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Prognosis in marginal zone lymphoma: a comprehensive review

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ABSTRACT

Marginal zone lymphomas (MZLs) represent a distinct subset of indolent B-cell lymphomas, including extranodal, nodal, and splenic variants. Despite shared histopathological and immunophenotypic features, their clinical presentation varies significantly based on the site of origin and genetic abnormalities. The heterogeneity of the disease is reflected in its management, particularly in therapeutic strategies and prognosis determination.

Several prognostic tools have been developed to refine risk assessment in MZL subtypes, including the Mucosa-Associated Lymphoid Tissue International Prognostic Index (MALT-IPI), the Haemoglobin Platelets Lactate Dehydrogenase Lymphadenopathy (HPLL) score and its simplified version. Recently, the Marginal Zone Lymphoma International Prognostic Index (MZL-IPI) has emerged as a comprehensive model integrating data from all MZL subtypes and incorporating rigorously validated clinical parameters.

This review aims to synthesize current knowledge on MZL prognosis, critically assess existing prognostic models, and highlight the potential clinical impact of identifying risk stratification.

1. INTRODUCTION

Marginal zone lymphomas (MZLs) account for 7-8% of non-Hodgkin lymphomas, representing the third most common type of B-cell non-Hodgkin lymphoma[1,2]. MZLs encompass three pathology subtypes: extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT lymphoma), splenic MZL (SMZL), and nodal MZL (NMZL). The latest classifications of mature B-cell lymphomas, including the International Consensus Classification (ICC)[3] and the 5th edition of the WHO classification (WHO-HAEM5)[4], agree on diagnostic criteria for NMZL and EMZL and for SMZL, which is classified under the splenic lymphomas/leukaemias category of WHO-HAEM[5].
Environmental, genetic factors, infections, and autoimmune disorders contribute significantly to the pathogenesis of MZLs, particularly EMZLs[6–14]. Chronic antigenic stimulation leads to the expansion of reactive B-cell clones, eventually resulting in malignant transformation[9]. Key genetic alterations identified in MZL, comprising mutations in NOTCH2, KLF2, and TNFAIP3 genes, affect critical pathways regulating cell survival, proliferation, and immune response[15–17].
In recent years, the incidence of MZL has increased by approximately 1.0% per year, likely due to improved diagnostic tools[1,18]. Changes in MZL subtype prevalence have also been observed, with an increased frequency of SMZL and a relative decrease in EMZLs, potentially reflecting variations in predisposing conditions[19–21].
MZL typically has an indolent course, with early-stage disease having an excellent prognosis[1,22,23]. Both gastric and extragastric MALT lymphomas exhibit favourable survival outcomes, with 5-year overall survival (OS) rates exceeding 90% and 10-year survival rates of 75-80%[24]. SMZL also generally has a good prognosis, with about two-thirds of patients surviving five years post-diagnosis and around 20% remaining therapy-free for several years[25,26]. With the introduction of the CD20 antibody rituximab in the treatment, the prognosis of NMZL has improved over the last few years[27]. In different case series, the OS at 5 years was between 57% and 97%[25]; the heterogeneity of the diagnosis might partially explain this difference because of the changes in the pathological delineation and the staging procedures, as well as in the treatment.
Although the median survival exceeds 10 years, MZL still negatively impacts life expectancy compared with the general population, with the exception of gastric MALT, which has a survival similar to that of the general population, especially when diagnosed in early stages[22,23]. In EMZL recurrence is common, affecting 50-60% of patients, with a median time to relapse of approximately 5 years[24]. One-third of patients with SMZL may develop an aggressive disease course, with a median survival of approximately 4 years[28]. Generally, advanced-stage disease and genetic complexity correlate with poorer outcomes across all subtypes, often requiring more aggressive therapeutic strategies and close monitoring[22,23,29].

Furthermore, early disease progression (i.e. progression of disease at 24 months, POD24) and histological aggressive transformation (HT) have emerged as key adverse prognostic factors in relapsed/refractory (R/R) MZL, similar to other indolent non-Hodgkin lymphomas[30–32].
Treatment strategies vary according to subtype and disease stage[29,33]. Overall, therapeutic approaches follow general principles: if an infectious pathogenetic association exists, it is treated regardless of disease stage and symptoms[34–39], radiotherapy is used with curative intent for localized disease[40–42], whereas systemic treatments are generally deferred until symptoms arise. In R/R setting, when histological transformation is excluded, the use of non-cross-resistant chemotherapies is being increasingly replaced by targeted immunotherapies[43–45]. Additionally, emerging monoclonal antibodies such as tafasitamab[46] and loncastuximab[47], and bispecific antibodies[48–51] and CAR-T cell therapy[52] are currently being evaluated in R/R MZL.
Extensive efforts have been made to develop reliable prognostic models for MZL. The International Prognostic Index (IPI) for diffuse large B-cell lymphomas[53] has been used to stratify MZL patients, but its relevance for low-grade lymphomas remains controversial. Similarly, lymphoma-specific indices, such as the Follicular Lymphoma International Prognostic Index (FLIPI and FLIPI2)[54,55] and the Mantle Cell Lymphoma International Prognostic Index (MIPI)[56,57] have been explored. However, these models lack proper validation in MZL[58,59]. Some parameters used in these models, such as white blood cell count and the number of extranodal or nodal sites, may have limited relevance for this lymphoma subtype. For example, while MALT lymphoma commonly involves extranodal sites, its prognosis is not significantly impacted by the extent of nodal dissemination or leukaemic involvement.
As a result, several MZL-tailored prognostic scores have to been proposed, integrating different clinical and biological factors of the disease.
This review aims to provide a comprehensive evaluation of MZL prognosis, highlighting key prognostic factors, differences across subtypes, advancements in molecular and genetic understanding, and the impact of treatment strategies on patient outcomes.

