DOI: 10.14744/ejmi.2025.88777
EJMI 2025;9(2):72–78

Research Article

Comparison of the Prognostic Scoring Systems in Patients with Splenic Marginal Zone Lymphoma

Erkam Kocaaslan,[1] Fatma Arıkan,[2] Asu Fergün Yılmaz,[2] Işık Atagündüz,[2] Ayşe Tülin Tuğlular,[2] Tayfur Toptaş[2]

[1]Department of Medical Oncology, Marmara University Hospital, Istanbul, Türkiye
[2]Department of Hematology Marmara University Hospital, Istanbul, Türkiye

Abstract

Objectives: SMZL is a rare disease that typically progresses slowly. However, some patients experience poorer outcomes compared to others. Two important scoring systems have been developed to predict prognosis in SMZL. The Italian Lymphoma Intergroup (IIL) scoring system was primarily created based on a cohort of patients treated before the era of rituximab. On the other hand, the Splenic Marginal Zone Lymphoma Study Group (SMZLSG) scoring system includes patients who were treated with rituximab. Our objective was to compare these two prognostic scoring systems in terms of predicting overall survival and time-to-next treatment in SMZL patients.

Methods: We classified thirty-two patients, who received various types of treatment, using both scoring systems. The risk categories defined by each scoring system were compared. Cox regression analysis was performed to evaluate the predictive value of each score on time-to-next treatment and treatment/follow-up modalities.

Results: We observed that the IIL system classified more patients into higher-risk groups compared to the SMZLSG scoring system. In Cox regression analysis, the SMZLSG risk score was found to be an independent and strong predictor of time-to-next treatment and treatment/follow-up modalities (OR: 3.72, 95% CI: 1.82–7.62, $p < 0.001$).

Conclusions: Based on our findings, we conclude that while both prognostic systems perform well, the SMZLSG scoring system provides better stratification of patients compared to the IIL system.

Keywords: SMZL, Splenic marginal zone lymphoma, Prognostic score, IIL, SMZLSG, Time-to-next treatment, Overall survival

Cite This Article: *Kocaaslan E, Arıkan F, Yılmaz AF, Atagündüz I, Tuğlular AT, Toptaş T. Comparison of the Prognostic Scoring Systems in Patients with Splenic Marginal Zone Lymphoma. EJMI 2025;9(2):72–78.*

Splenic marginal zone lymphoma (SMZL) is a rare subgroup of slowly progressing non-Hodgkin lymphoma (NHL). It occurs in approximately 1% of all NHL cases and about 20% of marginal zone lymphomas. The disease usually begins at ages 65-70 and is less common under age 50. While SMZL can be observed worldwide, it is more commonly diagnosed in individuals of white race, occurring twice as often compared to other racial groups. It is seen at similar rates among men and women. Incidence of SMZL is reported to be 1.3 cases per 1,000,000 individuals, and this rate has been increasing over time.[1]

Two main scoring systems are used to predict prognosis in SMZL patients. The first one is the IIL (Italian Lymphoma Intergroup) prognostic index, which was developed using data from 309 patients diagnosed with SMZL between 1989 and 2004. Most of these patients were treated during the pre-rituximab era.[2] The second scoring system is the SMZLSG (Splenic Marginal Zone Lymphoma Study Group) prognostic index. It was developed using data from 366 patients diagnosed with SMZL. This index was also applied to a group of 227 patients, including individuals who received rituximab as part of their treatment.[3]

Address for correspondence: Erkam Kocaaslan, MD. Department of Medical Oncology, Marmara University Hospital, Istanbul, Türkiye
Phone: +90 553 053 31 92 **E-mail:** erkamkocaaslan@gmail.com

Submitted Date: March 19, 2025 **Revision Date:** April 07, 2025 **Accepted Date:** April 17, 2025 **Available Online Date:** July 11, 2025

Due to the rarity and indolent nature of SMZL, determining the optimal management and standard treatment for the disease poses challenges. Many studies conducted on SMZL consist of prospective studies that have either been completed or are currently ongoing. Rituximab, a targeted therapy, is considered an active treatment option for SMZL. It has demonstrated high rates of complete response when used as monotherapy, and it is associated with extended periods of time-to-next treatment. Additionally, rituximab has been associated with good long-term progression-free survival in patients with SMZL.[4]

In addition to active treatment options, a watch-and-wait strategy is considered a valid approach for many SMZL patients. Due to the slow progression of the disease, patients with a low risk of progression can be closely monitored without immediate treatment for extended periods of time. While the choice of treatment is not solely determined by the prognostic scoring systems, predicting survival and time-to-next treatment is crucial for providing patients with proper information and making informed decisions about their care. The aim of our study was to compare scoring systems used for prognosis in patients with SMZL. By evaluating these scoring systems, we can gain insights into their effectiveness in predicting outcomes and informing clinical management decisions for SMZL patients.

