Low-Risk HPLLs/ABC score patients with splenic marginal zone lymphoma (SMZL) can be safely managed without treatment: results from a prospective Spanish study

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ABSTRACT

Introduction: The aims of our study were to analyze compliance with the 2014 GELTAMO SMZL Guidelines, in patients with Splenic marginal zone lymphoma (SMZL) and to evaluate the outcome according to the HPLLs/ABC-adapted therapeutic strategy.

Methods: Observational prospective multicenter study of 181 SMZL patients diagnosed between 2014 and 2020. Lymphoma Specific Survival (LSS), Composite event-free survival (CEFS) and response rates were assessed.

Results: 57% of the 168 patients included in the analysis followed the Guidelines. The overall response rate was higher in the rituximab-chemotherapy and in the rituximab arms compared to the splenectomy arm ($p<0.001$). The 5-year overall survival was 77%, and the 5-year LSS of 93%. There were no differences in the 5-year LSS according to the treatment received ($p=0.68$). The 5-year CEFS in the overall series was 45% and there were significant differences between scores A and B ($p=0.036$). There were no significant differences when comparing LSS and progression-free survival in patients treated with rituximab or rituximab-chemotherapy at diagnosis or after observation.

Conclusions: Our data support HPLLs/ABC score as a practical tool for the management of SMZL, observation as the best approach for patients in group A and rituximab as the best treatment for the group B.

KEYWORDS:

Splenic marginal zone lymphoma (SMZL), HPLLs/ABC score, therapeutic management, SMZL Spanish guidelines

INTRODUCTION

Splenic marginal zone lymphoma (SMZL) is an uncommon subtype of B-cell neoplasm[1], thus currently available knowledge regarding diagnosis, prognostic factors and treatment are mainly based on retrospective studies and/or expert consensus[2,3]. Historically, histologic evaluation of the spleen through splenectomy was considered essential for diagnosis and treatment. However, current recommendations consider that, in most cases, the diagnosis of SMZL can be reached without splenectomy, by integrating data from peripheral blood and bone marrow morphology and immunophenotyping, along with some cytogenetic markers[2,3] to rule out other indolent lymphomas. Given the paucity of high-quality evidence such as large randomized clinical trials in SMZL, optimal management and treatment are not well-established.

Even though splenectomy has been the treatment of choice for many years, it is only a debulking procedure with no effect on the tumoral population and with a considerable rate of surgical and other medium/long-term complications (6-10%)[4,5]. Moreover, despite the fact that 56% of splenectomized patients did not require further treatment, up to 52% of deaths were lymphoma-related[4]. All these data indicate that splenectomy is far from being the optimal treatment for SMZL. Chemotherapy alone is

also a less convenient treatment due either to limited activity (alkylating agents) or toxicity (combination of agents) [2,6,7,8]. Rituximab provides quick and high complete remission (CR) rates (31-90%), and lymphoma-specific (LSS) and overall survival (OS) at 5 years are 60-86% and 81-98%, respectively[9-11]. The addition of chemotherapy to rituximab does not seem to improve its effectiveness and entails a higher toxicity[9,12]. When studies comparing different treatment modalities: splenectomy, rituximab and rituximab plus chemotherapy [with fludarabine-based regimens or with other regimens including cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)] are analyzed, all of them show rather similar response rates and outcomes, as revised elsewhere[10,13-19]. In addition to that, there is no evidence from randomized trials to select the best treatment in every case.

Many clinical and biological parameters have been eventually considered to have a prognostic but inconsistent effect. Optimal treatment has not been established, and in larger (pre-rituximab) series there was no differences among the different therapies used[15,17,18]. The combination of clinical factors in the Italian Lymphoma Intergroup (ILI) score, which included low hemoglobin and albumin levels and elevated lactate dehydrogenase (LDH), separated 3 risk groups with significantly different lymphoma survival[17] but could not be validated in another study including a larger number of patients[15]. In the SMZL Study Group (SMZLSG) series, incremental levels of anemia and thrombocytopenia, high levels of LDH and the presence of lymphadenopathy outside the splenic or hepatic hilum conformed the HPLL/ABC score (derived of the prognostic factors: **H**emoglobin level, **P**latelet count, **L**ymphadenopathy and high **L**DH) and separated 3 different prognostic groups[15]. Moreover, when cutoff points for hemoglobin and platelets were established, 3 risk groups with significantly different

LSS defined the simplified HPLL/ABC score (HPLLs/ABC)[18], which has been validated in an independent retrospective series and seems to be a consistent ~~a~~ prognostic tool in the clinical practice[19].

The present prospective study aims to analyze the management of the SMZL in Spain in a real-life setting, as well as the feasibility and practicability of using the HPLLs/ABC score in routine clinical practice. We also explored its possible usefulness in tailoring the intensity of frontline treatment to the individual patient risk, that is, the predictive value of the score.

