bjh research paper

Superior outcome for splenectomised patients in a population-based study of splenic marginal zone lymphoma in Sweden

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Summary

Splenic marginal zone lymphoma (SMZL) is a rare low-grade B-cell lymphoma where associations with viral hepatitis and autoimmune and inflammatory diseases (AID) have been indicated. We aimed at assessing the prevalence of viral hepatitis and AID at SMZL diagnosis and outcome by treatment in a Swedish population-based study. A total of 277 SMZL patients registered in the Swedish Lymphoma Register in 2007–2017 were included. A history of viral hepatitis was reported in five (2%) patients and AID prior to SMZL in 72/240 (30%) patients. Treatment was given up front for 207 (75%) patients. Splenectomy with or without systemic treatment was performed in 119 (57%) and was associated with statistically significantly better overall survival [hazard ratio, HR = 0·47 (95% confidence interval, CI: 0·23–0·93), $P = 0·03$] and progression-free survival (HR = 0·55, 95% CI: 0·35–0·86, $P = 0·008$) compared to non-splenectomised patients in multivariable analyses. The up-front splenectomised group was younger and generally had a lower Ann Arbor stage, but also more frequently B symptoms and high lactate dehydrogenase than the non-splenectomised group. Viral hepatitis and AID history did not affect SMZL outcome. We report high incidence of AIDs and low incidence of viral hepatitis in this population-based study of SMZL. Splenectomy up front was associated with a favourable outcome.

Keywords: splenic marginal zone lymphoma, splenectomy, hepatitis C, hepatitis B, treatment.

Introduction

Splenic marginal zone lymphoma (SMZL) is a rare and indolent B-cell lymphoma and accounts for <2% of lymphomas. At onset, the disease is often disseminated while patients are usually asymptomatic, rarely exhibit B symptoms and have good performance status according to the Eastern Cooperative Oncology Group (ECOG) score.[1,2] A more aggressive disease course is seen in approximately 30% and transformation to high grade lymphomas is observed in 5–10%[3–5] of cases.

The cause of SMZL is unknown. However, associations with autoimmune and inflammatory diseases (AID) and infection with hepatitis C virus (HCV) or hepatitis B virus (HBV)[6] have led to theories of chronic inflammatory conditions being a contributory cause of SMZL.[2] Previous studies, mainly from southern Europe, have described an association between HCV infection and SMZL in up to 35% of cases.[2,7–9]

In about 20% of SMZL cases, autoimmune manifestations[2] are seen at diagnosis, such as autoimmune idiopathic haemolytic anaemia (AIHA)[10,11] and idiopathic thrombocytopenic purpura (ITP).[12] Furthermore, AIDs such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren's syndrome have been associated in previous studies with an increased risk of developing lymphomas,[13–15] although specific associations with SMZL remain largely unexplored.

Presently, there is no standard treatment of SMZL, mainly due to the rarity of SMZL and the lack of clinical trials. Splenectomy is often used for both diagnostic and treatment purposes. In cases where splenectomy cannot be performed, rituximab (R)[16–18] is given as monotherapy or in combination

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with chemotherapy. There is a lack of comprehensive population-based studies on outcomes for patients treated with modern treatment modalities[3] and most previous observational studies have included a small number of cases[4,16–20] and lack information on outcome in patients treated with R. Therefore, the aims of this study were to investigate the clinical characteristics and outcome of SMZL in the Swedish population in relation to different modern treatment modalities. Furthermore, we aimed to explore the prevalence of HBV, HCV and AIDs in this population-based cohort.

Patients and methods

Patients

In total, 289 patients with SMZL were prospectively recorded in the Swedish Lymphoma Register between 2007 and 2017. The Swedish Lymphoma Register covers over 95% of the entire Swedish lymphoma population.[21,22] Twelve patients were excluded since, according to the medical records, the registered SMZL diagnosis had been changed to another lymphoma subtype, and thus a total of 277 patients were included. In addition to the register data, patient records have been reviewed for the purpose of collecting supplementary data. In 34 cases, patient records were not available. The study was approved by the Regional Ethical Committee in Uppsala (Dnr 2017/551). Informed consent was not mandatory for living patients according to the Ethical Committee decision.

In addition to the records, the HCV and HBV status was double-checked against data reported to the Swedish Institute for Infectious Disease Control. HCV and HBV are notifiable diseases in Sweden, and all cases diagnosed with HCV and HBV are mandatorily reported to the Swedish Institute for Infectious Disease Control. Furthermore, in the absence of information on the cause of death in the patient records, supplementary data from the Cause-of-Death register was requested.

Data collection

Data collection included age at lymphoma diagnosis, sex, date of diagnosis and diagnosis modality (bone marrow, spleen, peripheral blood or lymph node), initial type of treatment (including watchful waiting) and treatment outcome [complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or unknown response (UR)], date of event (death, progression and transformation), cause of death (lymphoma-related/other cause of death), date of last follow-up, ECOG (0–4), B symptoms, stage at diagnosis according to Ann Arbor (I–IV), age-adjusted international prognostic index (aaIPI), lactate dehydrogenase (LDH; normal or elevated), M component (present or not present) and presence of extra-hilar (splenic) lymphadenopathy (yes/no). AIDs (in this study including inflammatory disorders without identified auto-antibodies) were categorised according to the InterLymph Consortium[13] into primarily B-cell- or T-cell-mediated or, if not known, as uncategorised. AIDs were separated into those diagnosed before, at, or after the SMZL diagnosis. In addition, lifestyle factors assessed included smoking status (smoker/former smoker/never smoker) and alcohol consumption (scanty/moderate/overconsumption/abuse) at diagnosis. Occupations were divided into categories (healthcare/desk jobs/legal/farmers and industry/teachers/service jobs).

