RESEARCH ARTICLE

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Prognostic Significance of Paraproteinemia in Marginal Zone Lymphoma

Marjinal Zon Lenfomada Paraproteineminin Prognostik Önemi

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Abstract

Objective: The prognostic significance of paraproteinemia (PP) in marginal zone lymphoma (MZL) is underexplored. We aimed to investigate the clinical and biological impact of PP and its association with survival outcomes in patients with MZL.

Materials and Methods: We retrospectively evaluated 73 patients diagnosed with MZL between 2000 and 2022 at a single center. Baseline clinical characteristics and survival outcomes were compared according to PP status.

Results: PP was present in 27.3% (20/73) of patients, predominantly of the immunoglobulin M (IgM) subtype. PP was significantly associated with older age (p<0.001), advanced disease stage (p=0.023), elevated β2-microglobulin (p=0.001), bone marrow involvement (p=0.026), and lower hemoglobin (p=0.002) and albumin (p<0.001) levels. Patients with PP had significantly shorter overall survival (OS) and progression-free survival (PFS) compared to those without PP (mean OS: 73.8 vs. 178.8 months, p=0.046; mean PFS: 63.5 vs. 159.7 months, p=0.049). The negative prognostic impact was more pronounced among patients with IgM PP (OS: 58.8 vs. 178.2 months, p=0.006; PFS: 45.2 vs. 157.4 months, p=0.004). In histological subtype analysis, only mucosa-associated lymphoid tissue lymphoma patients with IgM PP showed significantly shorter OS (70.5 vs. 152.6 months, p=0.010). Patients with IgM PP treated with R-CHOP-like regimens experienced significantly shorter PFS and OS.

Conclusion: PP, particularly of the IgM subtype, is associated with adverse clinical and biological features and predicts inferior survival in patients with MZL. Evaluating PP status at diagnosis as a potential prognostic marker may guide treatment strategies. Prospective studies are needed to confirm the prognostic utility of PP and support its incorporation into MZL treatment management.

Keywords: Lymphoma, B-cell, Marginal zone, Paraproteinemia, Immunoglobulin, Monoclonal, Retrospective studies, Prognosis, Survival analysis

Öz

Amaç: Paraproteineminin (PP) marjinal zon lenfomadaki (MZL) prognostik önemi yeterince araştırılmamıştır. Bu çalışmada MZL tanılı hastalarda PP varlığının klinik ve biyolojik etkilerinin hastaların sağkalımı ile ilişkisini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: 2000-2022 yılları arasında tek merkezde MZL tanısı almış 73 hasta retrospektif olarak değerlendirildi. Temel klinik özellikler ve sağkalım sonuçları PP durumuna göre karşılaştırıldı.

Bulgular: PP, hastaların %27,3'ünde (20/73) saptandı ve çoğunlukla immünoglobulin M (IgM) alt tipindeydi. PP varlığı ile ileri yaş (p<0,001), ileri evre hastalık (p=0,023), yüksek β2-mikroglobulin düzeyi (p=0,001), kemik iliği tutulumu (p=0,026), düşük hemoglobin (p=0,002) ve albümin düzeyleriyle (p<0,001) anlamlı ilişkiliydi. PP'si olan hastaların genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) süreleri PP olmayanlara göre anlamlı derecede daha kısaydı (ortalama OS: 73,8 vs. 178,8 ay, p=0,046; ortalama PFS: 63,5 vs. 159,7 ay, p=0,049). Bu olumsuz etki IgM PP'si olan hasta grubunda daha belirgindi (OS: 58,8 vs. 178,2 ay, p=0,006; PFS: 45,2 vs. 157,4 ay, p=0,004). Histolojik alt gruplar analiz edildiğinde, yalnızca IgM PP'si olan mukoza ilişkili lenfoid doku lenfomalı hastalarda OS anlamlı olarak daha kısaydı (70,5 vs. 152,6 ay, p=0,010). IgM PP'li ve R-CHOP benzeri rejimlerle tedavi edilen hastalarda OS ve PFS belirgin olarak daha kısa saptandı.