Methods

Study Design

In this study, we evaluated patients who were diagnosed with SMZL and received follow-up and treatment between 2005 and 2020. Various clinical and laboratory parameters were recorded, including age, gender, presence of B symptoms, spleen size, positron emission tomography/computed tomography (PET/CT) involvement pattern, bone marrow involvement, peripheral blood involvement, complete blood count parameters, albumin, lactate dehydrogenase (LDH), beta-2 microglobulin, sedimentation rate, hepatitis markers, and cytogenetic features. The patients were classified into prognostic risk categories according to both the IIL and SMZLSG scoring systems.

Patients aged 18 and over were included in the study. They also needed to have a pathology or flow cytometry report confirming the diagnosis of SMZL. Furthermore, patients were required to have information available regarding their previous treatments and the details of those treatments. Pediatric patients (those under 18 years of age) were excluded from the study. Patients whose medical files did not contain the necessary data required for meaningful study participation were also excluded.

We initially screened the institutional hematology database using the keyword "lymphoma" and obtained 1520 patient files. Out of these, 1178 patients with lymphoma subtypes other than MZL were excluded. This left us with 342 patients diagnosed with MZL. Among these, 282 patients were further excluded as they had a non-SMZL diagnosis. Additionally, 26 records were duplicates, and two patient files contained insufficient data. Ultimately, a total of 32 patients were included in our study (Fig. 1). Our study was conducted in accordance with the principles stated in the Declaration of Helsinki.

Definitions and Endpoints

In our study, overall survival (OS) was defined as the time from the diagnosis of SMZL to the date of death or the last time the patient was seen. Time to next treatment (TTNT) was defined as the time from the start of treatment to the date of starting a new treatment, death, or the last time the patient was seen. The primary and secondary endpoints of the study were to evaluate the impact of the scoring systems on TTNT and OS, respectively.

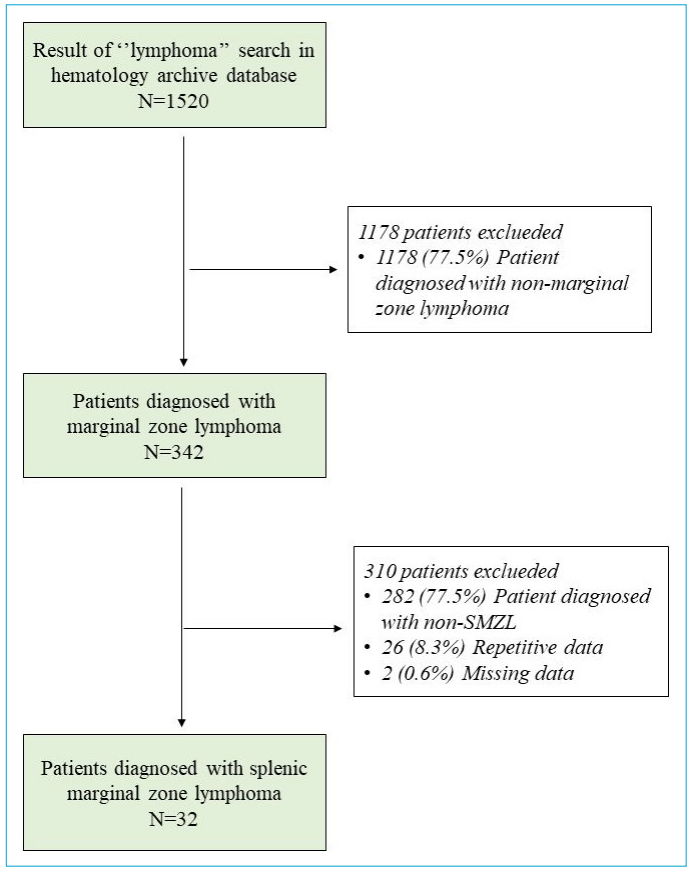

Figure 1. Consort diagram.