Statistical methods

Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause with censoring at date of last follow-up. Progression-free survival (PFS) was calculated from the time of diagnosis until the date of an event (with censoring at date of last follow-up). An event was defined as death from any cause or lymphoma progression (progression or transformation). Lymphoma-specific survival (LSS) was calculated from the time of diagnosis until the date of death due to lymphoma with censoring at date of last follow-up. In order to avoid immortal time bias, OS, PFS and LSS were calculated from the estimated date of splenectomy in cases where systemic treatment was given prior to splenectomy ($n = 14$). Cases where the dates for splenectomy and systemic treatment were unavailable ($n = 4$) were not included in the main survival analyses. Survival curves and univariable survival analyses were performed using the Kaplan–Meier method, the log-rank test and Cox proportional hazards regression. The chi-squared test or Fischer's exact test was used to compare tabulated values. Variables relevant to disease outcome (OS, PFS and LSS) with $P < 0{\cdot}05$ from the univariable analyses were included in the multivariable-adjusted Cox regression analyses. In addition, Ann Arbor stage I–II *versus* ≥III, B symptoms (present *versus* absent) and LDH (normal *versus* elevated) were added to the multivariable analyses since the distribution of these variables differed in the group treated with splenectomy up front, compared to other patients. Occupation and M component were not included in the multivariable models due to information being available in only a minority of the patients. Cases with missing information on any variable were omitted from the multivariable analyses. We tested the proportional hazards assumption, which was not violated. A $P < 0{\cdot}05$ was considered to be statistically significant. Pairwise tests for interaction between the groups treated with splenectomy up front and significant variables from the multivariable Cox regression analyses and Ann Arbor stage ≥III were performed. Propensity score matching was performed including clinical variables (age ≥60 years, Ann Arbor stage ≥III, B symptoms, elevated LDH) differing between splenectomised and non-splenectomised patients. In supplementary sensitivity analyses, watchful waiting was excluded from the non-splenectomised group. Statistical analyses were performed using SPSS version 26 for Windows Armonk, NY: IBM Corp, R 4·0.3 and Rstudio 1·3.1093 (www.r-project.org).

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Table I. Clinical characteristics of patients with SMZL diagnosed 2007–2017 in Sweden.

Variable	Whole c ohort, *n* (%; *n* = 277)	Splenectomised, *n* (%)* (*n* = 119)	Non-splenectomised, *n* (%)† (*n* = 131)	*P* value‡
Sex				
Female	167 (59%)	77 (65)	75 (57)	0·28
Male	110 (41%)	42 (35)	56 (43)	
Age ≥60 years				
Yes	229 (83)	84 (71)	120 (92)	**<0·001**
No	48 (17)	35 (29)	11 (8)	
Mean/median age at diagnosis (range)	70/72 (25–95)	65/68 (25–85)	73/74 (44–91)	–
Ann Arbor stage				
≥III	229 (83)	91 (76)	118 (90)	**<0·001**
≤II	36 (13)	25 (21)	7 (5)	
Missing data	12 (4)	3 (3)	6 (5)	
Performance status				
ECOG ≥1	121 (44)	54 (45)	59 (45)	0·99
ECOG <1	148 (53)	63 (53)	69 (53)	
Missing data	7 (3)	2 (2)	3 (2)	
B symptoms				
Present	136 (49)	67 (56)	54 (41)	**0·03**
Absent	110 (40)	44 (37)	66 (50)	
Missing data	31 (11)	8 (7)	11 (8)	
aaIPI				
≥2	120 (43)	59 (50)	54 (41)	0·99
<2	54 (19)	26 (22)	25 (19)	
Missing data	103 (37)	34 (29)	52 (40)	
Extra-hilar lymphadenopathy				
Present	91 (33)	42 (35)	48 (37)	0·99
Absent	91 (33)	40 (34)	48 (37)	
Missing data	95 (34)	37 (31)	35 (27)	
LDH				
Elevated	141 (51)	68 (57)	48 (37)	**0·001**
Not elevated	126 (45)	46 (39)	78 (60)	
Missing data	12 (4)	5 (4)	5 (4)	
M component				
Present	48 (17)	21 (18)	27 (21)	0·99
Absent	71 (26)	29 (24)	39 (30)	
Missing data	158 (57)	69 (58)	65 (50)	
Autoimmune conditions§				
Present	72 (26)	38 (32)	32 (24)	0·22
Absent	168 (61)	72 (61)	90 (69)	
Missing data	37 (13)	9 (9)	9 (7)	
Diagnosis				
Bone marrow	167 (60)	41 (34)	108 (82)	**<0·001**
Spleen	97 (35)	78 (66)	12 (9)	
Lymph node	5 (2)	0 (0)	5 (4)	
Blood	8 (3)	0 (0)	6 (5)	
Missing data	0 (0)	0 (0)	0 (0)	
Treatment				
Up front	207¶ (75)	119 (100)	83 (63)	**<0·001**
Watchful waiting	51 (18)	0 (0)	48 (37)	
Missing data	19 (7)	0 (0)	0 (0)	
Smoker				
No and non-former	88 (32)	42 (35)	44 (33)	0·66
Smoker or former smoker	91 (33)	39 (33)	49 (37)	
Missing data	98 (35)	38 (32)	38 (29)	