Sonuç: PP, özellikle IgM alt tipi, MZL hastalarında olumsuz klinik ve biyolojik özelliklerle ilişkili olup azalmış sağkalımı öngördürmektedir. Tanı anında potansiyel bir prognostik belirteç olarak PP durumunun değerlendirilmesi tedavi stratejilerine yol gösterebilir. PP'nin prognostik yararını doğrulamak ve MZL tedavisinin yönetimine dahil edilmesini desteklemek için prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Lenfoma, B-hücre, Marjinal bölge, Paraproteinemiler, İmmünoglobulin, Monoklonal, Retrospektif çalışmalar, Prognoz, Sağkalım analizi

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Introduction

Marginal zone lymphomas (MZLs) are B-cell lymphomas derived from post-germinal center marginal zone B-cells [1]. MZL accounts for 7%-8% of all non-Hodgkin lymphoma (NHL) cases. It is the third most common type of lymphoma among all NHLs. There are three distinct subtypes: mucosa-associated lymphoid tissue (MALT) lymphoma (50%-70%), splenic MZL (SMZL) (10%-20%), and nodal MZL (NMZL) (10%-20%) [2].

Unlike diffuse large B-cell lymphoma, which is aggressive and requires immediate treatment, or follicular lymphoma (FL), which is indolent but clinically predictable, MZL shows clinical and prognostic heterogeneity [3,4]. MALT lymphoma is often localized with a favorable prognosis, while SMZL and NMZL are more commonly disseminated at diagnosis and may follow a more progressive course [5]. Moreover, aggressive transformation is less frequent than in FL, though it remains a clinical concern [6].

Given this heterogeneity, the treatment of MZL must be individualized based on clinical presentation and disease progression. Management strategies include watchful waiting, antibiotic therapy, surgical resection, radiotherapy, chemoimmunotherapy, and targeted therapies [7,8]. Despite the generally favorable outcomes, the risk of progression with relapses and aggressive lymphoma transformation indicates the need for additional prognostic factors to guide individualized treatment. Prognosis assessment is essential for selecting the optimal treatment strategy [1,7].

The ability of B-cells to secrete immunoglobulins (Ig) is a regulated process acquired during terminal differentiation into plasma cells or long-lived memory B-cells. In B-cell lymphomas, malignant clones may retain or acquire this secretory function, resulting in the production of monoclonal Igs, detectable as serum paraproteins. Paraproteinemia (PP) is classically associated with monoclonal gammopathy of undetermined significance, multiple myeloma, Waldenström macroglobulinemia/lymphoplasmacytic lymphoma, and light chain amyloidosis. However, nearly all types of B-cell lymphomas can secrete paraproteins. PP reflects the capacity of the malignant B-cell clone to undergo plasmacytic differentiation, which has been linked with high-risk biological features and poor outcomes in certain lymphomas [8,9,10,11]. Few studies have assessed its impact on survival in MZL. The frequency of monoclonal gammopathy in MZL subtypes ranges from 5% to 46% [12,13,14,15,16,17,18,19] and it has been correlated with plasmacytic differentiation, advanced disease, and bone marrow involvement in MALT lymphoma [15,20]. However, current prognostic models do not include biological features such as PP, which may carry additional prognostic value [21,22,23].

In this study, we evaluated the clinical characteristics associated with PP in MZL patients and assessed its impact on survival.

Materials and Methods

Study Design and Patient Selection

Between January 2000 and June 2022, 73 patients diagnosed with MZL and followed at our center were included. Diagnoses were made according to the World Health Organization's classification of tumors of hematopoietic and lymphoid tissues valid at the time of diagnosis (2008 and 2016 editions). We included only patients evaluated for monoclonal gammopathy via serum immunofixation electrophoresis (SIFE) and serum protein electrophoresis (SPEP). Patients under 18 years of age and those with <1 month of follow-up, insufficient clinical data, or a second solid organ malignancy were excluded. The study was approved by the Dokuz Eylül University Faculty of Medicine's Local Ethics Committee (decision no: 2022/15-11; date: 20 April 2022). The study was conducted in accordance with the Declaration of Helsinki.