2. PROGNOSTIC FACTORS IN MZL

Studies on the prognosis of MZL have led to the identification of biological and clinical factors. The former include specific molecular features, while the latter include subtypes, disease involvement at diagnosis, and laboratory parameters.
The integration of these variables has resulted in the development of multiple prognostic models; however, these scores rely on heterogeneous and non-standardized endpoints, reflecting the lack of consensus on the most informative outcome measures and limiting cross-study comparability and

clinical applicability. Overall survival, although traditionally regarded as the most robust endpoint, is suboptimal in indolent lymphomas such as MZL because of prolonged survival, competing causes of death, and the impact of subsequent lines of therapy. Consequently, progression-based endpoints, including PFS (progression-free survival) and EFS (event-free survival), have been preferentially adopted in most MZL-specific prognostic models, as they are more sensitive to disease-related events and better capture early biological aggressiveness. More recently, time-dependent surrogate endpoints have gained relevance. POD24 is now recognized as a robust surrogate endpoint marker of inferior OS across MZL subtype[30]. In selected settings, particularly EMZL, response-based metrics, such as CR24 (complete response at 24 months) and TTCR24 (time to complete response within 24 months), have also demonstrated prognostic value[60].

While the adoption of unified endpoints would facilitate comparisons across studies and support the development of global prognostic tools, the optimal prognostic endpoint in MZL is likely context-dependent, varying according to disease subtype, clinical presentation, and treatment strategy. An additional limitation shared by all currently available prognostic models is their intrinsic treatment dependency. Most scores were developed in retrospective cohorts treated with heterogeneous strategies and across different therapeutic eras. As a result, the prognostic impact of individual variables may vary according to the type and timing of treatment and depth of response. This aspect should be carefully considered when applying prognostic indices in contemporary practice, particularly in the context of evolving therapy paradigms.

In addition to clinical and laboratory parameters such as advanced age and systemic symptoms, histological transformation to diffuse large B-cell lymphoma represents a clinically relevant adverse event. Although not formally incorporated into existing prognostic indices, HT is consistently associated with inferior outcomes compared with indolent-phase MZL, with survival largely driven by response to aggressive lymphoma–directed therapy. HT occurs in about 5–10% of MZL cases (about 1% per year)[61]. In a recent meta-analysis of 12 studies, 5- and 10-year cumulative incidence rates of transformation were lower in EMZL (3% and 5%, respectively) than in SMZL (7% and 13%) and NMZL (9% and 13%)[62]. Histologic transformation was associated with a nearly fourfold increased risk of death (subdistribution hazard ratio 3.95), confirming its major negative prognostic impact. Overall survival after transformation remains limited, with reported 5- and 10-year OS rates of approximately 79% and 55%, respectively. To date, no validated prognostic model specifically predicting the risk of histologic transformation in MZL has been developed, and available evidence derives mainly from retrospective analyses and post hoc evaluations. Reported risk factors include failure to achieve complete response to initial therapy, elevated serum levels of lactate dehydrogenase, involvement of more than 4 nodal sites at diagnosis, multiple mucosal sites, CD5

expression, and complex karyotype[63–65]. Moreover and similar to FL, the occurrence of transformation is highly correlated with early progression with up to 7 POD24 subject showing transformed MZL according to a recent report[30]. Molecular data suggest that transformation reflects clonal evolution of the indolent component rather than de novo aggressive lymphoma, with alterations involving epigenetic regulators, along with subtype-specific drivers such as TNFAIP3, TP53, and CDKN2A/B, and genetic lesions affecting the cell cycle, NF-κB pathway, rearrangements of MYC, and loss of p16 protein, contributing to large-cell histological progression[66].

2.1 Biological factors

In SMZL, while easily measurable parameters have demonstrated prognostic significance[26,67,68], the value of molecular markers to predict outcomes is much less clear. Cytogenetically, SMZL is marked by deletion of chromosome 7q in about 40% of cases. Recurrent mutations are found in KLF2, NOTCH, and NF-κB signalling pathways. KLF2 mutations (20-40%) affect NF-κB activation, NOTCH2 mutations occur in 40%, and NF-κB pathway mutations in one-third of SMZLs, while TP53 mutations are present in 15% of cases[15,69,70]. A large IELSG46 study of 303 SMZL spleen samples defined two major molecular clusters: NNK (58%, enriched for NF-κB, NOTCH, and KLF2 alterations) and DMT (32%, with DNA-damage, MAPK, and TLR pathways). NNK cases showed worse survival. Immune profiling revealed two microenvironment types, immune-suppressive and immune-silent, each with distinct genetics and clinical implications, suggesting a refined SMZL classification and targets for tailored therapy[71].

After the study by Baldini et al.[72] focused on investigating the prognostic implications of TP53 mutations in SMZL, researchers analysed unmutated immunoglobulin heavy variable (IGHV) genes, karyotypic complexity, TP53 loss/mutation alone or in combination with del(8p), and del(14q) which have all been suggested to have an adverse prognostic significance in univariable analyses, but none have been confirmed in multivariable analyses[15,73–77].

Candidate gene screening and, more recently, whole genome (WGS) or whole exome sequencing (WES) studies in small patient cohorts have identified recurrent mutations of genes involved in NOTCH, BcR, Toll-like receptor (TLR), and NF-κB signalling pathways, chromatin remodelling, and the cytoskeleton[78–81]. However, targeted resequencing of larger patient cohorts has resulted in conflicting data on the incidence and prognostic significance of NOTCH2 mutations, whereas little is known about the clinical significance of other gene mutations[78,79].