Statistical Analysis

P<0.05 was considered statistically significant. Survival analyses were conducted using the Kaplan-Meier method. The log-rank test was used for survival data, and Cox proportional hazard regression analysis was used for multivariate analysis. The magnitude of risk was expressed as the hazard ratio (HR) along with the corresponding 95% confidence interval (95% CI). To assess the discriminatory ability of the stratification systems, the follow-up period was restricted to 48 months.

Results

Patient Characteristics

Median age of our study population was 63 years, with half of the patients being male. B symptoms were present in 43.8% of the cases. Physical examination revealed palpable splenomegaly in 84.4% of the patients. The median spleen length determined by imaging was 193 cm in diameter. Splenic 18fluorodeoxyglucose (FDG) uptake, assessed by PET/CT, was available in 22 patients, with a median FDG SUVmax of 4.4. Bone marrow involvement was observed in 96.9% of the patients, while peripheral blood involvement was seen in 81.2% of them (Table 1).

The median values of white blood cells, hemoglobin, and platelets in the cases were 5,700/μL, 12.1 mg/dL, and 124,000/μL, respectively. Half of the patients had LDH values above the upper limit of normal. Among the 29 patients who underwent viral hepatitis serology at the time of diagnosis, four (12.5%) tested positive for HbsAg, and one patient (3.1%) tested positive for anti-HCV. Deletion 7q was detected in only one (3.1%) out of the 20 patients (Table 2).

Treatment

Out of the total number of patients, 13 (40.6%) were managed with a watch and wait strategy. Five patients (15.6%) received rituximab monotherapy, while nine patients (15.6%) were treated with R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, prednisolone). Additionally, five patients (15.6%) underwent splenectomy. Only two patients (6.2%) received rituximab maintenance after first-line therapy. For second-line therapy, single-agent rituximab, R-CHOP, and splenectomy were used (Table 3).

Prognostic Stratification

According to SMZLSG, 15.6% of patients were at high risk. In contrast, 37.5% of patients were at high risk according to IIL. Among the patients classified as high-risk by the IIL classification, seven patients (21.9%) were reclassified as intermediate risk according to the SMZLSG system. Conversely, four patients (12.5%) who were initially classified as intermediate risk according to the IIL scoring system were categorized as low risk according to the SMZLSG system. It was observed that the IIL scoring system tended to place patients in higher-risk groups compared to the SMZLSG system (p<0.001, Table 4).

Impact of Prognostic Scoring Systems on Survival

Median follow-up was 57 months (range: 5 to 200 months). Median overall survival has not been reached. Overall survival probability at 5 years was 64.1% (95% CI: 41.5% to 79.5%) (Fig. 2). Median TTNT was 48.0 months (95% CI: 29.5 to 64.1 months). The probability of TTNT at 5 years was 30.8% (95% CI: 15.5% to 47.5%) (Fig. 3).

According to SMZLSG, 4-year overall survival was 60.0% in

Table 1. Demographic and the clinical characteristics of the patients

Variable	N	Value
Age, median (range)	32	63 (32-83)
Male, n (%)	32	16 (50)
B symptoms, n (%)	32	14 (43.8)
Splenomegaly, n (%)	32	27 (84.4)
Spleen long axis size cm, median (range)	32	193 (100-340)
Spleen index cm^3, median (range)	32	1.124 (400-7,040)
PET-CT spleen FDG uptake SUVmax, median (range)	22	4.4 (2.3-7.7)
PET-CT Deauville value of spleen involvement, median (range)	22	4 (1-4)
Extrahilar lymph node involvement, n (%)	32	17 (53.1)
Bone marrow involvement, n (%)	32	31 (96.9)
Intrasinusoidal involvement in bone marrow, n (%)	32	5 (15.6)
Peripheral blood involvement, n (%)	32	26 (81.2)

PET/CT: positron emission tomography / computer tomography; cm: centimeter; FDG: fluorodeoxyglucose; SUVmax: maximum standardized uptake value.

