	25 (78.1%)	35 (100%)	3 (25.0%)	0.130
Ann Arbor Stage III-IV	64 (81.0%)	28 (87.5%)	24 (68.6%)	12 (100%)	0.065
Hemoglobin of <10 g/dL	10 (12.7%)	3 (9.4%)	4 (11.4%)	3 (25.0%)	0.532
Lymphocytosis	36 (45.6%)	10 (31.3%)	18 (51.4%)	8 (66.7%)	0.692
LDH > ULN	26 (32.9%)	5 (15.6%)	15 (42.9%)	6 (50.0%)	<b>0.025</b>
$\beta 2$ -microglobulin of >2.2 mg/L	25 (53.2%)	9 (56.3%)	14 (58.3%)	2 (28.6%)	0.372
Monoclonality	15 (25.9%)	6 (28.6%)	7 (25.0%)	2 (22.2%)	0.927
<b>Types of monoclonality</b>					
IgM	12 (80.0%)	4 (66.7%)	7 (100%)	1 (50.0%)	0.170
IgG	3 (20.0%)	2 (33.3%)	0 (0.0%)	1 (50.0%)	
IPI score of 0-2	49 (62.0%)	17 (53.1%)	23 (65.7%)	9 (75.0%)	0.345
IPI score of $\geq 3$	30 (38.0%)	15 (46.9%)	12 (34.3%)	3 (25.0%)	
<i>Helicobacter pylori</i>	15 (27.3%)	7 (31.8%)	5 (21.7%)	3 (30.0%)	0.737
Hepatitis B	4 (5.1%)	2 (6.3%)	1 (25.0%)	1 (8.3%)	0.184
Hepatitis C	2 (2.5%)	1 (3.1%)	1 (2.9%)	0 (0.0%)	

EMZL: Extranodal marginal zone lymphoma; NMZL: nodal marginal zone lymphoma; SMZL: splenic marginal zone lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; ULN: upper limit of normal; IgM: immunoglobulin M; IgG: immunoglobulin G; IPI: International Prognostic Index.

**Table 2. Results of Spearman rho correlation analysis evaluating relationships between hematological parameters measured at diagnosis and overall survival time.**

Parameters	n	Mean	Median	Min.	Max.	p
White blood cell count ( $10^3/\mu\text{L}$ )	79	15.76	8.46	1.32	193.0	0.423
Hemoglobin (g/dL)	79	12.4	12.2	8.1	17.5	0.03
Platelet count ( $10^3/\mu\text{L}$ )	79	230.28	224.0	3.8	565.0	0.412
Neutrophils ( $10^3/\mu\text{L}$ )	79	4.4	4.02	0.26	10.2	0.8
Lymphocytes ( $10^3/\mu\text{L}$ )	79	8.66	2.5	0.42	138.61	0.503
Creatinine (mg/dL)	79	1.62	0.76	0.45	65.0	0.255
Lactate dehydrogenase (U/L)	79	245.18	218.0	95.0	718.0	0.245
$\beta$ 2-microglobulin (mg/L)	47	3.0	2.4	0.19	9.3	<b>0.006</b>
Uric acid (mg/dL)	79	5.49	5.1	2.9	9.9	0.593
Quantitative immunoglobulin G (mg/dL)	58	1271.45	1050.0	193.0	7300.0	0.084
Immunoglobulin A (mg/dL)	43	119.04	96.1	18.1	336.0	0.212
Quantitative immunoglobulin M (mg/dL)	43	821.52	75.4	16.8	9321.0	<b>0.015</b>
Erythrocyte sedimentation rate (mm/h)	71	29.74	20.0	2.0	140.0	0.291
C-reactive protein (mg/L)	71	25.69	8.2	0.8	571.0	<b>0.04</b>

Min.: Minimum; Max.: maximum.

**Figure 1.** Kaplan-Meier curves showing the relationships between disease-free survival and overall survival and marginal zone lymphoma (MZL) subtypes.

individually, a significant difference was found between a score of 4 and a score of 2 ( $p=0.004$ ; 95% CI: 3.09-106.64). The mean survival of patients with an IPI score of 4 was significantly shorter than that of patients with an IPI score of 2. In Cox regression

analysis performed within MZL subgroups, patients with EMZL and an IPI score of  $\geq 3$  had a 10-fold increased risk of death (Figure 3B).