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Table I. (*Continued*)

Variable	Whole c ohort, *n* (%; *n* = 277)	Splenectomised, *n* (%)* (*n* = 119)	Non-splenectomised, *n* (%)† (*n* = 131)	*P* value‡
Alcohol				
None to moderate	111 (40)	51 (43)	59 (45)	0·63
Overconsumption or abuse	14 (5)	8 (7)	6 (5)	
Missing data	151 (55)	60 (50)	66 (50)	
Year of diagnosis				
2007–2012	141 (51)	77 (65)	48 (37)	**<0·001**
2013–2017	136 (49)	42 (35)	83 (63)	

Statistical significance ($P < 0·05$) is indicated by boldface font.

aaIPI, age-adjusted International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; SMZL, splenic marginal zone lymphoma.

*Splenectomised up front, including patients only treated with splenectomy and patients treated with splenectomy in combination with systemic treatment (in cases where information on date for splenectomy and systemic treatment was available).

†Non-splenectomised as up-front treatment.

‡Comparing splenectomised with non-splenectomised patients with chi-squared or Fischer's exact test.

§Autoimmune and inflammatory diseases diagnosed prior to SMZL.

¶Including one case treated with RT, not included in the non-splenectomised subgroup.

Results

Clinical characteristics

Clinical data for the entire cohort (*n* = 277) are summarised in Table I. The median follow-up time was 53·4 months (range 0·5–154·4).

Autoimmune disorders

Among 240 cases, a history of AIDs before lymphoma diagnosis was found in 72 (30%) patients. Fifteen patients had two or more AIDs and a total of 95 AID diagnoses were reported. The most common AIDs were autoimmune thyroid disease (*n* = 34), RA (*n* = 9), psoriasis (*n* = 9) and AIHA (*n* = 6). A total of 60 diagnoses were regarded as primarily B-cell-mediated, 16 diagnoses as primarily T-cell-mediated and 19 were left in the uncategorised group. In addition, 25 patients were diagnosed with AID in conjunction with the SMZL diagnosis, most commonly AIHA (*n* = 16) and ITP (*n* = 2). Nine patients were diagnosed with AID after the SMZL diagnosis, most commonly autoimmune thyroid disease (*n* = 2) and AIHA (*n* = 2). In three patients, the timing of onset of AID in relation to the SMZL diagnosis was not possible to determine (Table II). AIDs were more common in females (*n* = 78) than in males (*n* = 31).

Hepatitis

No patient was reported to have an active HCV or HBV disease at SMZL diagnosis. There were five cases with a history of hepatitis; two HCV, two HBV and one of unknown type, reported as having previously been diagnosed with hepatitis but with uncertainty concerning the time point of infection.

Treatment and outcome

At the onset of disease, 48 patients were not considered to have treatment indication and were selected for clinical follow-up, i.e. watchful waiting. A total of 207 (75%) patients received treatment up front, 123 (59%) were splenectomised and of these, 97 underwent splenectomy only. Splenectomy was more common in the first part of the study (2007–2012) compared to patients treated later (2013–2017; Table I). Twenty-six patients received systemic therapy in addition to the splenectomy, eight of whom received systemic therapy after splenectomy, 14 received systemic therapy prior to splenectomy and in four cases the dates for splenectomy and systemic treatment were unavailable. Systemic treatment, regardless of splenectomy, was given in 109 (53%) patients accordingly: single R (*n* = 48; 44%), R-bendamustine (*n* = 24; 22%), chlorambucil (*n* = 17; 16%), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; *n* = 8; 2%) and R in combination with other chemotherapeutic agents (*n* = 8; 2%; Table III). The treatment response was CR for 141 (68%) and PR for 41 (20%), SD for 13 (6%), PD in eight (4%) and UR in five (2%) patients. In total, 95 patients died during follow-up, of whom 44 due to lymphoma. Progression of SMZL was observed in 77 (32%) patients. Seventeen cases transformed into diffuse large B-cell lymphoma (DLBCL) and four cases into Hodgkin lymphoma (HL).

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Table II. Autoimmune and inflammatory conditions in patients with SMZL divided into primarily B-cell-mediated, T-cell-mediated or uncategorised.

Autoimmune conditions	All AID (n = 109 patients*) n (%)†	Splenectomised AID prior to diagnosis (n = 38 patients)	Non-splenectomised AID prior to diagnosis (n = 32 patients)
Primarily B-cell-mediated			
Autoimmune thyroid disease	38 (27)	14	18
Autoimmune haemolytic anaemia	34 (24)	8	3
Rheumatoid arthritis	9 (6)	5	3
Primary Sjögren's syndrome	3 (2)	2	1
Other B-cell-mediated	8 (6)	5	3
Primarily T-cell-mediated			
Psoriasis‡	9 (6)	4	5
Celiac disease	4 (3)	2	2
Other T-cell-mediated	6 (4)	1	2
Uncategorised			
Polymyalgia rheumatica	6 (4)	3	2
Raynaud's syndrome	5 (4)	4	1
Idiopathic thrombocytopenic purpura	4 (3)	1	0
Presence of lupus anticoagulant	3 (2)	0	0
Other uncategorised	12 (9)	5	1

Other primarily B-cell-mediated include systemic lupus erythematosus, pernicious anaemia, C1-inhibitor deficiency, myasthenia gravis and multiple sclerosis; other primarily T-cell-mediated include ulcerative colitis, primary sclerosing cholangitis, Crohn's disease, pityriasis lichnoid sclerosus, ankylosing spondylitis; other uncategorised include systemic sclerosis, minimal change disease, type 1 diabetes, Guillain–Barré syndrome, non-specific interstitial pneumonitis, chronic recurrent multifocal osteomyelitis, autoimmune hepatitis, skin vasculitis, complement component 2 deficiency. AID, autoimmune and inflammatory diseases; SMZL, splenic marginal zone lymphoma.