Table 2. Laboratory data

Variable	N	Value
WBC, median (range) x10³/µL	32	5.7 (1.5-95.0)
Neutrophil median (range) x10³/µL	32	2.5 (0.3-6)
Lymphocyte, median (range) x10³/µL	32	2.1 (0.4-88)
Hemoglobin, median (range) /g/dL	32	12.1 (6.7-15.2)
Thrombocyte, median (range) x10³/µL	32	124 (39-341)
Albümin, median (range) mg/dL	32	3.9 (3-5)
LDH, median (range) U/L	32	249 (97-1200)
Beta-2 microglobulin, median (range)	15	2,458 (1,567-26,143)
Erythrocyte sedimentation rate, median (range)	30	22 (1-120)
HbsAg positive, n (%)	29	4 (12.5)
Anti-HCV positive, n (%)	29	1 (3.1)
Anti-HIV positive, n (%)	29	0 (0)
Cytogenetic, n (%)	32	
7q deletion, n (%)		1 (3.1)
Normal karyotype, n (%)		19 (59.3)
Unknown, n (%)		12 (37.5)

WBC: White Blood Cell; LDH: Lactate Dehydrogenase; HbsAg: Hepatitis B surface antigen; Anti-HCV: anti hepatitis-C virus; Anti-HIV: anti-human immunodeficiency virus.

Table 3. Treatments

Treatment	N (%)
First Line	
Watch and wait	13 (40.6)
Rituximab	5 (15.6)
R-CHOP	9 (28.1)
Splenectomy	5 (15.6)
Rituximab maintenance after first line treatment	2 (6.2)
Second Line	
Watch and wait	25 (78.1)
Rituximab	3 (9.4)
R-CHOP	1 (3.1)
Splenectomy	3 (9.4)
Third Line	
Watch and wait	31 (96.9)
Rituximab-lenalidomide	1 (3.1)

R-CHOP: rituximab, cyclophosphamide, Adriamycin, vincristine, prednisolone.

Table 4. Stratification of patients with different prognostic scoring systems

	SMZLSG			
Risk category, n (%)	Low	Medium	High	Total
IIL				
Low	9 (28.1)	0	0	9 (28.1)
Medium	4 (12.5)	7 (21.9)	0	11 (34.4)
High	0	7 (21.9)	5 (15.6)	12 (37.5)
Total	13 (40.6)	14 (43.8)	5 (15.6)	32

SMZLSG: denotes splenic marginal zone lymphoma study group.

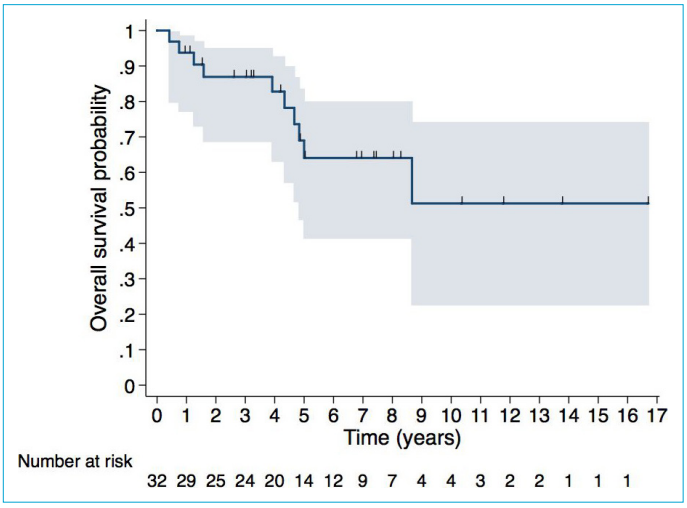

Figure 2. Overall survival in all cohorts.

the high-risk group, 76.0% in the intermediate-risk group, and 100% in the low-risk group (p=0.06, Fig. 4). Conversely, the four-year OS rates were 74.1%, 77.1%, and 100% for high, intermediate, and low-risk patients, respectively, based on the IIL prognostic stratification (p=0.26, Fig. 5). According to IIL, TTNT was not reached in the low-risk group, 47 months (95% CI: 28.8-64.2) in the intermediate risk group and 30 months (95% CI: 1.1-58.9) in the high-risk group (p=0.08, Fig. 6). According to SMZLSG, median TTNT