Parry et al.[82] review critical genetic mutations that influence disease progression and patient outcomes of SMZL. Their study, involving targeted resequencing of 175 patients, revealed

recurrent mutations including TP53 (16%), KLF2 (12%), NOTCH2 (10%), TNFAIP3 (7%), MLL2 (11%), MYD88 (7%), and ARID1A (6%). The results of the multivariable survival analysis revealed some significant insights into how various factors affect time to first treatment, event-free survival, and OS in SMZL patients. For time to first treatment, lower haemoglobin levels (below 12 g/dL), IGHV identity of 100%, and NOTCH2 mutation status indicated a higher likelihood of earlier treatment. For OS, lower haemoglobin and lymphocyte levels showed an increased risk of mortality, as did having a TP53 mutation. In contrast, younger patients had a much lower risk of mortality, indicating a strong protective effect. Notably, no molecular marker was independently associated with event-free survival. In contrast, low platelet count $<100 \times 10^9$/L (HR of 3.75, 95% CI: 1.68–8.41, P=0.001) was associated with a higher risk of an event, while younger age at diagnosis (<65 years; HR of 0.45 (95% CI: 0.21–0.96, P=0.038) and unexpectedly lymphocyte count $<4\times 10^9$/L (HR=0.41, 95% CI: 0.17–0.96, P=0.04) demonstrated a protective effect on EFS. Consistent with these observations, a large international meta-analysis recently confirmed the negative prognostic impact of NOTCH2 and TNFAIP3 mutations. This pooled analysis demonstrated that these alterations are associated with significantly inferior survival outcomes in SMZL and in ocular adnexal MZL, showing measurable adverse effects on 5-year overall survival and PFS[83].

Overall, these findings highlight the complex role of genetic factors in influencing patient outcomes and survival and assess the clinical utility of mutation screening in the diagnosis and management of SMZL.

Although molecular prognostic data are most extensively characterized in SMZL, relevant biomarkers have also been identified in extranodal MZL. In gastric MALT lymphoma, chromosomal translocations involving MALT1, particularly t(11;18)(q21;q21)/ BIRC3(API2)–MALT1, are associated with resistance to Helicobacter pylori eradication and reduced sensitivity to antibiotic therapy, often resulting in persistent disease and an increased risk of relapse[84–86]. Notably, subsequent studies have demonstrated clinically meaningful activity of rituximab in patients harbouring the BIRC3(API2)–MALT1 fusion, with about 46% achieving pathological and clinical complete response[87]. These findings suggest that the introduction of immunotherapy may mitigate the negative predictive impact of t(11;18)(q21;q21) on treatment response and relapse risk.

For the other MZL subtypes, cytogenetic factors are less well-defined, and further studies are needed to clarify their potential prognostic significance. For the time being, with the exception of TP53, both in terms of deletion and mutation, the use of molecular prognostic factors plays a very limited role in daily practice.

2.2 Clinical factors

Clinical parameters have been shown to have the greatest impact on prognosis. This has led to the formulation of the main prognostic indices for the different subtypes of MZL.

2.2.1 Extranodal Marginal Zone Lymphoma (EMZL)

Several prognostic indices have been proposed for MALT lymphomas. A Korean study involving 205 patients with nongastric MZL identified nodal MZL, ECOG performance status >1, and advanced-stage disease (III/IV) as predictors of poorer PFS and OS, leading to the development of a prognostic index. This index outperformed IPI and FLIPI in predictive accuracy, but its broader applicability remains uncertain[88]. Similarly, a study of 275 MZL patients, 77% of whom had extranodal disease, found that neither the IPI nor FLIPI reliably predicted outcomes. Instead, elevated serum β2-microglobulin (β2-M), male sex, and the presence of B symptoms were identified as prognostic markers for relapse-free survival and OS[89]. Despite their potential utility, these indices have not been widely adopted due to limited external validation. Regarding β2-M, its prognostic role is well established in indolent lymphomas. β2-M is included in the FLIPI-2 score[55], and available data suggest a possible prognostic impact also in MZL. Retrospective studies in MALT lymphoma have reported an association between elevated serum β2-M with OS[90,91], while results in non-gastric MZL have been inconsistent, with limited or no independent prognostic impact in multivariable analyses[92,93]. More recent data from non-gastric MALT lymphoma cohorts suggest that elevated β2-M is associated with inferior PFS and OS, and that dynamic increases in β2-M after immunochemotherapy could identify patients at higher risk of relapse[94]. Despite these findings, the clinical utility of β2-M in MZL remains limited by its lack of disease specificity and by confounding factors such as renal function, age, and systemic inflammation. Consequently, β2-M has not been consistently incorporated into MZL-specific prognostic models.

To enhance prognostic accuracy, Thieblemont et al. [95] developed a new prognostic score (MALT-IPI) using data from 401 patients in the IELSG19 trial[96]. This score incorporates age >70 years, Ann Arbor stage III/IV, and elevated lactate dehydrogenase levels, each with significant prognostic impact on EFS. These variables effectively stratify patients into low, intermediate, and high-risk groups, with 5-year EFS rates of 70%, 56%, and 29%, respectively. The MALT-IPI also distinguishes between different PFS, OS, and cause-specific survival outcomes. Its utility was validated across various treatment regimens (chlorambucil, rituximab, and rituximab plus chlorambucil) and confirmed in a validation set of 633 patients from three independent MALT lymphoma cohorts.

Building on this, the Revised MALT-IPI represents a significant advancement in predicting EMZL outcomes. Validated across three independent cohorts from the US and Europe, this novel prognostic index focuses on PFS, a key endpoint in indolent lymphomas, to create a more accurate and clinically useful tool[97]. The Revised MALT-IPI incorporates four key prognostic factors: age over 60 years, elevated lactate dehydrogenase (LDH), stage III-IV disease, and the presence of multiple extranodal sites (MMS). The inclusion of MMS, absent in the original MALT-IPI, significantly enhances predictive accuracy, as MMS correlates with more aggressive disease. Compared to the original MALT-IPI, the revised version focuses more on disease characteristics rather than patient age, allowing for earlier identification of high-risk patients, crucial for designing clinical trials and targeting therapeutic strategies. One of the standout features of the Revised MALT-IPI is its ability to stratify patients into four distinct risk categories: low, low-medium, medium-high, and high risk. Each category is associated with markedly different median PFS outcomes. This level of stratification is an improvement over the traditional MALT-IPI, as it better identifies patients at high risk for disease progression. The high-risk group has expanded from 17% to 26%, which is crucial for more precise targeting of therapeutic interventions and monitoring strategies. Moreover, this score effectively identified patients at risk of shorter lymphoma-specific survival.