PATIENTS AND METHODS

Case ascertainment and data collection

In 2014, GELTAMO (Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea) proposed a guideline with recommendations for the diagnosis, staging, management and treatment of SMZL (GEL-LZME-2014-14) to be used in daily clinical practice in its nation-wide network of collaborative hospitals. In this prospective study, inclusion criteria were HIV-negative patients older than 18 years, consecutively diagnosed with SMZL from January 2014 to December 2020 in all GELTAMO centers included in the RELINF registry[20]. Participating institutions provided data on patients occurring since the date of the initial recommendations. The diagnosis in the contributing institutions was performed by local experienced hematopathologists and was based on already established criteria[2]. No central pathologic review was performed, and patients were considered as *bona fide* SMZL. The ultimate therapeutic

decisions were made entirely by the treating physicians, who may have or have not followed the recommendations in each individual case. In the contributing institutions, patients' characteristics, clinical data and details of the treatment, follow-up and cause of death were obtained from the medical records by local physicians, entered in a database and cross-checked. The data cut-off of the study was January 31st, 2021.

Regarding SMZL guidelines, work-up followed consensus recommendations[2], including standard blood and biochemistry parameters (including LDH and β2-microglobulin), immunoglobulin levels and protein electrophoresis, autoimmunity parameters (i.e., rheumatoid factor, anti-nuclear antibodies, among others), viral serologies (HCV, HBV, HIV), peripheral blood morphology, bone marrow biopsy, as well as flow cytometric (FCM) analyses from both sources. Cytogenetic and/or FISH studies were strongly recommended. CT scan of the thorax, abdomen and pelvis was mandatory, and PET/CT was optional. Other specific immunologic and laboratory parameters or image procedures in special situations were optional. In accordance with the SMZLSG proposal, splenectomy was not routinely recommended for diagnosis[2].

The HPLLs/ABC score was recommended for stratification. This index includes four factors: hemoglobin level below 9.5 g/dL, platelet count below 80.000/μL, high serum LDH (above upper normal limit according to the local laboratory) and presence of lymphadenopathy out of splenic or hepatic hilum as detected by CT (or PET/CT). The presence of each of these factors accounts for one point and their accumulation defines 3 risk groups: A, B and C, with no risk factors, 1-2 factors and ≥3 factors, respectively, and with significantly different 5-year LSS (95%, 87% and 68%, respectively) [18].

As mentioned above, treatment of SMZL has not been established in randomized trials, thus the hypothesis was that treatment may be adapted to the clinical situation of the patient. According to previously published data[15,17], our guidelines recommended: W&W policy for group A (considering W&W when more than 3 months have elapsed between the diagnosis and the start of treatment), single-agent rituximab for group B[9,10,14,21,22], and rituximab-chemotherapy (R/Ch) for group C[9,10,15,17]. Rituximab was scheduled at weekly doses for 4-6 weeks, and maintenance was not recommended[21]. Given that a small group of SMZL patients (both, according to ILI[17] and to HPLLs/ACB[15]) with more aggressive disease and shorter survival has already been reported, we considered it reasonable to add chemotherapy to rituximab in group C, using combinations usually administered in low grade/indolent lymphomas, such as rituximab-cyclophosphamide, vincristine and prednisone, rituximab-bendamustine and others. Finally, we considered mandatory that SMZL associated with HCV be treated initially with antiviral agents (interferon-free regimens)[23].

Response assessment and survival endpoints

Response assessment followed the currently established criteria[2]. CR required the disappearance of the clinical symptoms, normalization of the spleen size, the disappearance of the enlarged lymph nodes, normalization of the cytopenias and lymphocytosis and disappearance of the B-cell clonal population (by FCM) in the PB. Bone marrow biopsy was desirable but not mandatory to demonstrate the disappearance of the tumor in all the compartments. Partial remission (PR) required a reduction of at least 50% of the volume of the spleen or lymph nodes and of the clonal

population in PB. As splenectomy has no effect on the clonal population, CR cannot be considered with this treatment option.

The primary endpoint was lymphoma-specific survival (LSS) which was calculated from the date of diagnosis to death due to lymphoma or treatment, as this was the endpoint considered in the original SMZLSG, ILI and Surveillance Epidemiology and End Results (SEER) studies[15,16,17,18,24]. Event-free survival (EFS) was also used but restricted to patients who received treatment[17]. As mentioned above, some patients with SMZL did not require treatment immediately after diagnosis and were followed according to a W&W policy[15,17]. Therefore, for a general view of the outcome of the whole population, we also investigated a composite endpoint, named composite event-free survival (CEFS). CEFS included both treated and untreated patients and was defined as follows: 1) in treated patients: early treatment discontinuation, relapse, transformation to an aggressive lymphoma or death due to lymphoma or treatment, whichever occurred first; 2) in patients who did not require immediate treatment: the time from diagnosis to treatment initiation, transformation to an aggressive lymphoma or death from any cause, whichever occurred first. Progression Free Survival (PFS), calculated from the response to frontline treatment to disease progression, transformation, or death due to lymphoma or treatment complications, whichever occurred first, was used to evaluate the impact of delaying treatment with either rituximab or rituximab-QT.