*Including AID diagnosed prior to, at onset or after the SMZL diagnosis. Eighty-five patients (58 females and 27 males) had one AID. Two AIDs were found in 18 patients (15 females and 3 males). Four patients had three AIDs and all were females. One man and one female had four AIDs.

†Percentage of all AIDs.

‡ Including two patients with psoriasis type PPP (pustulosis palmaris et plantaris).

Table III. Treatment and response in 254 patients with SMZL.

Type of treatment	Number of patients (%)	CR	PR	SD	PD	UR
Splenectomy only	97 (38)	74	15	4	–	4
Systemic treatment and splenectomy	26 (10)	15	6	1	4	–
R and splenectomy	11	7	1		3	–
Chemotherapy and splenectomy	7	2	4	1	–	–
R, chemotherapy and splenectomy	8	6	1	–	1	–
Systemic treatment	83 (33)					
Chemotherapy without R	14	–	5	4	3	2
Chemotherapy with R	32	21	8	2	–	1
R monotherapy	37	26	7	1	1	2
Watchful waiting	48 (19)	2*	–	23†	21‡	2

CR, complete response; PD, progressive disease; PR, partial response; R, rituximab; SD, stable disease; SMZL, splenic marginal zone lymphoma; UR, unknown response.

*Splenectomy was performed in two due to other causes than lymphoma.

†One patient was considered to receive best supportive care.

‡One patient developed a myeloma. Patients were treated with R (n = 7), chemotherapy with R (n = 5), R and splenectomy (n = 2) and splenectomy only (n = 2), chemotherapy only (n = 1).

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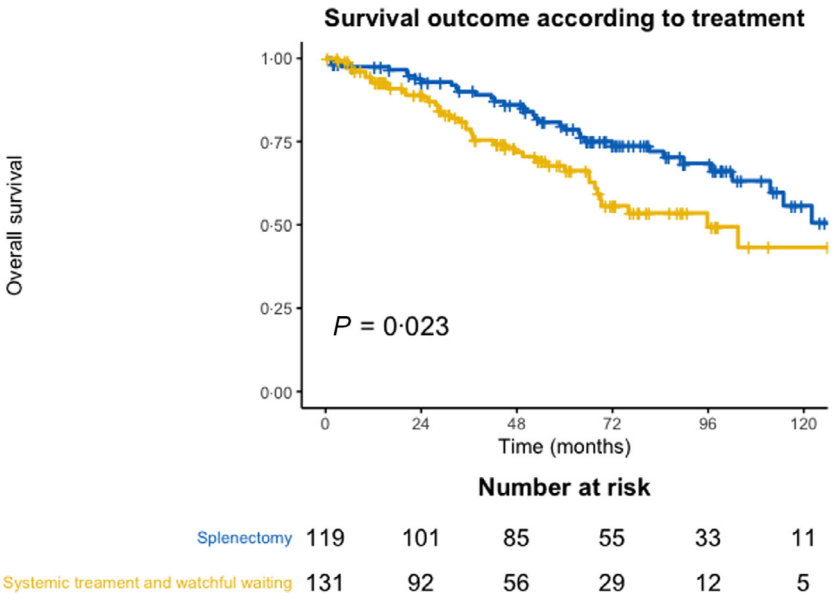

Fig 1. Kaplan–Meier curve for overall survival in patients treated with splenectomy (n = 119), systemic treatment and watchful waiting (n = 131). [Colour figure can be viewed at wile yonlinelibrary.com]

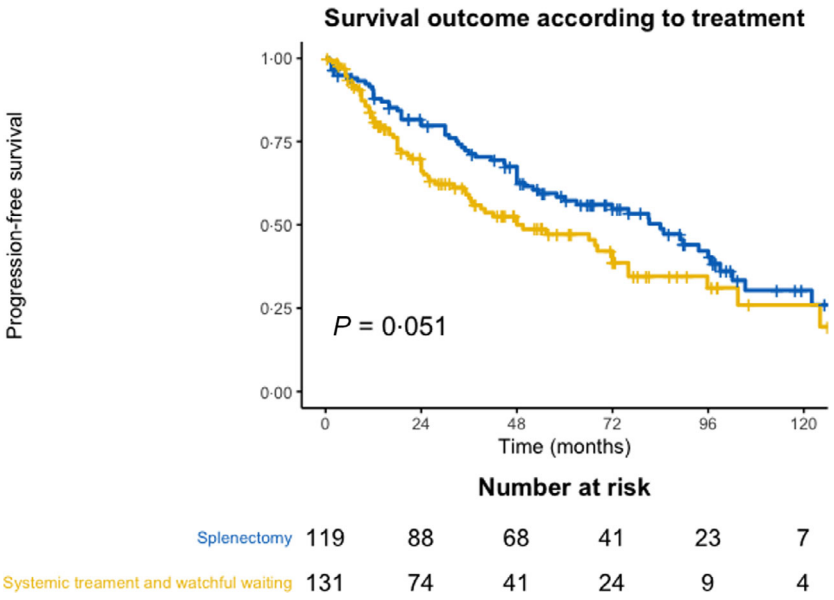

Fig 2. Kaplan–Meier curve for progression-free survival in patients treated with splenectomy (n = 119), systemic treatment and watchful waiting (n = 131). [Colour figure can be viewed at wileyonlinelibrary.com]