According to the MZL-IPI score, 19% ( $n=15$ ) of cases were classified as low risk, while the intermediate- and high-risk groups accounted for 62% ( $n=49$ ) and 19% ( $n=15$ ), respectively. Among patients with EMZL, the percentage of intermediate-risk cases was 59.4%. In patients with NMZL, the high-risk group accounted for 28.6%, which was higher than the rates of the other MZL subtypes ( $p=0.014$ ).

In our study, 12 patients (15.2%) were managed with a watch-and-wait treatment approach., while 43 (54.4%) received chemotherapy. Primary surgical treatment was performed for 8 patients (10.1%). Radiotherapy alone was administered to 6 patients (7.6%). Six patients (7.6%) underwent combined chemotherapy and radiotherapy, whereas 3 patients (3.8%) received chemotherapy in combination with surgical intervention. One patient (1.3%) was treated with surgery followed by radiotherapy. Among the 12 patients who underwent surgical treatment, splenectomy was performed for 7 patients, scleral and eyelid surgery for 2 patients, thyroidectomy for 1 patient, mastectomy for 1 patient, and excision of a mass from the dura mater for 1 patient. The proportion of patients who received first- and second-line therapy was 54.4%. Among first-line regimens, rituximab monotherapy was the most frequently administered (20.3%) (Figure 4). In second-line treatments, rituximab combined with bendamustine was the most commonly used regimen (12.7%). Maintenance rituximab therapy was administered to 13.9% of the patients ( $n=11$ ).

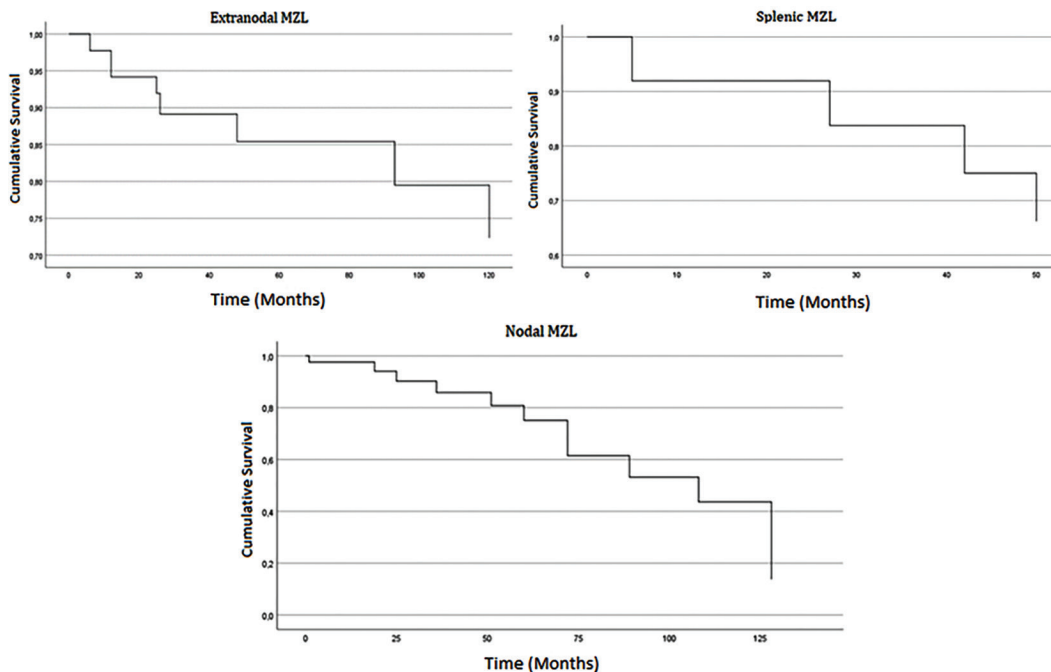


Figure 2. Survival analysis of patients diagnosed with extranodal, nodal, and splenic marginal zone lymphoma (MZL).