Definition of Paraproteinemia

PP was defined as a monoclonal band detected on SIFE with demonstration of an M-spike on SPEP. Free light chain (FLC) testing was not routinely available and was thus excluded from the definition. We included only patients who were evaluated with both SPEP and SIFE. We excluded patients with FLC results alone, without confirmatory SIFE, to avoid potential diagnostic bias.

Staging and Baseline Assessments

Staging evaluation consisted of a complete physical examination; imaging of the neck, thorax, abdomen, and pelvis with computed tomography (CT); and positron emission tomography/CT. Magnetic resonance imaging, endoscopy, and bone marrow biopsy were performed in selected cases. Assessment of bone marrow involvement was defined exclusively by bone marrow biopsy with histopathological ± immunohistochemical confirmation. All cases were retrospectively reassessed with the modified Ann Arbor staging system. Treatment response was retrospectively evaluated based on clinical records and imaging according to International Working Group criteria [24] and categorized as complete response (CR), partial response, stable disease, or progressive disease.

Data Collection

Baseline clinical characteristics collected from the medical record system included age, sex, comorbidities, Eastern Cooperative Oncology Group performance status, primary disease site, extranodal involvement, lymph node status, B symptoms, laboratory workup at the initial evaluation (hemoglobin,

leukocyte and platelet counts, lactate dehydrogenase (LDH), serum β2-microglobulin, and calcium), hepatitis B, hepatitis C, HIV status, and serum Ig levels (IgG, IgA and IgM). None of the patients tested positive for hepatitis C or HIV.

Statistical Analysis

We used IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Descriptive statistics were generated for categorical variables using frequencies and percentages and for continuous variables using mean, median, standard deviation, and range values. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were compared using Student's t-test, whereas non-normally distributed variables were compared using the Mann-Whitney U test. The chi-square test or Fisher's exact test was used for comparisons of categorical data.

Overall survival (OS) was defined as the time from diagnosis to death from any cause. Progression-free survival (PFS) was defined as the time from the start of first-line therapy to relapse/progression or death from any cause. OS and PFS were calculated with the Kaplan-Meier method and compared with the log-rank test. All estimates were reported with 95% confidence intervals; values of $p \leq 0.05$ were considered statistically significant.

Results

Baseline Characteristics

A total of 73 patients were analyzed in this study. Their baseline characteristics are summarized in Table 1. PP was detected in 20 of 73 patients (27.3%). PP was most frequently observed in patients with NMZL. It was present in 11 (55%) patients with NMZL, 7 (35%) with MALT lymphoma, and 2 (10%) with SMZL. IgM was the most common paraprotein found in this study (Table 2).

Eleven of the 20 confirmed cases of PP were of the IgM type. Most of these cases were IgM-κ (n=9, 45%), followed by IgG-κ (n=7, 35%), IgM-λ (n=2, 10%), IgA-λ (n=1, 5%), and IgA-κ (n=1, 5%). The presence of PP was significantly associated with advanced age ($p<0.001$), advanced disease stage (III-IV) ($p=0.023$), elevated

Table 1. Baseline clinical characteristics of patients.