Univariable survival analyses

For all patients, median OS time was 112 months and PFS was 66 months, while median LSS time was not reached. At five years, OS, PFS and LSS were 76%, 57% and 86%, respectively. Patients treated up front with splenectomy (with or without additional systemic therapy) had a superior five-year survival rate of 82% for OS, 62% for PFS and 90% for LSS, compared to non-splenectomised patients with 75% for OS, 56% for PFS and 85% for LSS (Figs 1–3). Variables associated with inferior OS, PFS and LSS included age ≥60 years, ECOG performance status ≥1, smoker or former smoker and B symptoms (Tables IV–VI). AID diagnosed prior to SMZL was not associated with survival, including when AIDs were stratified into primarily B-cell-mediated, T-cell-mediated and uncategorised or when separated into distinct diseases (RA, SLE, Sjögren's syndrome; Table SVI). Teachers had an inferior PFS compared to healthcare workers in univariable analyses (Table SVII).

Multivariable Cox regression analyses

For the multivariable OS analysis, up-front splenectomy, age ≥60 years, stage ≥III, ECOG performance status ≥1, B symptoms, high LDH and smoking status were included (Table IV). Splenectomy remained statistically significantly associated with superior OS (HR = 0·47, 95% CI 0·23–0·93),

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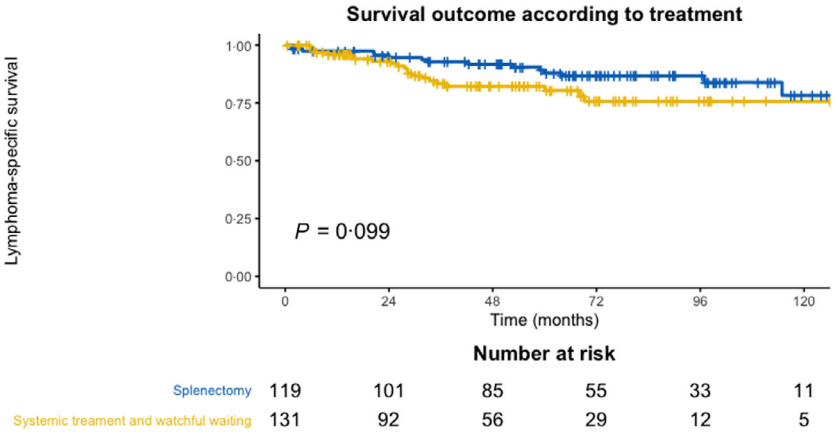

Fig 3. Kaplan–Meier curve for lymphoma-specific survival in patients treated with splenectomy (n = 119), systemic treatment and watchful waiting (n = 131). [Colour figure can be viewed at wileyonlinelibrary.com]

Table IV. Univariable and multivariable Cox regression analyses of overall survival (death due to any cause) estimated as hazard ratios with 95% confidence intervals and P values by putative prognostic factors in SMZL patients. Statistical significance ($P < 0·05$) is indicated by boldface font.

	Overall survival	
	Univariable	Multivariable
Splenectomy*	**0·59, 0·38–0·94, 0·02**	**0·47, 0·23–0·93, 0·03**
Male	0·95, 0·63–1·44, 0·81	–
Age ≥60 years	**3·68, 1·70–7·96, <0·001**	**6·10, 1·42–26·20, 0·02**
Stage ≥III	0·69, 0·41–1·16, 0·17	0·63, 0·25–1·59, 0·33
ECOG performance status ≥1	**1·99, 1·31–3·02, 0·001**	1·87, 0·94–3·72, 0·08
B symptoms	1·49, 0·95–2·33, 0·08	1·75, 0·88–3·50, 0·11
aaIPI ≥ 2	0·96, 0·57–1·62, 0·88	–
Extra-hilar lymphadenopathy	0·93, 0·57–1·50, 0·76	–
High LDH	1·03, 0·68–1·55, 0·89	1·20, 0·63–2·28, 0·57
M component	**0·44, 0·20–0·95, 0·04**	†
Autoimmune conditions‡	0·67, 0·38–1·17, 0·16	–
Up-front treatment	1·13, 0·61–2·10, 0·69	–
Smoker or former smoker	**2·10, 1·17–3·77, 0·01**	**1·91, 1·002–3·64, 0·049**
Overconsumption or abuse of alcohol	0·51, 0·16–1·66, 0·26	–

aaIPI, age-adjusted international prognostic index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; SMZL, splenic marginal zone lymphoma.

*Patients treated up front with splenectomy, with or without additional systemic treatment (in cases where information on date for splenectomy and systemic treatment was available) compared with all other patients.

† Not included in the multivariable model due to few cases with information on M component.