Finally, the effect of progression or transformation of the disease within 24 months from initial treatment (POD24) was evaluated for LSS[25]. For the statistical analysis of LSS, the comparative group of non-POD24 cases (i.e., non-relapsed patients and those

relapsing beyond 24 months after treatment), should have at least a 24 months follow-up.

Statistical analysis

We estimated the survival curves using the Kaplan–Meier method and compared them using the log-rank test. The statistical package SPSS, version 24.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses. Two-sided p values <0.05 were considered statistically significant. Survival of transformed patients compared to those who did develop transformation was estimated using Cox analysis with a time-dependent variable, the Mantel-Byar test.

Relative survival (RS) was analyzed with regards to sex- and age-matched Spanish population (www.mortality.org) using R software, version 3.3.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Relative survival is a net survival measure representing cancer survival in the absence of other causes of death and it is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer-free individuals. The formulation is based on the assumption of independent competing causes of death. The relative survival ratio (RSR), calculated by dividing the observed survival of our cohort by the expected survival of the general population, was intended to reflect the reduction in life expectancy due to lymphoma[26].

The study was approved by the Ethical Committee in the Fundació Assistencial Mútua Terrassa, Barcelona, Spain and was done in accordance with the Declaration of Helsinki.

RESULTS

Initial features and response to treatment

One-hundred eighty-one patients prospectively diagnosed with SMZL between January 2014 and December 2020 from 22 Spanish GELTAMO centers were included in the study. Clinical characteristics at diagnosis are summarized in Table 1. Median age was 71 years, 97 patients (54%) were female and only 24% and 10% of cases presented with B-symptoms or performance status (PS) $\geq$ 2, respectively. Regarding the HPLLs/ABC score, 79 (44%) cases were assigned to group A, 91 (50%) to group B and 11 (6%) to group C. When comparing characteristics at diagnosis between HPLLs/ABC risk groups A and B, statistically significant differences were found for sex (more women in group B), presence of B symptoms, PS $\geq$ 2, ~~performance of PET/CT at diagnosis,~~ presence of splenomegaly, development of histological transformation and frontline treatment strategy. Group C was not included in the comparison analysis as there were only 11 cases (Supplementary Table 1). For the analysis of response and survival, we excluded five cases diagnosed with HCV infection treated with antiviral therapy, three cases with histological transformation at the time of diagnosis (two patients from

group C and one from group B) as well as five patients managed with palliative care, resulting in a final cohort of 168 patients.

In terms of the initial management approach, 57% of the patients followed the recommendations of the GELTAMO guidelines. Overall, 75 out of 168 patients (45%) received some therapy, while 93 out of 168 (55%) remained on a W&W approach. As per guideline recommendations, 81% of patients from group A did not receive upfront therapy, 39% of patients from group B were initially treated with single-agent rituximab and 33% of cases from group C underwent frontline immunochemotherapy. Splenectomy was performed in 14 cases (8%) at diagnosis.

One hundred fourteen out of the 168 patients (68%) received treatment during follow-up and were included in the analysis for response. Seventy-five of them (66%) received treatment at diagnosis. For the remaining 39 patients (34%) receiving deferred therapy, the median time from diagnosis to first treatment was 21.8 months. Overall, 109 patients were finally evaluated for response (5 without available data of response were excluded). Overall response rates (ORR) are detailed in Table 2. The ORR was 83% (CR: 49%) in patients treated with rituximab, 97% (CR: 77%) in those treated with R/Ch and 79% in patients who underwent splenectomy at diagnosis. Patients treated with rituximab or R/Ch had a statistically significant higher ORR compared with those treated with splenectomy ($p<0.001$). However, no differences in ORR were found between patients treated with rituximab and those treated with R/Ch ($p=0.072$).

Analysis of survival

In the final cohort of 168 patients, with a median follow-up of 41.2 months, the 5-year overall survival (OS) and 5-year lymphoma-specific survival (LSS) were 77% and 93%, respectively (Figure 1A), with 32 patients (18%) dying, but only 13 (7%) due to the lymphoma or its treatment.

Survival analysis according to HPLLs/ABC score showed that 5-year LSS for scores A and B was 98% and 87%, respectively (p=0.048), but, unexpectedly, there were no deaths among the 9 evaluable patients in score C (5-year LSS: 100%) (Figure 1B). Overall, there were no statistically significant differences in the 5-year LSS according to the type of first-line treatment (p=0.68). Similarly, we did not find significant differences when scores A and B were analyzed separately.

Five-year CEFS was 45% (Figure 2A). According to HPLLs/ABC score, patients from score A showed a significantly better 5-year CEFS (49 %) compared with those patients from group B (45%) (p=0.036) (Figure 2B). There were also statistically significant differences in the 5-year CEFS according to treatment strategy, with better 5-y CEFS for patients managed with W&W (p=0.0046) (Figure 2C). When the effect of treatment was analyzed according to HPLLs/ABC score, W&W and splenectomy were significantly better than single-agent rituximab or R/Ch in patients from group A (p<0.001), whereas there were no differences among the treatment modalities in score B (p=0.421).