	All patients n=73 (%)	PP (–) n=53 (%)	PP (+) n=20 (%)	p
Median age, years (range)	59 (31-83)	56 (31-80)	66 (43-83)	**<0.001***
Sex, male (%)	38 (52%)	25 (47%)	13 (65%)	0.174
Hemoglobin (g/dL)	12.5 (6.6-15.7)	13.1 (9.2-15.7)	11.8 (6.6-14.9)	**0.002***
Albumin (g/dL)	4.13 (2.17-5.1)	4.28 (3.3-5.1)	3.73 (2.17-4.6)	**<0.001***
LDH (U/L)	193 (98-551)	196 (98-551)	177 (109-513)	0.790
B2MG (ng/mL)	2.92 (0.8-11.5)	2.52 (0.8-6.3)	4.72 (1.89-11.5)	**0.001***
Ki-67 (%)	20 (1-40)	20 (7-40)	20 (1-25)	0.955
EMZL (%)	38 (52)	31 (58)	7 (35)	**0.009***
SMZL (%)	14 (19)	12 (23)	2 (10)	
NMZL (%)	21 (29)	10 (19)	11 (55)	
Stage, III-IV (%)	39 (53)	24 (46)	15 (71)	**0.023***
ECOG-PS, ≥2 (%)	3 (4)	0 (0)	3 (15)	**0.018***
Bone marrow involvement, n (%)	32 (49)	18 (34)	14 (70)	**0.026***
B symptoms (%)	12 (16)	6 (11)	6 (30)	0.077
Systemic therapy (%)	44 (60)	30 (68)	14 (70)	0.297
Median follow-up (months)	58	63	54	-

Values of $p<0.05$ are considered statistically significant and shown in bold. PP: Paraproteinemia; LDH: lactate dehydrogenase; B2MG: beta-2 microglobulin; MZL: marginal zone lymphoma; EMZL: extranodal marginal zone lymphoma; SMZL: splenic marginal zone lymphoma; NMZL: nodal marginal zone lymphoma; ECOG-PS: Eastern Cooperative Oncology Group Performance Score.

Table 2. Distribution of paraprotein subtypes by marginal zone lymphoma subtypes.

Subtype	IgG-κ	IgM-λ	IgM-κ	IgA-λ	IgA-κ	Total
MALT lymphoma, n	3	1	2	0	1	7
SMZL, n	2	0	0	0	0	2
NMZL, n	2	1	7	1	0	11
Total, n	7	2	9	1	1	20

MALT: Mucosa-associated lymphoid tissue; SMZL: splenic marginal zone lymphoma; NMZL: nodal marginal zone lymphoma; Ig: immunoglobulin.

β2-microglobulin level (p=0.001), decreased hemoglobin level (p=0.002), decreased albumin level (p<0.001), and bone marrow involvement (p=0.026). Sex, elevated LDH level, and elevated Ki-67 level were not associated with PP.

Survival Analysis

The prognostic value of PP and other clinical outcomes is summarized in Table 3. The median follow-up period was 58 (range: 3-200) months, during which 18 relapsed or refractory cases were observed and 10 patients died. Among the deaths, three were attributed to sepsis. Four patients died due to lymphoma-related causes, including two deaths from aggressive lymphoma transformation and two from disease progression. For the remaining three patients, the exact causes of death could not be determined due to the deaths occurring outside the hospital.

Median OS and PFS were not reached. The mean OS and PFS were 169.9±8.5 and 146.4±10.6 months, respectively. The OS rates at 5 and 10 years were 87.2% and 81.9%, while the PFS rates were 71.5% and 68.3%, respectively.

Patients with PP had significantly shorter survival. The mean OS rates were 73.8 months versus 178.8 months (p=0.046) and the 5-year OS rates were 69.7% versus 93.0%, respectively, for patients with and without PP. Similarly, the mean PFS was 63.5 months in patients with PP versus 159.7 months in those without (p=0.049), with respective 5-year PFS rates of 56.8% and 76.8% (Figure 1).

The effect on survival was more pronounced among patients with IgM-type PP (IgM-PP). These patients had shorter OS (58.8 months vs. 178.2 months, p=0.006; 5-year OS: 48.5% vs. 92.8%) and PFS (45.2 months vs. 157.4 months, p=0.004; 5-year PFS: 25.3% vs. 78.5%) (Figure 2).