‡ Autoimmune and inflammatory diseases.

while age ≥60 years and smoker or former smoker remained statistically significantly associated with inferior OS. For the multivariable analysis of PFS, up-front splenectomy, age ≥60 years, stage ≥III, ECOG performance status ≥1, B symptoms and high LDH were included (Table V). Splenectomy remained significantly associated with superior PFS (HR = 0·55, 95% CI 0·35–0·86), while only age ≥60 years and B symptoms remained statistically significantly associated with inferior PFS. For the multivariable analysis of LSS, up-front splenectomy, age ≥60 years, stage ≥III, B symptoms, high LDH and smoking status were included (Table VI). Splenectomy was associated with superior LSS (HR = 0·43, 95% CI 0·17–1·10) with borderline significance (P = 0·08), while only age ≥60 years, B symptoms and smoker or former smoker remained statistically significantly associated with inferior LSS. Pairwise tests for interaction showed no statistically significant interactions between splenectomy and age ≥60 years (P = 0·62), smoker or former smoker (P = 0·08) and Ann Arbor stage ≥III (P = 0·88) for OS. Likewise, pairwise tests for interaction showed no statistically significant interactions between splenectomy and age ≥60 years (P = 0·48), B symptoms (P = 0·34) and Ann Arbor stage ≥III (P = 0·25) for PFS. The same was found regarding pairwise tests for interaction between splenectomy and age ≥60 years (P = 0·91), B symptoms (P = 0·12), smoker or former smoker (P = 0·54) and Ann Arbor stage ≥III

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Table V. Univariable and multivariable Cox regression analyses of progression-free survival (death due to any cause, progression and transformation) estimated as hazard ratios with 95% confidence intervals and *P* values by putative prognostic factors in SMZL patients. Statistical significance ($P < 0{\cdot}05$) is indicated by boldface font.

	Progression-free survival	
	Univariable	Multivariable
Splenectomy*	0·71, 0·50–1·003, 0·052	**0·55, 0·35–0·86, 0·008**
Male	0·85, 0·61–1·19, 0·35	–
Age ≥60 years	**2·13, 1·30–3·50, 0·003**	**1·88, 1·08–3·29, 0·03**
Stage ≥III	1·07, 0·67–1·70, 0·78	0·84, 0·47–1·48, 0·54
ECOG performance status ≥1	**1·48, 1·06–2·05, 0·02**	1·28, 0·86–1·91, 0·22
B symptoms	**1·56, 1·10–2·20, 0·01**	**1·66, 1·09–2·51, 0·02**
aaIPI ≥2	0·93, 0·62–1·42, 0·75	–
Extra-hilar lymphadenopathy	1·14, 0·78–1·67, 0·50	–
High LDH	1·06, 0·77–1·48, 0·71	1·10, 0·74–1·63, 0·62
M component	0·66, 0·40–1·10, 0·11	–
Autoimmune conditions	0·87, 0·59–1·30, 0·50	–
Up-front treatment	0·76, 0·50–1·16, 0·20	–
Smoker or former smoker	1·19, 0·79–1·78, 0·41	–
Overconsumption or abuse of alcohol	0·62, 0·28–1·36, 0·24	–

aaIPI, age-adjusted international prognostic index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; SMZL, splenic marginal zone lymphoma.
*Patients treated up front with splenectomy, with or without additional systemic treatment (in cases where information on date for splenectomy and systemic treatment was available) compared with all other patients.

Table VI. Univariable and multivariable Cox regression analyses of lymphoma-specific survival (death due to lymphoma) estimated as hazard ratios with 95% confidence intervals and *P* values by putative prognostic factors in SMZL patients. Statistical significance ($P < 0{\cdot}05$) is indicated by boldface font.

	Lymphoma-specific survival	
	Univariable	Multivariable
Splenectomy*	0·57, 0·29–1·12, 0·10	0·43, 0·17–1·10, 0·08
Male	1·31, 0·72–2·37, 0·38	–
Age ≥60 years	2·65, 0·95–7·43, 0·06	**7·98, 1·04–61·33, 0·046**
Stage ≥III	0·85, 0·38–1·91, 0·69	0·33, 0·10–1·09, 0·07
ECOG performance status ≥1	1·69, 0·92–3·10, 0·09	–
B symptoms	1·76, 0·92–3·37, 0·09	**5·04, 1·77–14·39, 0·002**
aaIPI ≥ 2	1·17, 0·49–2·78, 0·72	–
Extra-hilar lymphadenopathy	1·20, 0·61–2·35, 0·60	–
High LDH	1·33, 0·74–2·41, 0·34	1·81, 0·77–4·26, 0·18
M component	0·29, 0·08–1·02, 0·054	–
Autoimmune conditions	0·71, 0·32–1·58, 0·40	–
Up-front treatment	2·34, 0·72–7·64, 0·16	–
Smoker or former smoker	**3·40, 1·34–8·65, 0·01**	**3·48, 1·31–9·24, 0·01**
Overconsumption or abuse of alcohol	0·34, 0·05–2·56, 0·29	–

aaIPI, age-adjusted international prognostic index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; SMZL, splenic marginal zone lymphoma.
*Patients treated up front with splenectomy, with or without additional systemic treatment (in cases where information on date for splenectomy and systemic treatment was available) compared with all other patients.

($P = 0{\cdot}15$) for LSS. In propensity score-matched analyses splenectomy remained statistically significantly associated with a superior OS (Figure S1), PFS (Figure S2) and LSS (Figure S3) in univariable and multivariable analyses (data not shown). In supplementary analyses, watchful waiting was excluded from the non-splenectomised group, and splenectomy was associated with superior OS (Table SII) and LSS (Table SIV) in univariable and multivariable Cox regression

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analyses, while splenectomy was not statistically significantly associated with PFS (Table SIII).