The Revised MALT-IPI can also detect patients at risk of POD24. This early identification allows for timely interventions that can significantly improve patient outcomes.

While the Revised MALT-IPI is a robust tool, some limitations remain. Heterogeneity in treatment selection and baseline characteristics across cohorts introduces variability. Additionally, regional differences, such as the association of ocular adnexal EMZL with Chlamydia psittaci in Europe but not in the US, underscore the importance of geographical considerations. Prospective validation in clinical trials and further research into the biological mechanisms of aggressive EMZL, particularly MMS, will refine the index and enhance its clinical utility.

Recently, Bommier et al. conducted a study on systemic therapy outcomes for EMZL and validated early CR rates at 24 months as meaningful surrogate markers for long-term PFS. Achieving CR at 24 months explained about 90% of the overall treatment effect on 8-year PFS, and the newly defined endpoint TTCR24 captured about 95% of the treatment benefit at 8 years, supporting their value as early efficacy indicators[60].

2.2.2 Splenic Marginal Zone Lymphoma (SMZL)

The heterogeneity of the disease, which can affect the bone marrow, peripheral blood, and spleen while rarely involving nodal or extranodal sites, complicates the use of conventional staging and prognostic systems for low-grade lymphomas.

Chacon et al. found that patients with extranodal involvement and incomplete response to treatment had shorter survival compared to the classical form[28]. However, these patients had all previously been splenectomised and were all at higher risk, so there was probably a selection bias.

The first scoring system specifically developed for SMZL was built by the Intergruppo Italiano Linfomi (IIL). Arcaini et al.[26] conducted a comprehensive analysis on 309 patients and identified three key prognostic factors that significantly influenced OS: haemoglobin level <12 g/dL, elevated LDH level, and albumin level <3.5 g/dL. These factors maintained significance even after adjusting for HCV status and the use of anthracyclines. Based on these parameters, a prognostic model categorized patients into three risk groups: low-risk (41%), intermediate-risk (34%), and high-risk (25%). These groups exhibited distinct OS and cause-specific survival (CSS) outcomes, with 5-year CSS rates of 88%, 73%, and 50% respectively. High-risk patients experienced the highest lymphoma-related mortality rates, contributing to 54% of all deaths, compared to 16% and 30% in the low- and intermediate-risk groups. Differences in EFS across the risk categories were also statistically significant. As expected, treatment strategies varied significantly among the groups, with higher proportions of high-risk patients receiving upfront chemotherapy, compared to those in lower-risk categories. Additionally, splenectomy was more frequently utilized in low- and intermediate-risk patients than in the high-risk group. The model was validated effectively across patient subsets, showing significant survival differences. However, limitations include short follow-up and modest sample size, impacting long-term outcome assessment and subgroup analysis precision. The model informs risk but do not dictate treatments, and the role of splenectomy and HCV infection association remains debated.

Subsequently, an international retrospective study of 593 patients from the SMZL Study Group (SMZLSG) proposed a risk stratification system able not only to identify factors influencing lymphoma-specific survival (LSS) but also to determine indications for treatment. Montalbán et al.[67] conducted a comprehensive international study on SMZLs, identifying key variables—Hb, platelet count, LDH serum levels, and extrahilar lymphadenopathy—that guide treatment decisions and delineate patient groups with differing prognoses. To study the effect of clinical variables on LSS, the cohort of 593 patients was divided into two groups with a non-random split (two-thirds versus one-third), which reduced the similarity between the sets. Thus, a derivation cohort of 366 patients and a validation cohort of 227 patients were generated.

Regarding the probability of starting therapy, in the multivariate analysis, for which complete data were available from 419 patients, only Hb, extrahilar lymph nodes, and HCV status retained independent significance for the treatment decision. Treatment approaches generally appeared justified, as only 1.8% (3 out of 161) of untreated patients died from lymphoma, reinforcing SMZL's characterization as indolent lymphoma. Patients exhibiting anaemia and lymphadenopathy were considered to have more aggressive diseases requiring intervention. HCV positivity often led to deferred treatment due to potential hepatic complications, though current practices increasingly favour initial HCV-targeted therapy. Interestingly, treated patients showed worse outcomes than untreated ones. Various treatment modalities, including splenectomy, chemotherapy, rituximab, or their combinations, did not significantly impact survival rates. There was no observed survival benefit for patients treated with rituximab, possibly due to the small sample size (39 patients). This aligns with findings from Thieblemont et al.[98], which reported no survival difference between patients undergoing splenectomy, chemotherapy, or both. While splenectomy has shown prolonged remission in some cases, it is arguable that some patients may not have required treatment.
Regarding a possible prognostic role, in the multivariate analysis the haemoglobin value, platelet count, high lactate dehydrogenase level, and extrahilar lymphadenopathy were independently associated with LSS. A final model produced a prognostic index comprising a weighted combination of the predictors, named HPLL score for the factors used (Haemoglobin, Platelet count, Lactate dehydrogenase, and extrahilar Lymphadenopathy). HPLL score enabled the patients to be divided into three risk groups, with significantly different five-year LSS (94%, 78%, and 69%, respectively). The validation cohort was separated by the score into the three prognostic groups, with a 5-year LSS of 96%, 88%, and 44%, confirming the predictive accuracy of the resulting model.
A comparative analysis with the IIL score[26] revealed that HPLL more effectively distinguishes the LSS across risk groups, particularly between low- and intermediate-risk patients. The high-risk group of the IIL series had a five-year survival rate of 50%, whereas HPLL better identified varying risk levels, with distinct five-year LSS rates of 95%, 83%, and 67% for low, intermediate, and high-risk groups, respectively. It might depend on the level of Hb considered in the IIL score, 12.0 g/dL, which is a very high cut-off point, and this may fail to identify the intensity of the anaemia as an incrementally adverse risk factor in the IIL score. At the same time, it seems crucial with HPLL, allowing graduation of risk that increases with the intensity of the cytopenia. However, in the HPLL score, both Hb and platelet count are treated as continuous variables, and applying the score requires a calculation by a formula. Thus, the same authors provided a simplification of the risk stratification[68], and established clinically acceptable cut-off points of 9.5 g/dL for Hb and $80x10^9$/L