We further examined the impact of PP for each histological subtype. However, upon analyzing the subtypes individually, the effect of PP on survival was not statistically significant. For cases

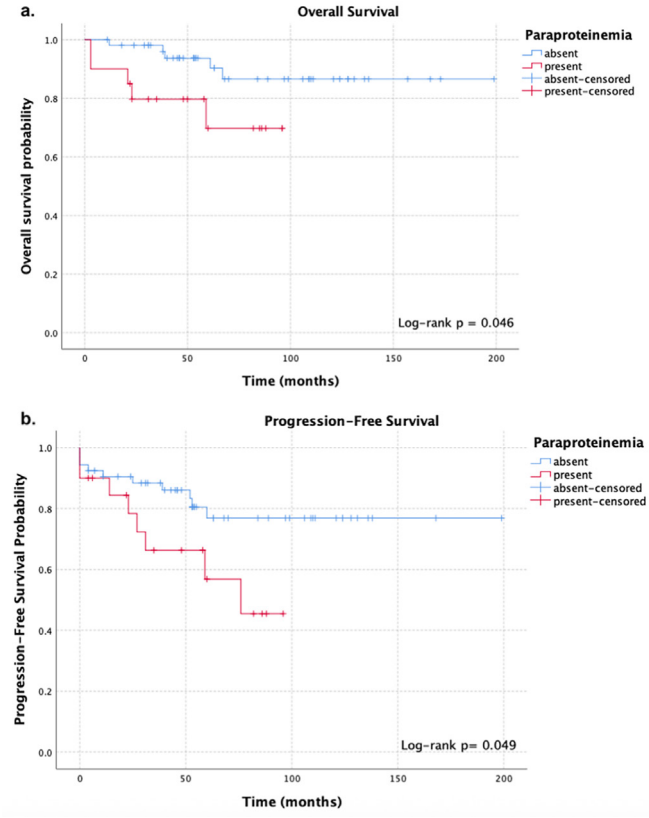

Figure 1. Kaplan-Meier curves for (a) overall survival and (b) progression-free survival according to paraproteinemia status.

Table 3. Prognostic value of paraproteinemia and clinical factors for survival outcomes.

	All patients, n=73	Deceased, n=10	OS p value	Relapsed or refractory disease, n=18	PFS p value
Sex, male, n (%)	38 (52)	7 (70)	0.191	12 (67)	0.128
EMZL, n (%)	38 (52)	2 (20)		6 (33)	
SMZL, n (%)	14 (19)	2 (20)	**0.017***	3 (17)	**0.009***
NMZL, n (%)	21 (29)	6 (60)		9 (50)	
PP, n (%)	20 (27)	5 (50)	**0.046***	8 (44)	**0.049***
IgM-PP, n (%)	11 (15)	6 (60)	**0.006***	6 (33)	**0.004***
Autoimmune disease, n (%)	22 (30)	1 (10)	0.143	6 (33)	0.920
ECOG-PS ≥ 2, n (%)	3 (4)	3 (30)	**<0.001***	3 (17)	**<0.001***
Stage III-IV disease, n (%)	39 (53)	8 (80)	0.059	13 (72)	**0.035***
Bulky disease (>5 cm), n (%)	5 (7)	1 (10)	0.910	3 (17)	0.051
Bone marrow infiltration, n (%)	32 (44)	7 (70)	0.083	10 (56)	0.297
B symptoms, n (%)	12 (16)	3 (30)	0.202	6 (33)	**0.009***
Systemic therapy, n (%)	44 (60)	7 (70)	0.466	14 (78)	**0.035***

Values of p<0.05 are considered statistically significant and shown in bold. PP: Paraproteinemia; IgM-PP: immunoglobulin M paraproteinemia; MZL: marginal zone lymphoma; EMZL: extranodal marginal zone lymphoma; SMZL: splenic marginal zone lymphoma; NMZL: nodal marginal zone lymphoma; ECOG-PS: Eastern Cooperative Oncology Group Performance Score; OS: overall survival; PFS: progression-free survival.