We analyzed LSS and PFS in patients treated with rituximab at diagnosis and those receiving rituximab after a period of W&W in order to evaluate whether or not delaying the time of initial treatment had an impact on the patient's outcome. There

were no statistically significant differences between the two groups in terms of LSS or PFS, as shown in Supplementary Figure 1, A and B. Similarly, we performed the analysis of LSS and PFS comparing patients treated with R/Ch at diagnosis or after the W&W period, and we did not find statistically significant differences between both groups (LSS p=0.78; PFS p=0.35) (Supplementary Figure 1 C and D). These results suggest that delaying treatment had no impact on the outcome of patients.

Finally, we compared our SMZL series to an age- and sex-matched Spanish control population in terms of 5-year OS (Figure 1C and D). Relative survival of SMZL patients showed a minimal decrease in life expectancy compared with the matched population (excess mortality of 5%) (ratio 0.95). When analyzing relative survival separately according to the HPLLs/ABC score groups, patients from group B had an excess mortality of 17% (relative survival ratio: 0.83) compared to the general matched population. Conversely, there was no significant decrease in relative survival for score A SMZL.

Events of special interest: histological transformation and early progression

Histological transformation (HT) was diagnosed in 11 out of 181 patients (6%), 10 of which were diffuse large B-cell lymphoma and one Hodgkin lymphoma. There were three patients with HT found at the time of lymphoma diagnosis, two of them in score C. Among the 8 cases in whom HT did not appear at diagnosis, only one patient (13%) presented histological transformation after the W&W period. Splenectomy was the initial therapy in 3 cases (37%), one of them also requiring R-CHOP before HT occurred. The remaining 4 patients (50%) received rituximab as first line treatment and

underwent HT more than one year later (range, 13-40 months). The median time from diagnosis to HT for the remaining eight patients was 21 months (range 10-40 months). Patients on score C had a higher risk of HT (HT at 5 years: 1.3%, 6.6% and 36% for scores A, B and C, respectively; p<0.001). As expected, HT was associated with a significantly lower OS (time-dependent Cox regression HR: 7.8, 95%CI: 3.2-19.2; p<0.001).

We analyzed the impact of early progression in our subgroup of SMZL patients who received treatment. LSS was specifically evaluated in patients with relapse or progression within the first 24 months after frontline treatment (POD24, n=26) and compared with that of non-POD24 patients (n=68). Of the 94 patients included in this analysis, 5-year LSS was significantly worse for POD24 patients compared with that of non-POD24 patients (60% vs 98%, respectively, p<0.001) (Supplementary Figure 2).

DISCUSSION

Our study describes real-world data on the management of 181 patients prospectively diagnosed with SMZL in Spain since 2014 and confirms the clinical value of the recommendations of the GELTAMO Guidelines. These data are especially relevant since this population can be considered informative about the real incidence and clinical features of SMZL patients. Considering that in the RELINF registry 286 patients with SMZL (representing a 2.5% of the 11.400 registered lymphoma cases) were included between 2014 and 2018[4], the present sample amounts to more than two

thirds (68%) of all the cases and is thus demonstrative of the patterns of care of this rare subtype of lymphoma in daily practice.

The first remarkable point is the approach to diagnosis. SMZL patients were diagnosed and treated by local hematopathologist and hematologist experts from the participating centers. Following the SMZLSG and GELTAMO recommendations, most cases were diagnosed with data obtained from the morphology and FCM of the bone marrow and peripheral blood, whereas diagnostic splenectomy was performed only in 8% of cases.

Importantly, the clinical characteristics of our patients are similar to those described in the two larger retrospective series, i.e., FIL[17] and SMZLSG[15]. In the FIL series, there was a higher proportion of splenomegaly and HCV positivity (HCV infection being more prevalent in Italy). In our series, leukemic disease was more frequent than in the FIL series (80% vs. 59%), which can be explained due to its assessment using FCM.

With a median follow-up of 41.2 months, the 5-year OS and LSS were 77% and 93%, respectively. Of note, only 40% were lymphoma-related deaths or related to its treatment. The outcome of our patients seems better than that described by the FIL (72% and 76% for 5-year OS and LSS, respectively)[17] or the US population-based study (73% and 72% 5-year OS and LSS, respectively)[16]. Moreover, our current survival estimates are also slightly more favorable than those reported in the SMZLSG study (77% and 88% OS and LSS at 5 years, respectively)[15] and in the IELSG19/IELSG-46 study (84.5% OS at 5 years)[17].