for platelet count. Together with the levels of LDH and the presence or absence of extrahilar lymphadenopathy, these variables defined HPLL group A (no adverse factors) versus HPLL group B (1-2 adverse factors) versus HPLL group C (≥3 adverse factors), with a 5-year LSS of 95%, 87%, and 68%, respectively. The 9.6% reduction in accuracy with this simplified score is considered acceptable since the advantages of it being clinically sound, easy to remember and use, and applicable in a routine setting.

These models confirm the importance of anaemia in the prognosis of lymphoproliferative disorders: the exact value of anaemia (less than 12 g/d) is one of the adverse factors included in the FLIPI score. Moreover, low serum albumin concentration, another adverse factor in the IIL model, proved to be of prognostic value in other scores for malignant lymphomas, such as Hodgkin lymphoma[99].

Given that a significant proportion of SMZL patients do not require treatment, and for those who do, there may be disagreement about the most appropriate approach, the proposed stratification system could also help to tailor the intensity of treatment, suggesting that a rational approach would be to reserve chemoimmunotherapy for those in high-risk groups.

2.2.3 Nodal Marginal Zone Lymphoma (NMZL)

For risk assessment, the IPI and FLIPI scores were evaluated in a retrospective series of NMZL patients. The FLIPI score demonstrated substantial prognostic value in MZL[59], suggesting that patients with high-risk FLIPI scores might be suitable candidates for novel treatment approaches. Several molecular risk factors were assessed, but none showed clear prognostic significance.

As part of efforts to identify new molecular and clinical prognostic factors, the International Extranodal Lymphoma Study Group has launched the IELSG52 study “Integrated Molecular and Clinical Profiling to Improve Disease Characterization and Outcome Prediction in Nodal Marginal Zone Lymphoma”. This trial addresses the challenge that nodal MZL lacks specific genetic markers and dedicated therapies, making diagnosis and management difficult. Using advanced molecular techniques, IELSG52 aims to define and validate clinically and biologically distinct NMZL subgroups, clarify the disease’s underlying mechanisms, improve diagnostic accuracy, and enhance prediction of disease progression, ultimately supporting the development of more effective treatment strategies.

2.3 Prognostic endpoints in R/R MZL

To date, no prognostic indices have been specifically developed or validated for patients with R/R MZL. In this setting, dynamic endpoints such as POD24 and early response are commonly used as surrogate markers of disease aggressiveness rather than formal prognostic tools. In a FIL study[30],

MZL patients with POD24 had a 3-year OS of 53%, compared to 88% in those without early progression, while the IELSG19 trial reported significantly lower 5- and 10-year OS rates (80% and 64%, respectively) among early progressors, versus 91% and 85% in patients without POD24[96]. Although POD24 identifies a subset of patients with early relapse and poor outcomes, it does not fully overlap with the definition of refractory disease. Similarly, response-based endpoints such as early complete response in terms of CR24 and TTCR24 reflect treatment sensitivity and favourable disease biology, particularly in extranodal MZL[60]. These metrics capture a substantial proportion of the long-term treatment effect on PFS and provide early indicators of durable disease control. However, they were not designed to specifically stratify prognosis after relapse. Overall, prognostic assessment in R/R MZL remains an unmet clinical need.

3. LOOKING AT MARGINAL ZONE LYMPHOMAS AS A WHOLE SPECTRUM: TOWARDS A UNIFIED PROGNOSTIC MODEL

The Marginal Zone Lymphoma International Prognostic Index (MZL-IPI) represents a significant step forward in the prognostic assessment of MZL, as it integrates data from all subtypes and incorporates clinically validated parameters. Research to date has primarily focused on identifying prognostic factors for specific MZL subtypes, leading to the creation of tailored scoring systems. However, no index has been developed specifically for MZL as a whole group. Its reliability has been confirmed through validation in an independent US cohort. It notably excludes age, a withdrawal from other models, allowing for better disease management without age-related treatment limitations. Although not intended for individualized patient decisions, the MZL-IPI is crucial for clinical development, aiding trial design, result interpretation, and cross-trial comparisons[100]. The development of such an index would be highly valuable, particularly as recent clinical trials increasingly include patients across the full spectrum of MZL subtypes[22,23,29]. Furthermore, a unified prognostic score could help in managing patients with extensive disease without a definitive primary origin in the spleen, lymph nodes, or extranodal sites. While the presence and prognostic implications of widespread disease in EMZL has been recognized [93,101], these cases have not been adequately represented in previous subtype-specific studies and are challenging to identify in published MZL series.