Survival by different treatment modalities

In order to investigate whether there were outcome differences between different treatment combinations, patients were divided accordingly: splenectomy only ($n = 97$), R ($n = 37$), chemotherapy and R ($n = 32$) and watchful waiting ($n = 48$). The small subgroups splenectomy and R ($n = 11$), splenectomy, chemotherapy and R ($n = 8$) and splenectomy and chemotherapy ($n = 7$) were pooled into one group ($n = 26$). One patient treated with splenic radiotherapy was excluded from the analyses. The overall test for heterogeneity showed statistical significance for OS (log-rank $P = 0{\cdot}03$; Figure S4) and LSS (log-rank $P = 0{\cdot}01$; Figure S6) and borderline significance for PFS (log-rank $P = 0{\cdot}06$; Figure S5). In supplementary univariable Cox regression analyses, each treatment modality was compared to all other treatment modalities (including watchful waiting). Patients treated with splenectomy only had a statistically significant favourable PFS (HR = 0·67, 95% CI 0·47–0·96) and borderline significance for OS (HR = 0·64, 95% CI 0·40–1·02) compared to all other treatment modalities (including watchful waiting) in univariable analyses (Table SV).

Discussion

In this large population-based cohort of patients with SMZL, we report that patients treated with up-front splenectomy have a statistically significantly better survival rate compared to non-splenectomised patients. The up-front splenectomised group was younger and had a generally lower Ann Arbor stage, but also more frequently B symptoms and high LDH than the non-splenectomised group. Importantly, when we adjusted for all clinical variables, only the splenectomised group along with a few other clinical variables remained statistically significantly associated with OS and PFS.

Splenectomy has traditionally and historically been the standard treatment of choice for SMZL. However, caution for splenectomy in elderly patients with comorbidity associated with high surgical risk has been raised. Monotherapy with R has become more common,[17,23] achieving high response rates and lately, this therapy has also been suggested as the first choice of treatment in SMZL patients.[18,24] Systemic therapy with chemotherapy, often accompanied with R, has also been used. Due to the rarity of SMZL, there are no randomised studies comparing different treatment modalities and thus, retrospective analyses of population-based cohorts such as the present study, are valuable. One recent comprehensive study from the US found no favourable survival outcome in association with any specific treatment modality (splenectomy, chemotherapy only, splenectomy plus chemotherapy or watchful waiting); however this study lacked information on cases treated with monotherapy R.[3] In supplementary analyses in our study, R was compared to the rest of the treatment modalities but was not statistically significantly associated with OS or PFS. Although R has begun to gain more ground, and previous studies[4,23] indicate that maintenance R therapy could be an alternative, splenectomy still appears to play a significant role in SMZL treatment.[25] In addition, splenectomy also allows for a histopathologically confirmed diagnosis of this rare disease entity. It cannot be fully ruled out that non-splenectomised patients were diagnosed incorrectly with SMZL, where other potential misdiagnoses may influence the results such as splenic diffuse red pulp small B-cell lymphoma in the non-splenectomised patients, although this is an even more unusual lymphoma entity.[26] Selection bias cannot be fully ruled out since patients who initially were chosen for watchful waiting would probably be expected to have a more indolent-behaving disease than those treated up front. Splenectomy up front was also performed for diagnostic purposes in some patients with lower stager I–II disease.

The patients in our population-based study were more often women, as has been reported in some previous studies,[3,11,27,28] although this has not been a consistent finding; variation between studies has shown male predominance[12,16,29] or no gender difference.[30,31] Transformation to DLBCL was observed in 17 cases, which is in accordance with previous studies with similar follow-up times[4,16] although somewhat lower than in one other study.[3] In addition, we report four cases of HL, which is an unusual finding, although this has previously been observed in rare cases.[5]

HCV and HBV infection or reactivation did not appear to be a contributing factor to the course of SMZL in this Swedish cohort, since none of the patients were diagnosed with active HCV or HBV infection. Up to 35% of SMZL patients in previous studies have been infected with HCV.[2,7–9] Furthermore, a causal association has been strengthened by the fact that treatment of HCV has led to lymphoma remission in some cases.[9,32–35] The Swedish Public Health Agency reported in 2017 that the incidence of HCV is 16·5 and HBV 11 cases per 100 000 persons per year. For HBV, approximately 90% of the cases in 2007 were infected outside Sweden, and in 2019 only 4% were estimated to be infected in Sweden. HCV is considered to be very widespread globally,[2,36,37] whereas in Sweden the prevalence is considered to be relatively low, which could explain why HCV infection was rare in our population. HBV was recently shown to be associated with SMZL,[6] but we could not confirm this association. Thus, HBV and HCV infections do not seem to be major contributors to the development of SMZL in populations with a low prevalence of these infections.

AIDs are associated with an increased risk of lymphoma development,[15] but their association with SMZL remains largely undetermined. Overall, the proportion of AIDs diagnosed prior to SMZL (30%), was greater in our cohort compared to

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other studies in SMZL with reported frequencies of about 20%.[2,27,38] RA has a prevalence of 0·5–1% in the Swedish population,[39] while 3% of patients in our cohort had RA. The high incidence of AIDs compared to previous studies is an intriguing finding, suggesting that AID partakes in the pathogenesis of SMZL to a higher degree than previously believed and this association is perhaps particularly strong in countries like Sweden with low prevalence of HBV and HCV. In addition, there is some support that lymphomas related to AID could have different pathobiology and clinical features compared to non-AID-related lymphomas,[14] but whether this is true for AIDs in SMZL patients is not known. Nevertheless, AID diagnosed prior to the SMZL diagnosis did not influence OS or PFS in our study.