Nevertheless, in such an indolent lymphoma, OS and LSS do not appear to be the most appropriate parameters to define the course of the disease. Although PFS is a relevant

endpoint, it is only calculated for treated patients in all series, disregarding the large subgroup of patients who underwent a W&W approach and, thus, introducing an important bias in the evaluation of the outcome of the whole population of patients. However, despite not using surgical or pharmacological elements, W&W is an important management decision and constitutes an unequivocal form of treatment itself. As mentioned, a substantial number of SMZL patients undergo a W&W policy[15,17] and their outcome must also be considered. Therefore, we selected CEFS as an endpoint considering both treated and non-treated (W&W) patients. Interestingly, in our series, W&W and splenectomy provided significantly better results than single-agent rituximab or R/Ch in patients from group A. Moreover, this low-risk group had a similar relative survival compared to the age- and sex- matched Spanish population. With these data, it is reasonable to assume that the most convenient and less toxic approach for score A is the best option, which clearly points to W&W. This is a very important consequence of the scoring system to qualitatively define a group of patients not needing therapy. For score B patients, the situation is more uncertain, as neither W&W nor splenectomy seem to be appropriate for a group of patients with various adverse factors (i.e., cytopenias and/or lymph node dissemination). For this subgroup, rituximab could be the optimal and less toxic therapy. Although there is much data regarding targeted agents, such as BTK inhibitors, PI3K inhibitors and immunomodulatory drugs, mostly in the relapsed or refractory settings[27], their definitive role requires further confirmation, they are not at all devoid of toxicity and there is a lack of randomized trials comparing these new drugs to rituximab.

In this study, ORR were similar between rituximab and R/Ch, although both modalities achieved significantly better rates of response than splenectomy. In contrast to older

series[15,23], a remarkable finding is that splenectomy was used in only 14 patients (8%). In addition, the time of treatment onset (at diagnosis or after a W&W period) with rituximab or R/Ch had no impact in PFS, supporting the fact that there is no detrimental effect of delaying treatment with either modality as also shown in the Hospital Clinic of Barcelona series[28].

In our series, the HPLLs/ABC score has predictive ability for LSS in score A and B patients, but not in score C patients. Although the percentage of patients allocated to each risk group is similar to those reported in the original publication[18], the C group in our study is less representative. Only 9 out of 11 cases were evaluable for analysis for response and survival (2/11 were histologically transformed at diagnosis and were excluded upfront). In addition, unexpectedly, there were no deaths in the remaining 9 evaluable patients, therefore leading to a 5-year LSS of 100%. This may be due to the low number of cases, as opposed to 41 in the original HPLLs/ABC study, in which a similar proportion (~7%), but four times as many patients were classified as score C. Another explanation for such good outcomes of score C patients is that 44% of them (4/9) received immunochemotherapy following the recommendations of the Guidelines. Thus, we can suggest that using more strategies that are intensive might overcome the adverse prognosis previously reported for that subgroup and, in fact, reinforce the clinical usefulness of our Guidelines. However, no conclusion can be drawn due to the small number of patients.

The occurrence of transformation was the most relevant adverse prognostic factor in our series. Transformation was seen in 6% of our patients, and importantly, the development of HT multiplies the risk of death by a factor of 7.8, which doubles the

risk reported in the large series by Bastidas-Mora et al[28]. Transformation may appear at diagnosis (in 27% of cases) or at any time during the course of the disease (in 73% of cases) and it occurred with increasing frequency from scores A through C, suggesting a dynamic evolution. In the Hospital Clinic of Barcelona series[28], the cumulative incidence of transformation at 5 years from diagnosis was 15%, being documented in others in a range from 5% to 19%[4,9,29].

A time to progression shorter than 24 months (POD24) was found to be a determinant for reduced survival in patients that had received initial treatment, as reported by others[25]. Unfortunately, whether a patient will be POD24 or not is not known at diagnosis, and we are in need of other tools to predict outcomes at the time of diagnosis. On the contrary, the clinical HPLLs/ABC stratification, with all its limitations, is easily available at diagnosis in everyday practice and can confidently separate two risk groups (A and B), as shown in the present study. Certainly, more accurate tools would be desirable. For this purpose, the recent molecular characterization of SMZL combining genomic, transcriptomic and microenvironmental data has allowed for the identification of the most frequently mutated genes and has defined subsets of patients with different prognoses[30]. However, this has yet to be confirmed and the technical difficulties of this approach make its practical use impossible, at least for the time being.

In summary, the use of HPLLs/ABC score allows to identify patients with score A who do not need immediate treatment and can be followed-up with a W&W policy avoiding toxicities derived from unnecessary treatments. Moreover, considering effectiveness and toxicity, rituximab seems to be the preferential option in patients from group B requiring a more active treatment. Prospective and larger studies including

homogeneously treated SMZL patients are eagerly awaited. Until then, and whilst there is no standard treatment for this lymphoma, therapeutic decisions must still consider clinical aspects and individual physician expertise.