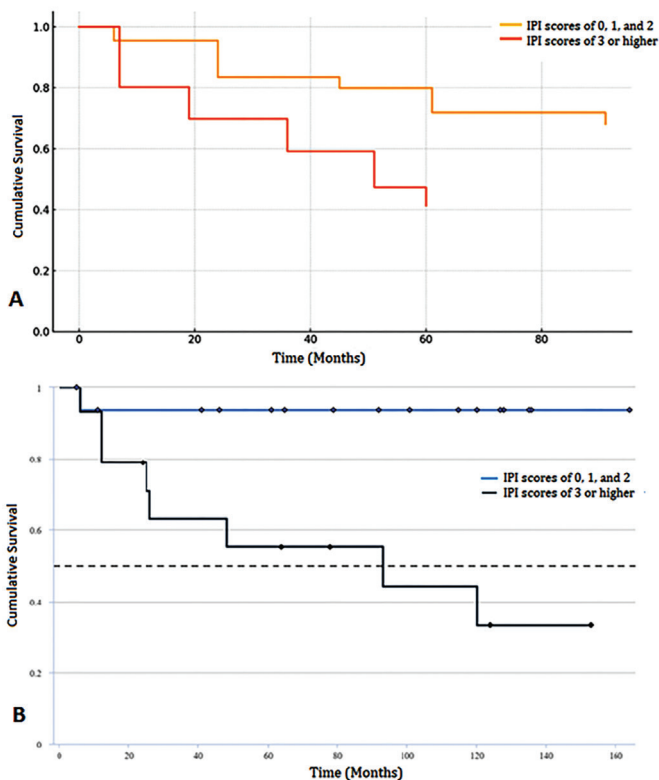


Figure 3. Survival analysis according to International Prognostic Index (IPI) score. A) Overall survival analysis of all marginal zone lymphoma subtypes. B) Survival analysis of patients with extranodal marginal zone lymphoma.

Relapse occurred in 17% of cases, with a median time to relapse of 47 months (range: 6-87 months). Relapse within the first 24

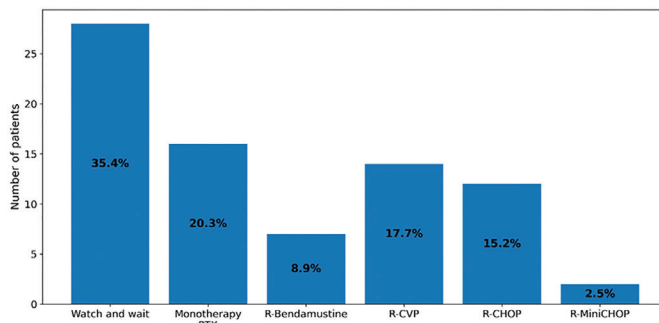


Figure 4. First treatment options applied for patients included in the study.

months was observed in 6.3% of cases (n=5). The subtype with the highest relapse rate was NMZL (50%), while the lowest was observed in SMZL. No significant relationship was found between relapse and MZL subtype (p=0.891). At the time of relapse, among the 14 patients evaluated, only 1 patient underwent histological transformation and was diagnosed with high-grade lymphoma at month 33.

In patients with EMZL, the most common treatment modality was chemotherapy, applied in 62.5% of cases. Among patients who received radiotherapy, 66.7% were in this group. The NMZL group had the highest proportion of patients managed with follow-up alone, while surgery-based approaches were more frequent in the SMZL group.

Because a watch-and-wait treatment approach was applied for 12 patients, these patients were not included in the response

evaluation. One patient died before response assessment could be performed. When treatment responses were evaluated, the rate of patients achieving complete remission with any treatment modality was 51.8% (n=41), while the rate of disease progression was 12.7% (n=10). In EMZL, the complete remission rate was higher than in other subtypes, with a rate of 51.2%.

Overall, 30.4% of the patients died, with 62.5% of deaths attributed to non-disease-related causes.

## Discussion

MZL is divided into three main subtypes (EMZL, SMZL, and NMZL) and accounts for 10.5%-11.8% of B-cell lymphomas. Although generally indolent, an aggressive course may be observed in some patients [7]. The median age at diagnosis is 67 years, and studies have shown a female predominance of about 53% [4]. In our study, the median age was 62 years, with female predominance of 59.5%.