The study used data from the large observational cohort study NF10. A biopsy confirming MZL, assessed by a local immunopathologist, was mandatory, with peripheral and/or bone marrow flow cytometry performed when available. Patients with histological MZL and involvement of bone marrow, spleen, lymph nodes, and/or extranodal sites were classified as disseminated MZL (dissMZL). Clinical characteristics and radiological findings were recorded at diagnosis. Laboratory

evaluations included HIV serology, hepatitis B and C status, LDH, β2-M, albumin, absolute lymphocyte count (ALC), and platelet count, incorporating prognostic indices such as the MALT-IPI for EMZL[95], SMZL-specific scores[26,67,68], and FLIPI for nodal and dissMZL[102]. A total of 501 patients received treatment (at diagnosis or after a watch-and-wait approach) and were considered eligible for the study. Specifically, 197 (39%) were EMZLs, 166 were SMZLs, 60 were NMZLs, and 78 were dissMZLs.

A multivariable analysis on 456 patients identified five independent prognostic factors, each assigned a score of 1 to unfavourable outcomes: elevated LDH, anaemia (Hb <12 g/dL), platelet count below $100x10^9$/L, ALC less than $1x10^9$/L, and MZL subtype. Based on these factors, the authors developed the MZL-IPI score, stratifying patients into three risk categories: low-risk (0 factors), intermediate-risk (1–2 factors), and high-risk (3 or more factors). This model demonstrated clear stratification in both PFS and OS, with significant differences across the risk groups. Specifically, the 5-year PFS rates for the MZL-IPI risk groups were 85% for low-risk, 66% for intermediate-risk, and 37% for high-risk patients. Compared to the low-risk group, the intermediate-risk group had a significantly higher likelihood of progression (HR=2.30, 95% CI 1.39–3.80), as did the high-risk group (HR=5.41, 95% CI 3.12–9.38). Regarding OS, the MZL-IPI effectively identified groups with distinct risks of death, showing significant differences between intermediate- and low-risk groups (P=0.020) and between high- and intermediate-risk groups (P <0.001).

The MZL-IPI model was externally validated in two independent US cohorts, confirming its ability to stratify patients into different risk groups for both PFS and OS. While there were minor discrepancies in PFS outcomes for the intermediate-risk group, the low- and high-risk groups remained separated in both validation cohorts.

The authors reported 64 early progressions as defined by POD24, with a significantly different distribution across risk groups: 6% of early progressions occurred in the low-risk group, 15% in the intermediate-risk group (OR 2.60, 95% CI 1.13–6.14, P=0.024), and 34% in the high-risk group (OR 7.67, 95% CI 3.05–19.3, P <0.001).

Table 1 summarizes and compares the various prognostic models for MZL, highlighting their specific parameters, applicability, risk groups, and key features.

4. FUTURE PROGNOSTIC FACTORS

Regarding potential prognostic factors in MZL, increasing attention has been focused on the role of PET/CT for both initial staging and disease re-evaluation. The 2014 Lugano classification recommends PET/CT as the standard imaging modality for lymphoma except for certain indolent

subtypes, including MZL[103]. Over the past decade, accumulating evidence has shown FDG uptake in more than 75% of SMZL and NMZL cases, supporting its value in these settings[104–106]. In contrast, FDG avidity in EMZL remains more variable, being strongly influenced by disease site and lesion size, and PET/CT is still considered suboptimal for detecting bone-marrow involvement[107–109]. To address these uncertainties, Alderuccio et al.[110] performed a retrospective study of 190 extranodal MZL lesions in 152 patients, demonstrating FDG uptake in 79.5% of sites with a median SUVmax of 4.5. Among patients with multiple lesions, 82% showed concordant uptake, and lesion size correlated with SUVmax and with blood-pool and liver indices. Importantly, FDG-avid disease allowed more precise assessment of treatment response. These findings indicate that extranodal MZL is frequently FDG-avid and support the routine use of PET/CT for both staging and response evaluation.

In the same setting, the IELSG44 trial was designed to define the staging and prognostic role of PET/CT across all MZL subtypes. Although full results are still under analysis, preliminary data in 156 patients who underwent both baseline and end-of-treatment (EOT) 18F-FDG PET/CT scans showed that a complete metabolic response (CMR) defined by a Deauville score ≤2 is associated with significantly longer time to progression, particularly in patients with baseline SUVmax exceeding liver uptake, supporting rational use of PET/CT for risk refinement in MZL.

Another rapidly evolving field is the study of circulating tumor DNA (ctDNA) as a non-invasive source of molecular information. Early reports in MZL show high concordance between ctDNA and tissue-based genotyping, highlighting the potential of plasma assays to detect somatic mutations from peripheral blood[111]. This approach is particularly attractive in EMZL, where tissue biopsies can be difficult to obtain, and may help identify patients at higher risk of treatment failure or uncover predictive biomarkers. Beyond staging, ctDNA monitoring could also inform molecular response, analogous to BCL2/IGH PCR tracking in follicular lymphoma[112]. Although data on ctDNA kinetics in MZL remain limited, the development of more sensitive platforms capable of detecting and longitudinally tracking multiple mutations in single cell-free DNA molecules may capture disease biology more comprehensively and pave the way for truly personalized management.

An additional emerging area of investigation is the concept of leukaemic disease. As mentioned previously, the operational definition of disseminated MZL does not formally include leukaemic involvement. Recent findings from a large US multicentre cohort have demonstrated that detection of circulating lymphoma cells (CL) in peripheral blood by flow cytometry at diagnosis is not associated with inferior PFS across any MZL subtype, and may instead correlate with numerically longer PFS and significantly superior OS [113]. These data support the concept that leukaemic

dissemination alone should not be considered an adverse prognostic feature. However, in the study a relevant exception emerged in EMZL: among patients treated with immunochemotherapy, the presence of CL was associated with shorter PFS. This observation may reflect an increased propensity for hematogenous spread, consistent with the recognition of multiple mucosal site involvement as a risk factor for inferior survival, or the coexistence of unfavourable molecular or cytogenetic drivers that are not entirely mitigated by immunochemotherapy. Although current recommendations do not support routine PB flow cytometry assessment at diagnosis for EMZL, these data suggest it may add prognostic refinement when immunochemotherapy is being considered. In a recent retrospective analysis, Lossos et al. similarly observed that positive peripheral blood flow cytometry (PBFC) in extranodal MZL is associated with advanced stage and increased risk of pulmonary and bone marrow involvement, and proposed that patients with early-stage EMZL and PBFC positivity might benefit from frontline systemic therapy in order to mitigate the risk of late relapses and subsequent disease recurrence[114].