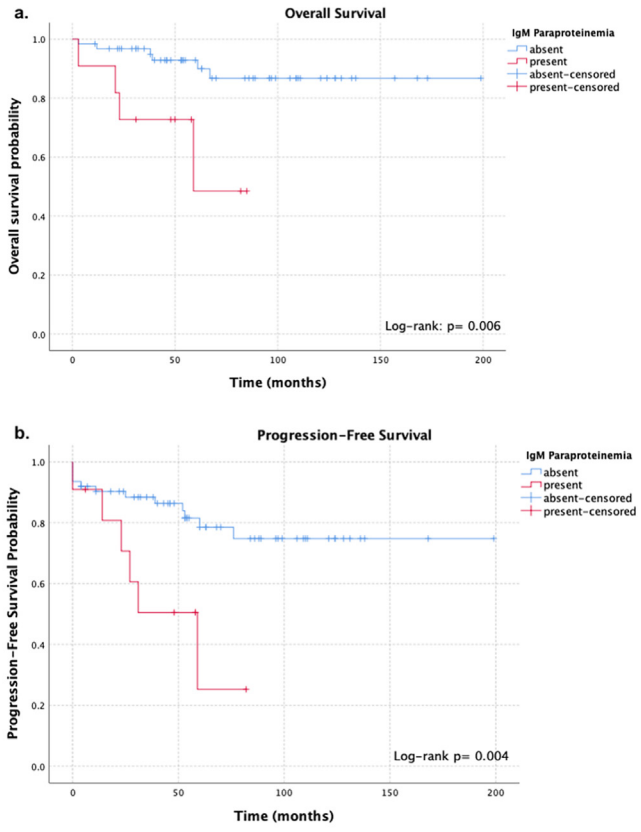

Figure 2. Kaplan-Meier curves for (a) overall survival and (b) progression-free survival according to IgM paraproteinemia status.
IgM: Immunoglobulin M.

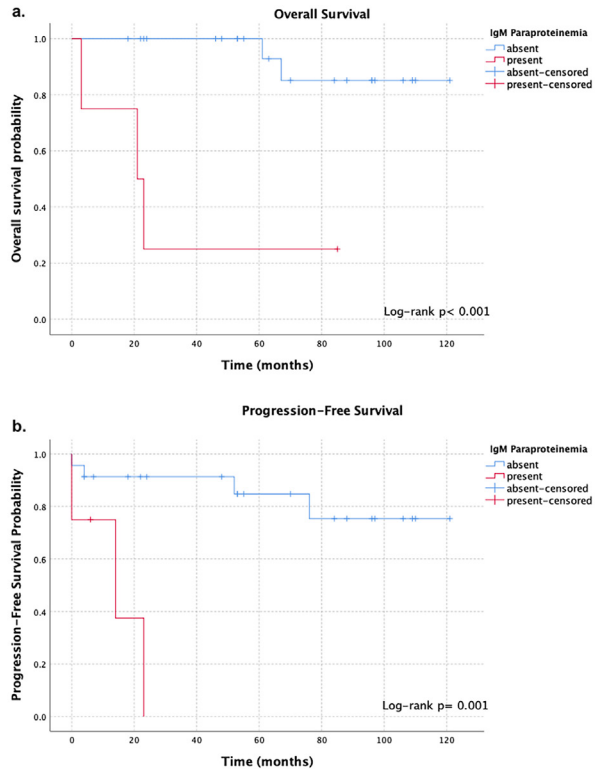

Figure 3. Kaplan-Meier curves for (a) overall survival and (b) progression-free survival in patients treated with R-CHOP-like regimens, stratified by IgM paraproteinemia status.
IgM: Immunoglobulin M.

of MALT lymphoma, the IgM-PP group was very small (n=3), but these patients had significantly shorter OS than the others (70.5 months vs. 152.6 months, p=0.010), a result that should be interpreted with caution due to the small sample size (Table 2). There was no significant difference in OS or PFS among other PP subtypes (p=0.553 and p=0.476, respectively).