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Conflict of interest statement

AM has received a speaker honorarium and travel grants from Roche, Abbvie, AstraZeneca and Janssen and has participated in advisory boards for Roche, Abbvie, AstraZeneca and Janssen. MTV has received a speaker honorarium Abbvie, Janssen and GSK. MBO received honoraria for speaker activities from Roche, Janssen, Takeda, Novartis, Gilead, BMS and Incyte and research funding from Roche. JMS has received honoraria as speaker from Roche, Gilead-Kite, Celgene-BMS, Janssen, Novartis, Incyte and Takeda and has participated in advisory boards for Roche, Gilead-Kite, Celgene-BMS, Janssen, Novartis, Incyte, Beigene, Lilly and Miltenyi Biomedicine. TG has received honoraria from Janssen, Abbvie, Roche and Gilead. PA has received honoraria from Janssen, Roche, BMS, Abbvie, Incyte, Beigene and Astrazeneca. ALG served on the advisory board of Roche, Celgene, Novartis, Gilead/Kite and received grants from Celgene, Gilead/Kite. AS has received honoraria from Roche (Research Funding, Speakers Bureau), Janssen Pharmaceuticals (Consultancy, Speakers Bureau), Abbvie (Research Funding), Gilead (Research Funding) and BMS/Celgene (Consultancy).

The remaining authors (SGV, MJRS, AJU, GBM, RC, MI, MJV, FJD, MB, CP, BN, LE, MJT, RC, PM, CM) declare no conflict of interest.

Autorship statements

AM provided and centralized clinical data, interpreted data, wrote the manuscript, performed statistical analyses, and contributed to the conception of the study. MTV provided and centralized clinical data, interpreted data, wrote the manuscript and performed statistical analyses. SGV, MJRS, AJU, GBM, RC, MI, MJV, FJD, MB, MBO, CP, JMS, BN, TG, LE, PA, MJT, RC and ALG provided clinical data. PM performed statistical analyses. AS designed the study, supervised the research, provided clinical data, interpreted data, and wrote the manuscript. CM designed the study, supervised the research, provided clinical data, interpreted data and wrote the manuscript. All authors reviewed the final version of the manuscript.

Author notes

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Ethics approval statement

The study was approved by the Ethics Committee at Hospital Universitari Mútua Terrassa.

Patient consent statement

Signed written informed consent was collected for all included patients.

TABLES & FIGURES

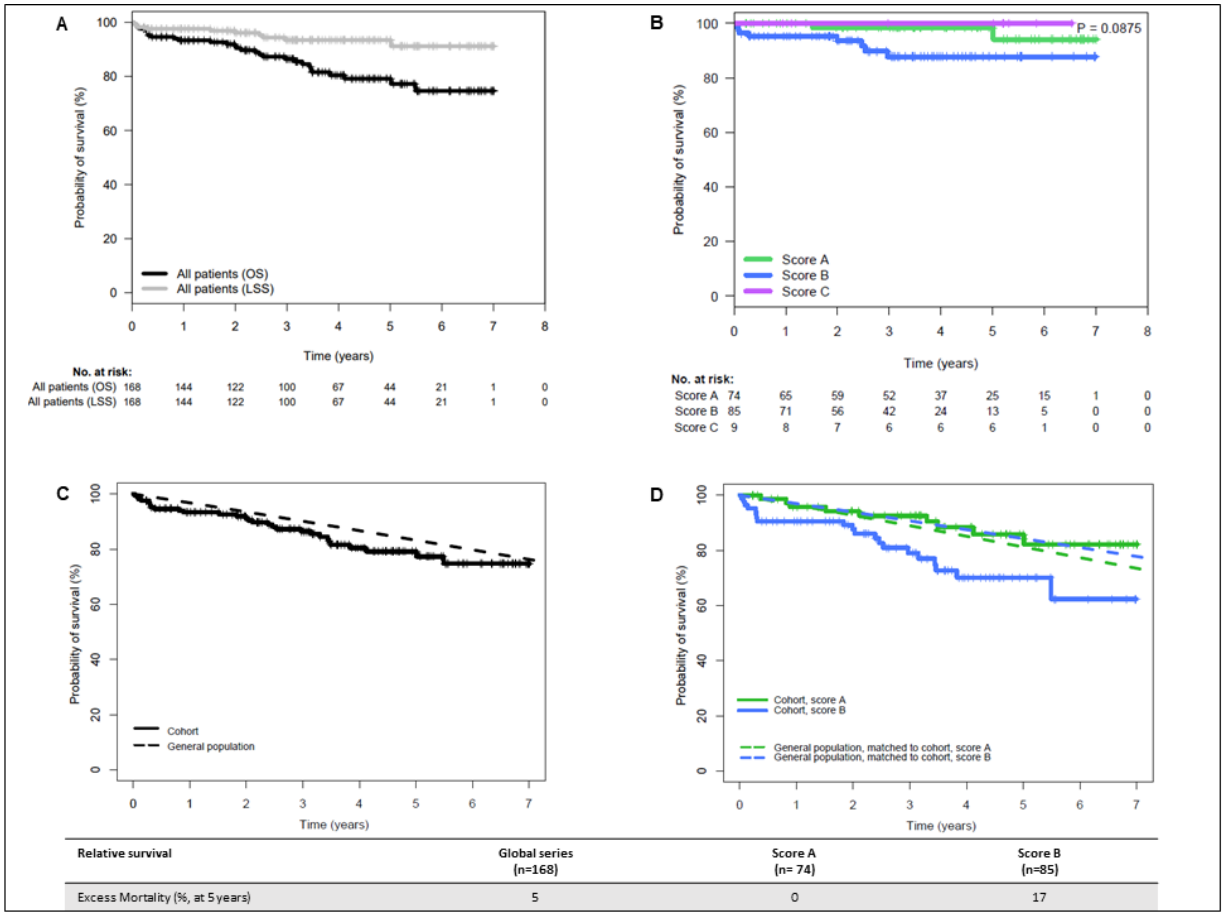
Table 1. Initial characteristics and frontline treatment (overall series, N=181)