MZL can arise in various sites, including the bone marrow, stomach, and lungs. Its pathogenesis is influenced by autoimmune diseases as well as certain infections, notably *H. pylori* and hepatitis C virus. The frequency of *H. pylori* infection in gastric mucosa-assisted lymphoid tissue (MALT) lymphoma has been reported to be approximately 80% [8]. In our study, *H. pylori* infection was detected in 50% of patients with gastric MALT lymphoma. This lower rate may reflect both the small number of patients in our cohort and the increasing use of proton pump inhibitors [9], which may hinder the detection of *H. pylori* infection.

EMZL is most commonly seen in the stomach and lungs. It accounts for approximately 7%-8% of non-Hodgkin lymphomas and 50%-70% of MZLs [2]. In our study, the most common site of involvement was the stomach (12.6%), followed by the lungs (11.3%) and liver (5.0%). Primary breast MZL accounts for 1.7%-2.2% of all extranodal non-Hodgkin lymphomas [10]. Pulmonary MZL accounts for approximately 9%-14% of all MALT lymphomas [11].

NMZL is the least common subtype of MZL, accounting for about 10%, and it has a worse prognosis [12]. In our study, the least common subtype was SMZL, while NMZL had the poorest prognosis, consistent with the literature.

SMZL usually presents with massive splenomegaly and bone marrow involvement. Autoimmune hemolytic anemia and thrombocytopenia may accompany the disease [13]. In our series, anemia was detected in 25% of patients with SMZL, giving this subtype the highest anemia rate.

Because bone marrow involvement is also observed in MZL, anemia, thrombocytopenia, and lymphopenia may occur. However, previous studies have not reported the specific

prevalence of lymphopenia. In our study, lymphopenia was observed in 6.3% of patients and lymphocytosis in 45.6%. By subtype, lymphopenia was most common in EMZL (12.5%). Lymphocytosis was observed most frequently in SMZL (66.7%). Previous studies have shown that the rate of lymphocytosis in SMZL is approximately 75% [14]. For EMZL and NMZL, specific rates of lymphocytosis or lymphopenia have not been clearly reported in the literature.

In a single-center study conducted by Epperla et al. [15], the presence of monoclonal protein at the time of diagnosis in patients with MZL was investigated and M-protein was detected in 32% of cases. When subtypes were evaluated, monoclonal protein was reported at rates of 27% in EMZL, 40% in NMZL, and 35% in SMZL. In our study, monoclonality was detected in 30% of patients, with kappa monoclonality being the most frequent (20.3%). Monoclonality was observed in 28.6% of patients with EMZL, 25.0% of patients with NMZL, and 22.2% of patients with SMZL.

The therapeutic approach in MZL should be individualized according to patient-related factors (age, comorbidities, and performance status), disease-related characteristics (site of involvement, stage, and presence of symptoms), and treatment goals. In asymptomatic cases, a watch-and-wait strategy is an appropriate option, whereas surgery, radiotherapy, or eradication therapy may be considered in patients with limited residual disease [16]. In contrast, in symptomatic patients or in the presence of advanced disease, chemotherapy regimens combined with rituximab (R), such as R-bendamustine, R-CHOP, R-chlorambucil, and R-CVP, as well as immunotherapy, are required. In gastric EMZL, antibiotic therapy for *H. pylori* eradication is the gold standard of treatment. With appropriate antibiotic therapy, complete remission rates of approximately 75%-80% are expected within 24 months [17]. Radiotherapy is preferred in localized cases that are refractory to antibiotic therapy or are *H. pylori*-negative. With radiotherapy complete remission and cure are achieved in nearly all cases, with relapse rates reported to be as low as approximately 5%-10% [18]. In advanced-stage and symptomatic MZL, rituximab-based regimens have been shown to provide favorable outcomes. Commonly used combinations include rituximab plus chlorambucil and rituximab plus bendamustine. Previous studies have demonstrated that the combination of bendamustine and rituximab achieves efficacy comparable to anthracycline-containing regimens such as R-CHOP, with a more favorable toxicity profile [19]. In cases of relapse with aggressive disease or histological transformation, treatment options include rituximab, lenalidomide, ibrutinib (a Bruton tyrosine kinase inhibitor), or PI3K inhibitors. For selected patients, autologous stem cell transplantation or chimeric antigen receptor T-cell therapy may also be indicated [20,21,22,23,24]. In our study, complete remission was achieved by the vast majority of patients (93.8%)

who received surgery-based treatment. Among patients treated with rituximab monotherapy, the complete remission rate was 56.3%, whereas more heterogeneous response patterns were observed with combination regimens such as R-bendamustine, R-CVP, and R-CHOP ( $p=0.027$ ).