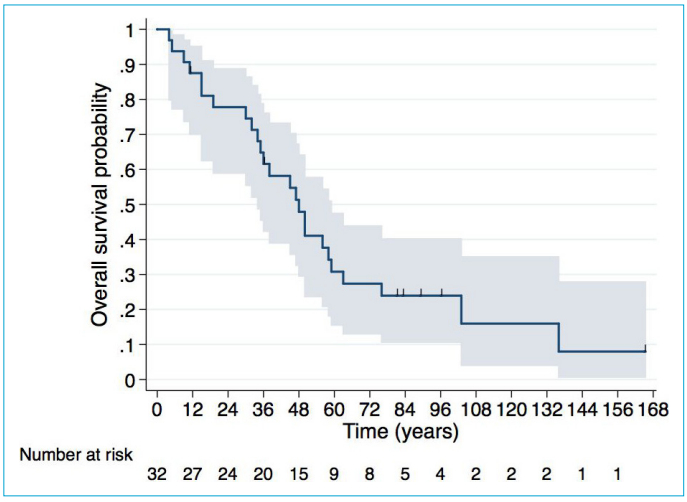

Figure 3. TTNT in all cohort.

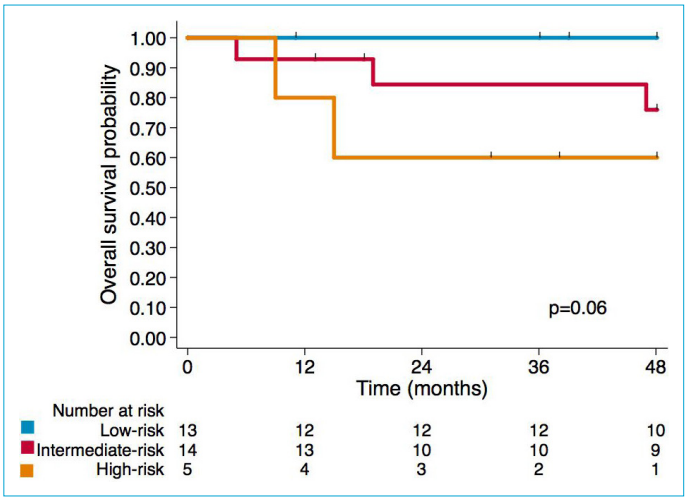

Figure 4. OS according to SMZLSG.

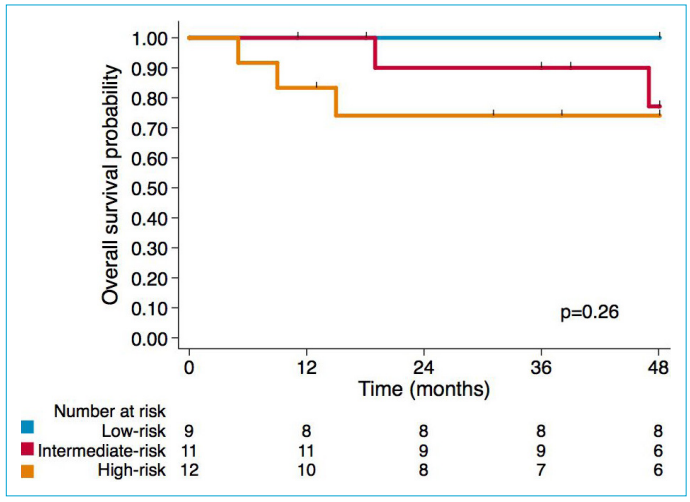

Figure 5. OS according to IIL.

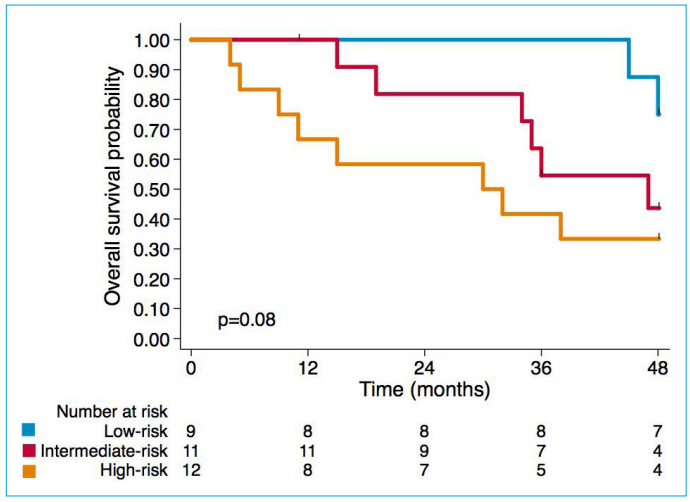

Figure 6. TTNT according to IIL.

was not reached in the risk groups. 59 months, 36 months (95% CI: 14-58) and 30 months (95% CI: 1.1-62.2), respectively (p=0.001, Fig. 7).