Other factors such as smoking habits indicated that being a non-smoker could have a beneficial impact on OS. For occupations, Cox regression adjusted for age and gender showed some impact on PFS for the teaching profession compared to healthcare workers. The reason for this remains unexplained, but the findings should be interpreted with caution since information regarding profession was only available in a few patients (n = 130) and there were few patients in each subgroup.

Strengths of our study include the population-based inclusion of virtually all SMZL cases diagnosed in Sweden during a period of more than 10 years in an era of modern treatment modalities. In addition, our thorough review of patient records and different registries enabled the inclusion of a vast array of well-known clinical variables, as well as socioeconomic variables such as tobacco and alcohol use, which we were able to adjust for in our statistical analyses. Weaknesses include the rather low number of cases included in several of the specific treatment groups in the supplementary analyses (e.g. monotherapy R, chemotherapy and R); thus, these results should be interpreted with caution. The results should be interpreted cautiously due to the inherent selection of patients to specific treatments or watchful waiting based on a number of confounding factors in a retrospective analysis. Other limitations were that we were unable to analyse the intention to splenectomise.

In addition, the inferior outcome observed in the non-splenectomised group might be partly explained by the fact that these patients were generally older, had a higher Ann Arbor stage and were maybe not fit for splenectomy. Still, the splenectomised group retained statistical significance when adjusted for clinical variables.

To summarise, in our population-based cohort of SMZL patients in Sweden, we found a relatively high prevalence of AIDs, a low prevalence of viral hepatitis and a superior survival outcome for splenectomised patients. Since SMZL is rare, randomised studies are lacking but are needed in order to fully evaluate the possible survival benefit observed in splenectomised patients compared to other treatment modalities.

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Author contributions

AS, EB, KES, GE and RMA designed the study. AS gathered clinical information. AS and PH performed the statistical analyses. AS, PH and RMA wrote the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

All authors declare no competing financial or non-financial interests.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Kaplan–Meier curve for overall survival in propensity score-matched patients treated with splenectomy (n = 70), systemic treatment and watchful waiting (n = 70).

Fig S2. Kaplan–Meier curve for progression-free survival in propensity score-matched patients treated with splenectomy (n = 70), systemic treatment and watchful waiting (n = 70).

Fig S3. Kaplan–Meier curve for lymphoma-specific survival in propensity score-matched patients treated with splenectomy (n = 70), systemic treatment and watchful waiting (n = 70).

Fig S4. Kaplan–Meier curve for overall survival according to treatment. * includes patients treated with splenectomy + chemotherapy, splenectomy + chemotherapy + rituximab or splenectomy + rituximab.

Fig S5. Kaplan–Meier curve for progression-free survival according to treatment. * includes patients treated with splenectomy + chemotherapy, splenectomy + chemotherapy + rituximab or splenectomy + rituximab.

Fig S6. Kaplan–Meier curve for lymphoma-specific survival according to treatment. * includes patients treated with splenectomy + chemotherapy, splenectomy + chemotherapy + rituximab or splenectomy + rituximab.

Table SI. Clinical characteristics of patients with SMZL diagnosed 2007-2017 in Sweden, excluding cases with watchful waiting (n = 48) from the non-splenectomised group.

Table SII. Univariable and multivariable Cox regression analyses of overall survival (death due to any cause) estimated as hazard ratios with 95% confidence intervals and P values by putative prognostic factors in SMZL patients. Statistical significance ($P < 0·05$) is indicated by boldface font. Patients treated up front with splenectomy (n = 119), with

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or without additional systemic treatment compared with non-splenectomised, excluding watchful waiting patients ($n = 83$).

Table SIII. Univariable and multivariable Cox regression analyses of progression-free survival (death due to any cause, progression and transformation) estimated as hazard ratios with 95% confidence intervals and *P* values by putative prognostic factors in SMZL patients. Statistical significance ($P < 0{\cdot}05$) is indicated by boldface font. Patients treated up front with splenectomy ($n = 119$), with or without additional systemic treatment compared with non-splenectomised, excluding watchful waiting patients ($n = 83$).

Table SIV. Univariable and multivariable Cox regression analyses of lymphoma-specific survival (death due to lymphoma) estimated as hazard ratios with 95% confidence intervals and *P* values by putative prognostic factors in SMZL patients. Statistical significance ($P < 0{\cdot}05$) is indicated by boldface font. Patients treated up front with splenectomy ($n = 119$), with or without additional systemic treatment compared with non-splenectomised, excluding watchful waiting patients ($n = 83$).

Table SV. Univariable Cox regression analyses of overall survival (death due to any cause) and progression-free survival (death due to any cause, lymphoma transformation or progression) estimated as hazard ratios with 95% confidence intervals and *P* values according to treatment in SMZL patients. Statistical significance ($P < 0{\cdot}05$) is indicated by boldface font.

Table SVI Univariate Cox regression analyses with relative risk of overall survival (death due to any cause) and progression-free survival (death due to any cause, lymphoma transformation or progression) estimated as hazard ratios with 95% confidence intervals and *P* values according to autoimmune conditions diagnosed prior to SMZL.

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