The overall response rate (ORR) of patients who were treated with chemoimmunotherapy and had PP was 12/14 (86%) compared to 27/29 (93%) for those without PP (p>0.05). The CR rate of patients with PP was 7/14 (50%) compared to 12/29 (59%) for those without PP (p>0.05). The ORR of patients who were treated with an R-CHOP-like regimen and had PP was 8/9 (89%) compared to 17/18 (94%) for those without PP (p>0.05). The CR rate of patients who were treated with an R-CHOP-like regimen and had PP was 4/9 (44%) compared to 11/18 (61%) for those without PP (p>0.05).

We further analyzed patients who required systemic therapy as first-line treatment. OS and PFS did not differ with the presence or absence of PP and IgM-PP at diagnosis. Patients with IgM-PP who received chemoimmunotherapy had shorter PFS (mean: 39.1 months vs. 96.2 months, p=0.036). Within the specific subgroup of patients with IgM-PP receiving an R-CHOP-like regimen as the most common systemic therapy, significantly shorter OS (mean: 33 months vs. 112.5 months, p<0.001) and PFS (mean: 13.9 months vs. 101.9 months, p=0.001) were observed compared to patients without IgM-PP (Figure 3). Due to the limited overall number of patients and the small number of patients receiving other systemic therapies, further survival analyses for other systemic regimens were not feasible.

Discussion

Although MZL is an indolent lymphoma, it may present with relapsed/refractory disease or histological transformation over time. Identifying prognostic factors is therefore crucial. In our study, the presence of PP was significantly associated with advanced age (≥65 years), advanced-stage disease, elevated β2-microglobulin, decreased hemoglobin and albumin levels, and bone marrow infiltration. Importantly, the presence of PP significantly shortened OS and PFS. When we analyzed MZL subtypes, we observed that only IgM-PP significantly shortened OS in patients with MALT lymphoma.

Previous studies reported the PP incidence in MZL to range from 5% to 46% [12,13,14,16,17,18,19,25]. In our cohort, PP was detected in 20 of 73 patients (27.3%), consistent with previous studies. Notably, the incidence of PP in NMZL has been previously reported to range from 5% to 40% [16,18,19]. In our study, 55% of NMZL patients had PP, which is higher than the rates previously reported for cohorts in the literature [12,13,16,18,26], possibly due to limited sample sizes or institutional differences in patient profiles.

There is growing evidence that the presence of PP is linked to poor prognosis in MZL and other lymphoma subtypes [8,10,11,15,27,28]. Cases of FL with PP were associated with decreased PFS and OS, and PP was an independent risk factor in patients over 60 years of age [1]. Similarly, chronic lymphocytic leukemia patients with IgM-PP were found to have more advanced stages, more del(17p)/TP53 mutations, and shortened survival [8]. Several studies have investigated the prognostic impact of PP in MZL. PP has been correlated with decreased survival, especially among patients with non-gastric MALT lymphoma and those with multiple mucosal sites involved [16,28,29]. Another study demonstrated that MALT lymphoma patients with Ig and IgM-PP had shortened OS and PFS; PP was identified as an independent prognostic factor and the authors suggested that incorporating PP into the MALT-Lymphoma International Prognostic Index (IPI) score could help in selecting optimal treatment and predicting prognosis [14].

Consistent with previous findings, our study demonstrated that PP, and particularly the IgM subtype, significantly shortened both OS and PFS. While this effect was observed across MZL subtypes, it reached statistical significance only for MALT lymphoma. Although PP is commonly linked with advanced stage, bone marrow involvement, and multiple extranodal sites, our data suggest that it reflects more than the overall tumor burden. Notably, some patients with early-stage disease also presented with PP despite the absence of significant tumor burden. This suggests that PP may serve as an independent prognostic marker rather than merely indicating disease extent and may provide insight into the underlying biological nature of tumors.