According to Cox regression analysis, SMZLSG was found to be a strong and independent predictor of TTNT (HR for SMZLSG: 3.72, 95% CI: 1.82-7.62, p<0.001; HR for treatments: 0.81, 95% CI: 0.57-1.17, p=0.27).

Discussion

In this study, our objective was to examine the influence of prognostic scoring systems on OS and TTNT in a cohort of 32 patients diagnosed with SMZL. Our findings revealed that risk stratification using the SMZLSG scoring system resulted in improved differentiation of patients across different risk groups. Notably, the prognostic significance of

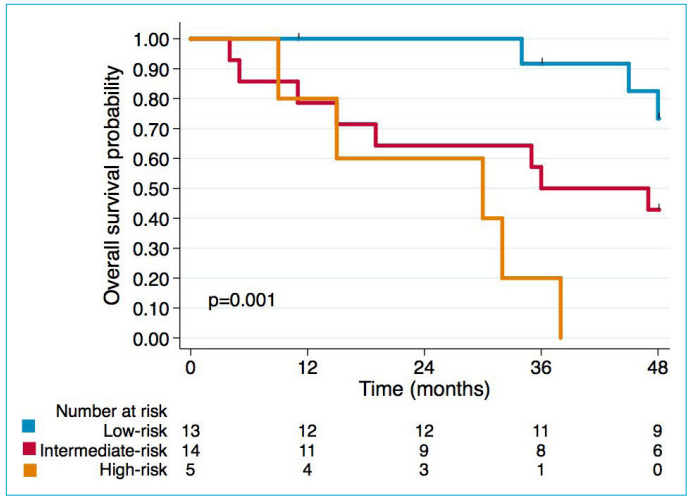

Figure 7. TTNT according to SMZLSG.

the SMZLSG scoring system remained independent of the effects of any treatment modalities.

Systemic treatment options for SMZL include rituximab monotherapy, chemoimmunotherapy (such as R-CHOP), and splenectomy, all of which have demonstrated effectiveness in managing the disease. Due to the rarity of SMZL, there is a lack of prospective randomized studies conducted on large cohorts of SMZL patients. So, treatment decisions primarily rely on findings from retrospective studies and experience gained from managing other low-grade B-cell lymphomas. Presently, the most effective treatment options for SMZL are splenectomy and rituximab monotherapy. Both approaches have shown high response rates and prolonged response durations.[5-7] In our study, nearly half of the patients were managed with a watch-and-wait approach. The remaining half of the patients received either rituximab monotherapy or chemoimmunotherapy. Interestingly, we did not observe any significant survival advantage among these different treatment modalities when comparing them to each other.

In studies conducted in Western countries, an association between SMZL and anti-HCV (hepatitis C virus) positivity has been traditionally reported. However, a recent study conducted in Turkey revealed a relationship between HbsAg (hepatitis B surface antigen) positivity and SMZL. This suggests that the association between viral infections and SMZL may vary across different geographic regions.[8, 9] Our study further supports the observation that HBsAg (hepatitis B surface antigen) positivity is more prevalent compared to anti-HCV (hepatitis C virus) positivity in patients with SMZL. This finding suggests that hepatitis B infection may have a stronger association with SMZL in our study population.

The course of SMZL is typically indolent, with a median OS exceeding 10 years, indicating a favorable prognosis. [10] However, it is evident that some patients exhibit a more aggressive disease course with a median survival of only 18 months.[11] In a shorter follow-up, we observed a 5-year OS rate of approximately 64.1%. Although the proportion of patients with a high-risk score was lower, the findings suggest that the median OS in our cohort might be less than 10 years, supports the previous observations. Therefore, it is crucial to identify patients with a poor prognosis, as they may benefit from investigational therapies. Distinguishing these individuals enables the implementation of targeted interventions and management strategies aimed at improving their outcomes. By identifying high-risk patients early on, healthcare providers can offer personalized treatment approaches and closely monitor their progress, potentially leading to better therapeutic responses and extended survival. This underscores the importance of accurate prognostic scoring systems in guiding clinical decision-making and optimizing patient care in the context of SMZL.