Variable at diagnosis	N =181 (%)
Age, years	
Median [range]	71 [41-93]
≥65	129 (71.2)
Sex, female	97 (54)
Hemoglobin (g/dL)	
Median [range]	118.8 [46-178]
<9.5 g/dL	30/179 (16.8)
Platelets (x 10^3/µl)	
Median [range]	159.9 [37-730]
<80 x 10^3/µl	17/179 (9.5)
Lymphocytes (x 10^9/L)	
Median [range]	7.99 [0.30-84.0]
≥5x 10^9/L	81/179 (45.3)
Clonal lymphocytosis	136/178 (76.4)
Bone marrow infiltration	153/177 (86.4)
Karyotype abnormalities	52/172 (40)
B symptoms	43/174 (24.7)
Splenomegaly	138/175 (78.9)
Monoclonal gammopathy (positive serum immunofixation)	48/174 (27.6)
Autoimmune disease	23/158 (14.6)
HCV positive	8/178 (4.4)
HBV positive	3/176 (1.7)
HIV positive	0/174 (0)
ECOG ≥ 2	18/175 (10.3)
Initial PET	31/180 (17.2)
Lymph nodes (CT scan and others)	63/175 (36)
Hilar	41/175 (23.4)
Extrahilar	51/175 (29)
Score HPLLs/ABC	A: 79 (43.6) B: 91 (50.3) C: 11 (6)
Diagnostic splenectomy	18 (9.9)
Patients managed with W&W at diagnosis	98 (54)
Histological transformation at diagnosis	3/11 (27)
Followed ABC Score for treatment decisions	104 (57.5)

Table 2. Treatment and response rates according to therapy.

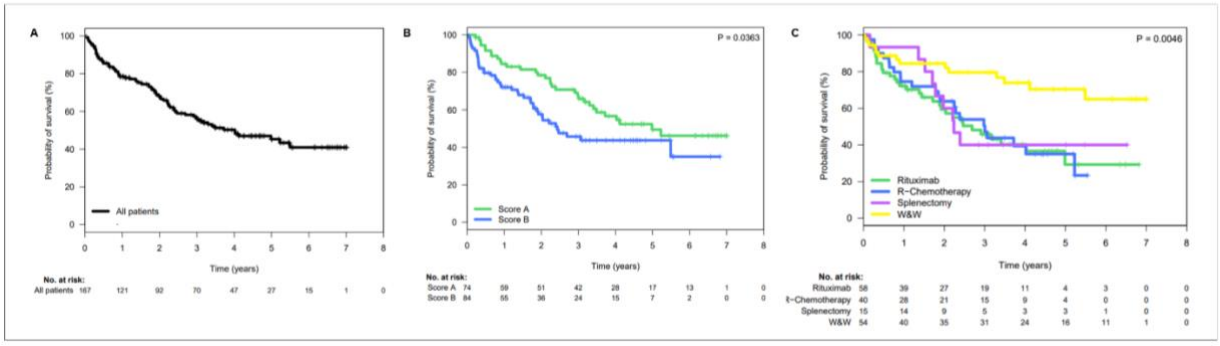
	Rituximab **N= 59** **n (%)**	**R-Chemotherapy** **N= 40** **n (%)**	**Splenectomy** **N=15** **n (%)**
Treated patients (n=114)			
At diagnosis	42 (71)	19 (48)	14 (93)
During follow-up	17 (29)	21 (52)	1 (7)
Responses rates			
Overall Response	49 (83)	38 (85)	11 (72)
Complete Response	29 (49)	30 (75)	-
Partial Response	20 (34)	8 (20)	11 (72)
Stable disease/Progressive disease	7 (12)	1 (2.5)	3 (27)
Not evaluable	3 (5)	1 (2.5)	1 (1)

Figure 1. Overall, lymphoma-specific and relative survival. **A.** Lymphoma specific survival and overall survival in all patients. **B**. Lymphoma specific survival (LSS) according to ABC score. **C.** Relative survival of SMZL patients compared to the age- and matched- general Spanish population in overall series. **D.** Relative survival of SMZL patients compared to the age- and matched- general Spanish population according to HPLLs/ABC score groups A and B.