Our findings, together with those of prior studies, indicate that PP, and especially the IgM subtype, may reflect more aggressive biological behavior in MZL, even in early-stage disease. These findings highlight the importance of thorough staging and may justify the consideration of systemic therapy instead of relying solely on localized treatment approaches in selected cases.

Several studies have linked IgM-PP with adverse biological features and poor outcomes under R-CHOP [10,30]. Some studies suggested that bendamustine-rituximab (BR) and chemoimmunotherapies may be preferred over R monotherapy in patients with PP [16]. In our cohort, patients with IgM-PP treated with R-CHOP-like regimens had significantly shorter OS and PFS. Similarly, among patients who received chemoimmunotherapy, inferior PFS was observed. These findings suggest that R-CHOP-like regimens could be associated with shorter survival in this subgroup, and it may be reasonable to prioritize BR treatment in this patient group. Nevertheless, further investigation is required to confirm this.

Histological transformation to aggressive lymphoma remains a concern in MZL. Some studies determined that the presence of M-protein may increase the risk [16]. In our study, during a median 58-month follow-up period, aggressive lymphoma transformation was observed in 2 of 73 patients (2.7%), both of whom did not have PP. The cumulative incidence of transformation did not significantly differ between groups in our study (p=0.402), although the number of events was too small to draw definitive conclusions. Clarifying the potential association will require studies with greater sample sizes and longer observation periods.

Recently, Arcaini et al. [21] established the MZL-IPI, which applies to all MZL patients and incorporates hemoglobin level, lymphocyte count, the presence of NMZL or disseminated disease, LDH level, and platelet count. In our cohort, PP was more frequent in NMZL patients and was associated with decreased hemoglobin level and inferior survival. Given the increasing evidence, we propose that PP be evaluated for incorporation into future prognostic models.

Study Limitations

Our study has several limitations. First, its retrospective single-center design and its relatively small sample size may have introduced selection biases and limited the generalizability. Second, quantitative values of Ig levels were not recorded, which limited our ability to assess their prognostic relevance. Third, the number of histological transformations was limited to only two cases in the entire cohort, which reduced the ability to draw definitive conclusions regarding the relationship between PP and transformation risk. Finally, the variety of treatment protocols limited the generalizability of our results. Considering the limited sample size of our study and the heterogeneity in the literature, future studies concentrating specifically on MZL patients are necessary. These new analyses could help resolve or clarify the prognostic role of PP in MZL. As more data accumulate, researchers will be able to perform meta-analyses to definitively clarify the prognostic role of PP in MZL and better guide clinical practice.

Conclusion

Our study provides evidence that PP, and particularly PP of the IgM subtype, is an adverse prognostic factor in MZL. We found that IgM-PP markedly shortened PFS and OS in patients with MZL. To our knowledge, this study is the first to demonstrate a

survival disadvantage for MZL patients with IgM-PP specifically, emphasizing the importance of assessing paraprotein status at diagnosis. Evaluating all MZL patients for PP as part of the initial workup may help in stratifying patients and choosing optimal treatment modalities. We recommend investigating PP in all patients regardless of histological subtype and stage, which could help clinicians choose more aggressive and appropriate treatment strategies from the outset. Further studies are needed to validate these findings and explore personalized treatment strategies for patients with PP.

Ethics

Ethics Committee Approval: This study was approved by the Dokuz Eylül University Faculty of Medicine's Local Ethics Committee (decision no: 2022/15-11; date: 20 April 2022) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: Due to the study's retrospective nature, informed consent was waived.

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The authors used ChatGPT (OpenAI, GPT-4; accessed April 2025) for language editing and table formatting. All content was reviewed and approved by the authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K.; Concept: B.K., B.Y., F.D.; Design: B.K., B.Y., F.D.; Data Collection or Processing: B.K., B.Y.; Analysis or Interpretation: B.K., B.Y., F.D.; Literature Search: B.K., B.Y.; Writing: B.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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