As discussed earlier, in the MZL-IPI study cases in which a dominant site of origin cannot be clearly defined, patients have been operationally grouped under the term disseminated MZL (Table 2). In parallel, other research groups have explored complementary strategies to support diagnostic subtype attribution in patients with complex, multi-site involvement. Notably, in the real-world REALMA study, conducted by the LYSA, a pragmatic clinical classification algorithm was proposed: patients presenting with extranodal disease without bone marrow or peripheral blood involvement were classified as EMZL, those lacking extranodal disease but showing splenic, isolated peripheral blood, or bone marrow involvement were labelled as SMZL, and NMZL was defined as a diagnosis of exclusion[115].

It is noteworthy that in the FIL system non-disseminated cases (SMZL, EMZL, NMZL) do not entirely fall in the category of limited disease (for instance advanced cases such as EMZL with multimucosal involvement and splenic marginal zone lymphoma with bone marrow involvement are still EMZL and SMZL, respectively); on the other hand a case with extranodal, splenic and nodal disease at the same time is clearly difficultly categorized in a WHO histotype and can operatively be defined as disseminated without clear extranodal, splenic or nodal origin.

This evolving effort reflects growing recognition that traditional staging and pathologic classification may insufficiently describe MZL biology, especially in multi-compartment or atypical presentations. Importantly, emerging data suggest that distinguishing advanced and or disseminated disease may not only assist more consistent diagnostic categorization, but also carry relevant prognostic implications in terms of PFS, as dissemination patterns appear to identify patient subsets with significantly different risks of progression.

5. CONCLUSION

MZL represents a heterogeneous group of indolent B-cell lymphomas, with distinct subtypes each characterized by unique clinical features, genetic abnormalities, and responses to treatment. Despite their generally favourable prognosis, disease heterogeneity poses challenges in risk stratification and management.

Prognostic models have been developed to refine risk assessment. Histological subtype, disease stage, and clinical parameters remain crucial for defining prognosis, leading to the development of subtype-specific prognostic indices. The main limitation is the lack of broad applicability across all MZL types, focusing on parameters unique to each variant.

MZL-IPI represents a significant advancement in this field. By integrating clinically validated parameters, including LDH, haemoglobin levels, platelet count, absolute lymphocyte count, and MZL subtype, this unified model offers a comprehensive approach to risk stratification and to predict PFS and OS applicable to all MZL subtypes, extending beyond patients with disseminated disease or an unclear site of origin. While subtype-specific prognostic models may better capture distinct biological features of individual entities, MZL-IPI provides a pragmatic and harmonized approach that improves consistency in prognostic assessment and facilitates data comparability in both real-world practice and clinical trials. Current prognostic models in MZL are not intended to directly guide therapeutic choices, but rather to support risk-adapted follow-up strategies and identify patients at higher risk of early progression or suboptimal outcomes.

Emerging tools are broadening this landscape. Recent advancements in molecular profiling and biomarker discovery have significantly refined prognostic assessment, with genetic alterations, such as NOTCH2 and KMT2D mutations, and markers of tumor microenvironment dysregulation providing insights into disease progression and treatment resistance[116–118]. In this field, circulating tumor DNA (ctDNA) could offer a minimally invasive method to detect genetic alterations and monitor molecular response, while functional imaging with PET/CT is gaining recognition for its potential prognostic value in staging and response assessment, supported by recent retrospective analyses and the ongoing IELSG44 trial.

Given the indolent nature of MZL, the most clinically meaningful prognostic factors may differ from those in aggressive lymphomas, where overall survival is the dominant endpoint. Markers predicting early progression (e.g., POD24), risk of histologic transformation, or durability of remission may ultimately prove more relevant for patient care than traditional survival metrics.

Future research should integrate biomarkers, molecular profiling, and functional imaging to refine risk stratification and define parameters with the greatest impact on long-term quality of life and disease control.

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Table 1. Comparison of Prognostic Models for MZL

Subtype	Score	Parameters	Categories	Key Features
SMZL	**IIL score**	Haemoglobin <12 g/dL LDH >ULN Albumin <3.5 g/dL	Low-risk (0 factor): 5-y CSS 88% Intermediate-risk (1 factor): 5-y CSS 73% High-risk: (2-3 factors): 5-y CSS 50%	
	HPLL score	Haemoglobin Platelets LDH Extrahilar lymphadenopathy	Low-risk (0 factor): 5-y LSS 94% Intermediate-risk (1 factor): 5-y LSS 78% High-risk group (2-3 factors): 5-y LSS 69	Significant differences in 5-year lymphoma-specific survival
	HPLL score simplified	Haemoglobin <9.5 g/dL Platelets $<80\times10^9$/L LDH >ULN Extrahilar lymphadenopathy	Group A (0 factor): 5-y LSS 95% Group B (1-2 factors): 5-y LSS 87% Group C (3-4 factors): 5-y LSS 68%	Slight reduction in accuracy (9.6%) but easier to use
EMZL	**MALT-IPI**	Age >70 years Stage III/IV LDH >ULN	Low-risk (0 factor): 5-y EFS 70% Intermediate-risk (1 factor): 5-y EFS 78% High-risk group (2-3 factors): 5-y EFS 69	Predicts 5-year EFS, validated across various treatment regimens
	Revised MALT-IPI	Age >60 years LDH Stage III-IV Multiple extranodal sites	Low Low-Medium Medium-High High	Improved stratification, early identification of high-risk patients
All MZL subtype	**MZL-IPI**	LDH >ULN Hb <12 g/dL Platelets $<100\times10^9$/L ALC $<1\times10^9$/L MZL subtype	Low Intermediate High	Comprehensive, excludes age, validated in independent cohort