In a cohort study involving 593 patients with SMZL, the SMZLSG prognostic index was compared to the IIL prognostic index. Both scoring systems were found to be effective in stratifying patients based on their prognosis. However, the SMZLSG scoring system exhibited better performance in terms of lymphoma-specific survival. This suggests that the SMZLSG prognostic index may provide more accurate risk stratification and prognostic information for SMZL patients, specifically in relation to their lymphoma-related survival.[12] In our analysis, both the SMZLSG and IIL risk scoring systems effectively classified patients with SMZL in terms of OS and TTNT. However, the SMZLSG scoring system demonstrated superior performance compared to the IIL scoring system in terms of both OS and TTNT. Notably, the IIL scoring system classified a greater number of patients into the high-risk group compared to the SMZLSG scoring system.

The retrospective nature of the study and the small number of patients may limit the predictability of the findings. Further validation and larger-scale studies are necessary to develop better scoring systems which may also incorporate molecular and cytogenetic data in predicting prognosis in SMZL.

In conclusion, this study provides into the prognostic performance of two scoring systems in SMZL patients. Both the SMZLSG and IIL prognostic scoring systems have shown their utility in effectively stratifying patients with SMZL. However, the SMZLSG risk score appears to provide more informative results for identifying patients who are at a higher risk of requiring treatment and facing mortality.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethics committee approval was obtained from Marmara University Faculty of Medicine Clinical Research Ethics Committee (Approval Number: 09.2020.1147, Date: 30.11.2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: No to authors declare conflict of interest.

Authorship Contributions: EK and TT designed the study, performed the statistical analyses, wrote the manuscript and prepared the final draft. FA, AFY, IKA and Tulin Tuglular contributed the data collection, intellectual conceptualization, and final preparation of manuscript draft.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

References

1. Liu, L., et al., Splenic marginal zone lymphoma: a population-based study on the 2001–2008 incidence and survival in the United States. 2013. 54(7): p. 1380-1386.
2. Arcaini, L., et al., Splenic marginal zone lymphoma: a prognostic model for clinical use. Blood, 2006. 107(12): p. 4643-4649.
3. Montalban, C., et al., Stratification approach for splenic marginal zone lymphoma based on hemoglobin, platelet count, high LDH and extrahilar lymphadenopathy: the HPLL/ABC system. 2011, American Society of Hematology.
4. Kalpadakis, C., et al., Rituximab monotherapy in splenic marginal zone lymphoma: prolonged responses and potential benefit from maintenance. Blood, The Journal of the American Society of Hematology, 2018. 132(6): p. 666-670.
5. Pata, G., et al., Peri-operative complications and hematologic improvement after first-line splenectomy for splenic marginal zone lymphoma. 2016. 57(6): p. 1467-1470.
6. Lenglet, J., et al., Long-term follow-up analysis of 100 patients with splenic marginal zone lymphoma treated with splenectomy as first-line treatment. 2014. 55(8): p. 1854-1860.
7. Xing, K.H., et al., Outcomes in splenic marginal zone lymphoma: analysis of 107 patients treated in British Columbia. 2015. 169(4): p. 520-527.
8. Hermine, O., et al., Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. 2002. 347(2): p. 89-94.
9. Okay, M., et al., Splenic marginal zone lymphoma in Turkey: association with hepatitis B instead of hepatitis C virus as an etiologic and possible prognostic factor-A multicenter cohort study. 2020. 37(2): p. 84.
10. Florindez, J.A., et al., Splenic marginal zone lymphoma: A US population-based survival analysis (1999-2016). Cancer, 2020. 126(21): p. 4706-4716.
11. Chacón, J.I., et al., Splenic marginal zone lymphoma: clinical characteristics and prognostic factors in a series of 60 patients. Blood, The Journal of the American Society of Hematology, 2002. 100(5): p. 1648-1654.
12. Montalbán, C., et al., Risk stratification for S plenic M arginal Z one L ymphoma based on haemoglobin concentration, platelet count, high lactate dehydrogenase level and extrahilar lymphadenopathy: development and validation on 593 cases. British journal of haematology, 2012. 159(2): p. 164-171.