Relative survival	Global series (n=168)	Score A (n= 74)	Score B (n=85)
Excess Mortality (%, at 5 years)	5	0	17

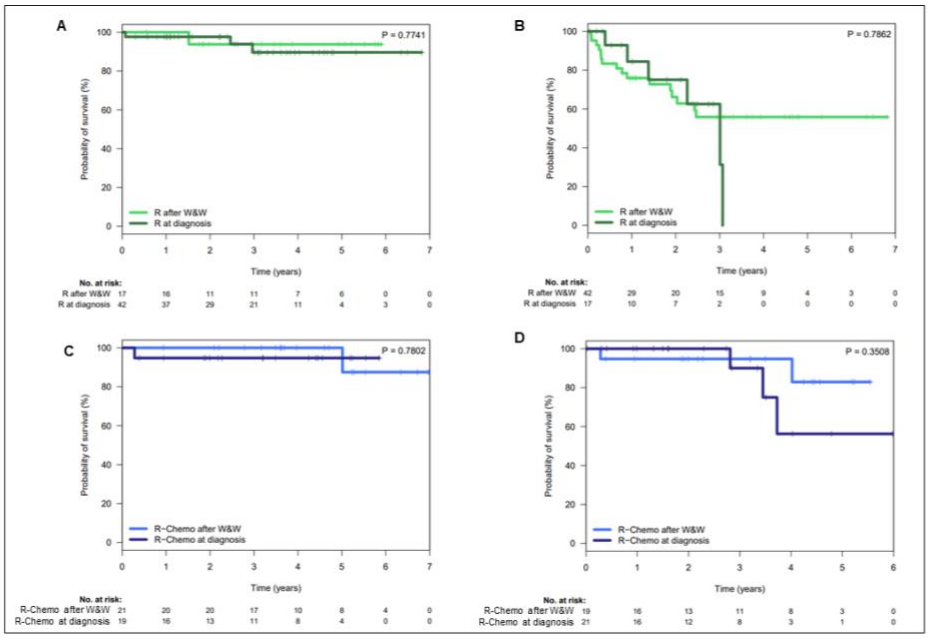
Figure 2. Composite event free survival (CEFS): **A**. All patients. **B**. According to HPLLs/ABC score. **C**. According to initial management.



Supplementary Table 1. Initial characteristics and frontline treatment according to HPLLs/ABC score.

Variable at diagnosis	P **A vs B**	**Score A** N= 79 n (%)	**Score B** N=91 n (%)	**Score C** N=11 n (%)	P **B vs C**
Age, years Median [range] ≥65	 0.656	 72 [48-91] 58 (73.4)	 70 [41-93] 64 (70.3)	 65 [51-82] 7 (63.3)	 0.648
Sex, female	**0.016**	34 (43)	56 (61.5)	7 (63.3)	0.892
B-symptoms	**0.001**	6 (7.6)	30 (33)	7 (63.3)	**0.041**
Lymphocytosis ≥5x 10^9/L	0.963	37 (46.8)	42 (46.2)	2 (18.2)	0.067
ECOG ≥ 2	**0.012**	3 (3.8)	14 (15.4)	1 (9.1)	0.714
Initial PET	0.076	8 (10.1)	18 (19.8)	5 (45.5)	0.057
Monoclonal gammopathy (positive serum immunofixation)	0.071	17 (21.5)	30 (33)	1 (9.1)	0.153
Splenomegaly	**0.004**	52 (65.8)	75 (82.4)	11 (100)	0.189
HCV Positive *HCV Treatment*	0.617	3 (3.8) 2 (66.7)	5 (5.5) 3 (60)	- -	0.423
Autoimmune disease	0.537	8 (10.1)	12 (13.2)	3 (27.3)	0.213
Histological transformation *At diagnosis*	0.081	1 (1.3) -	6 (6.6) 1 (16.7)	4 (36.4) 2 (50)	**0.002**
Management @ diagnosis *-Observation (W&W)* *-Treatment* Rituximab R-Chemotherapy Splenectomy Palliative care	 **< 0.001**	 38 (48.1) 41 (51.9) 16 (39) 15 (36.6) 7 (17.1) 3 (7.3)	 18 (19.8) 73 (80.2) 42 (57.6) 23 (31.5) 6 (8.2) 2 (2.7)	 - 11 (100) 2 (18.2) 5 (45.5) 4 (36.4) -	 **0.002**

Supplementary Figure 1. Outcomes according to treatment and time of initial therapy: Lymphoma specific survival **(A)** and progression free survival **(B)** according to single-agent rituximab treatment at diagnosis or at lymphoma progression. Lymphoma specific survival **(C)** and progression free survival **(D)** according to rituximab-chemotherapy treatment at diagnosis or at lymphoma progression.



Supplementary Figure 2. Lymphoma specific survival according to time of relapse or progression in 94 treated SMZL patients (POD24 *vs*. non-POD24) (landmark 24 months)