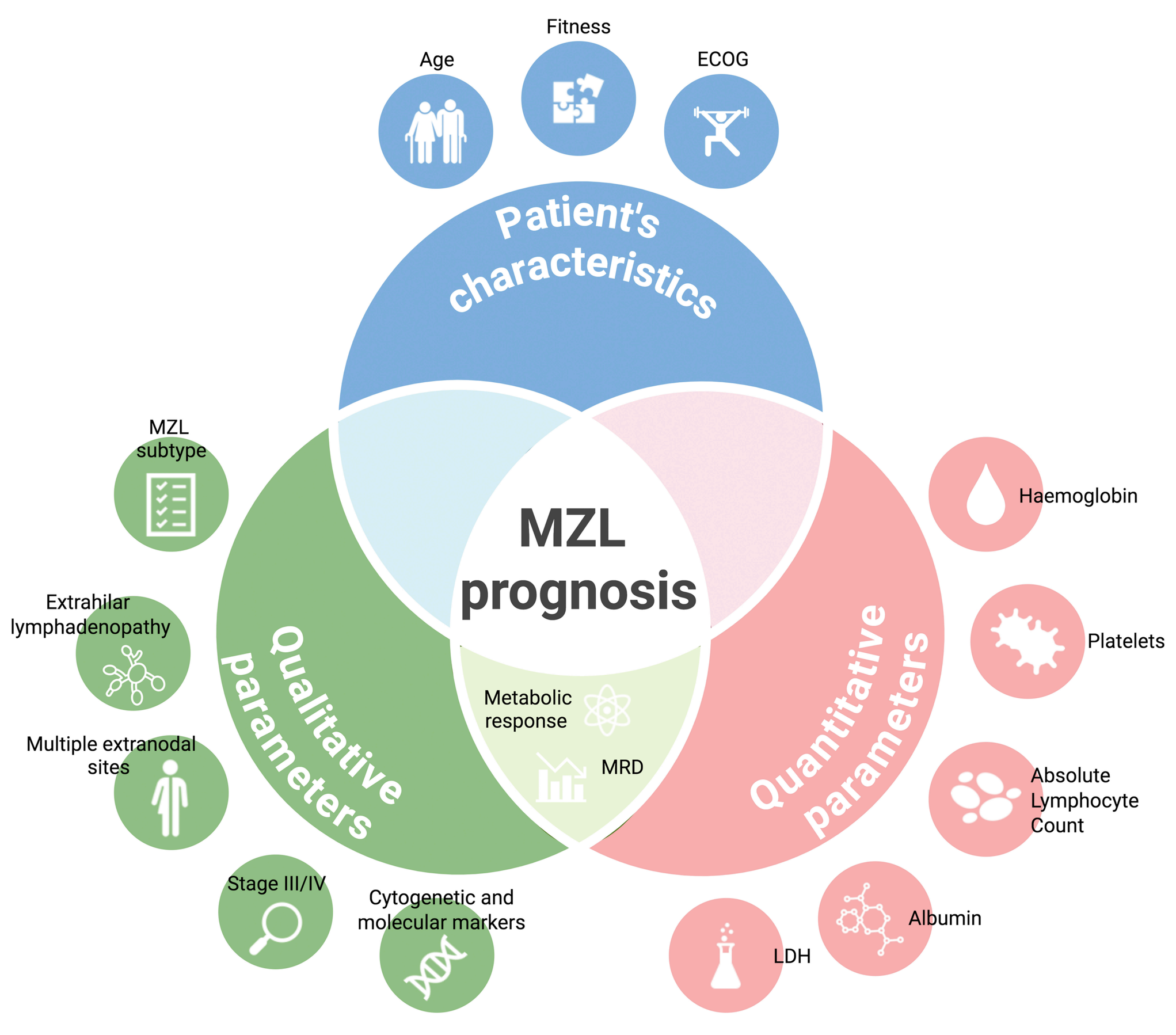
ALC, absolute lymphocyte count; CSS, cause-specific survival; EFS, event-free survival; LSS, lymphoma-specific survival; ULN, upper level of normal; y, years

Table 2. Rules adopted to define subtypes of marginal zone lymphomas

	Extranodal sites other than bone marrow	**Spleen***	**Lymph node****	**Bone marrow**	**Peripheral blood*****
EMZL	Required (single or multiple sites)	No	Only regional LN allowed	Allowed	No
SMZL	No	Required	Only splenic hilar LN	Allowed	Allowed
NMZL	No	No	Required	Allowed	No
DissMZL	Allowed	Allowed	Allowed	Allowed	Allowed

*Splenic involvement defined in case of splenic biopsy and/or nodular involvement and/or splenic enlargement (>13 cm in max diameter)
** as per Cheson 2007 criteria
*** clonal B-lymphocytes with features (cytology and/or flow cytometry) consistent with MZL. Cases with only PB involvement but without splenic or nodal or LN involvement were excluded
BM: bone marrow; LN: lymph node

Figure 1. Schematic representation of different prognostic factors in marginal zone lymphoma


Fitness
Age
ECOG
Patient's characteristics
MZL subtype
Extrahilar lymphadenopathy
Multiple extranodal sites
Stage III/IV
Cytogenetic and molecular markers
Qualitative parameters
MZL prognosis
Metabolic response
MRD
Quantitative parameters
Haemoglobin
Platelets
Absolute Lymphocyte Count
Albumin
LDH