In a study conducted by Yaman et al. [25], treatment responses included complete response in 22 patients (61.1%), stable disease in 9 (25.0%), and partial response in 5 (13.9%). In another study, despite treatment, relapse occurred in 20% of patients [26]. Relapse and progression within the first 24 months were observed more frequently in patients with nodal disease, at a rate of 27% [27]. In our cohort, complete response was achieved in 53.2% of cases, stable disease in 12.7%, partial response in 8.9%, progression in 12.7%, and relapse in 17.7%. When analyzed by MZL subtype, relapse and progression were most frequent in NMZL (20%), consistent with the literature.

In a previous study, the 5-year cumulative relapse/progression rate was 38% and the non-relapse mortality (NRM) rate was 9%. In the same study, the 5-year DFS rate was reported as 53%, while the OS rate was 73% [28]. In MZL, the NRM rate is generally low because these lymphomas are mostly indolent and have a good prognosis. In our study, however, the NRM rate was 15.2%.

In another study, the 10-year OS for all MZL subgroups combined was 79%. When subgroups were assessed, the survival rates were 78% for gastric MZL, 83% for non-gastric MZL, 70% for SMZL, and 56% for NMZL, with EMZL identified as the subtype with the best prognosis [29]. In our study, the 10-year OS rates for EMZL and NMZL were 75% and 50%, respectively. The 5-year OS rate for SMZL was 75%, consistent with the literature, and EMZL was again determined to be the subtype with the most favorable prognosis.

For all MZLs, advanced age, elevated LDH and  $\beta$ 2-microglobulin levels, anemia, thrombocytopenia, lymphopenia, hypoalbuminemia, poor performance status, systemic symptoms, failure to achieve complete remission after initial therapy, lymph node and bone marrow involvement at diagnosis, disease dissemination, advanced stage (Stage III-IV), and an IPI score of  $>2$  are associated with poor prognosis [30,31]. In our study, an IPI score of  $>2$  and increased LDH and  $\beta$ 2-microglobulin levels were found to negatively affect survival, while higher hemoglobin levels had a positive impact, consistent with the literature.

### Study Limitations

This retrospective, single-center study has limited generalizability. The small sample size in subgroups reduced the statistical power. Heterogeneity among MZL subtypes and differences in treatment approaches may have influenced survival outcomes. The lack of molecular data restricted the detailed evaluation of

underlying mechanisms, and variable follow-up durations may have limited the detection of late relapses.

### Conclusion

MZL is generally an indolent disease; however, in some cases, an aggressive clinical course may occur. Contrary to common expectations, MZL should be considered not only in patients with lymphocytosis but also when lymphopenia or monoclonal gammopathy is present. Studies have demonstrated that advanced age, advanced stage (stage III-IV), elevated serum LDH, and high IPI scores are associated with poor progression-free survival and OS in patients with MZL [32]. These findings highlight the heterogeneity of clinical behavior among MZL subtypes and their variable responses to treatment, underscoring the importance of an individualized, patient-specific approach to therapy.

### Ethics

**Ethics Committee Approval:** The study was approved by the Health Sciences Research Ethics Committee (decision no: 2024/86, dated 10 July 2024).

**Informed Consent:** Retrospective study.

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: Ş.E.Ü.; Concept: Ş.E.Ü., N.M.Ş.; Design: Ş.E.Ü., N.M.Ş.; Data Collection or Processing: Ş.E.Ü.; Analysis or Interpretation: Ş.E.Ü., N.M.Ş.; Literature Search: Ş.E.Ü.; Writing: Ş.E.Ü.

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