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Prognostic factors and primary treatment for Waldenström macroglobulinemia – a Swedish Lymphoma Registry study

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Abstract

We present a nationwide prospective Swedish registry-based study of Waldenström macroglobulinaemia (WM), that focuses on incidence and survival in relation to clinical prognostic factors and primary systemic therapies. A total of 1511 patients with WM and lymphoplasmocytic lymphoma (LPL) were registered in the Swedish Lymphoma Registry (SLR) between 1 January 2000 and 31 December 2014. The age-adjusted incidence of WM/LPL was 11·5 per million persons per year, three times higher than the reported incidence worldwide. Medical records were retrieved for 1135 patients (75%). A retrospective review showed that 981 (86·1%) of these patients fulfilled the World Health Organization diagnostic criteria for WM and these patients were analysed further. The overall survival (OS) improved between two periods – 2000–2006 and 2007–2014 – with a five-year OS of 61% and 70%, respectively. Significant prognostic factors for OS, evaluated at the time of diagnosis, were age, elevated lactate dehydrogenase level and haemoglobin ≤115 g/l for patients receiving therapy 0–3 months after diagnosis, and age, poor performance status, haemoglobin ≤115 g/l, and female sex in "watch and wait" patients (multivariable analysis). The level of the IgM monoclonal immunoglobulin had no significant prognostic value. Rituximab included in first-line therapy was associated with improved survival.

Keywords: Waldenström macroglobulinaemia, lymphoproliferative disease, prognostic factors, therapy, Waldenström macroglobulinaemia survival.

Waldenström macroglobulinaemia (WM)/lymphoplasmacytic lymphoma (LPL) is a rare disease, with a worldwide incidence of 3–4 per million persons per year (Wang *et al*, 2012; Brandefors *et al*, 2016). The diagnosis of WM requires infiltration of LPL cells in the bone marrow and any concentration of IgM monoclonal immunoglobulin (MI) (Owen *et al*, 2003; Swerdlow *et al*, 2008). Common clinical manifestations of WM include anaemia and thrombocytopenia due to tumour infiltration in bone marrow, enlarged lymph nodes and spleen, recurrent fever, night sweats, fatigue and weight loss. High concentrations of IgM MI can cause hyperviscosity and an increase in plasma volume with resulting anaemia due to dilution of red cells (Vitolo *et al*, 2008; Ghobrial, 2012).

Several prognostic factors have been identified, mostly in small patient cohorts and in non-population retrospective analyses (Facon *et al*, 1993; Morel *et al*, 2000; Owen *et al*, 2001; Dimopoulos *et al*, 2003; Merlini *et al*, 2003; Ghobrial *et al*, 2006; Dhodapkar *et al*, 2009; Kastritis *et al*, 2009). The most widely accepted prognostic index, the International Prognostic Scoring System for WM (IPSSWM; Morel *et al*, 2009), is based on disease parameters evaluated at the time of first-line treatment. The indications for therapy applied in the original IPSSWM cohort were defined by the 2nd International Workshop recommendations (Kyle *et al*, 2003) and a bone marrow lymphoplasmacytic infiltration of more than 20% was required. Many WM patients do not exhibit symptoms at diagnosis (i.e., smouldering or asymptomatic WM) and do not require any therapy, so why there is a need to explore prognostic factors at the time for diagnosis? In this article we explore the prognostic factors for patients treated 0–3 months after diagnosis, and also for asymptomatic patients managed with a "watch and wait" strategy.

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Waldenström macroglobulinaemia is a rare disease and only a few randomized studies on treatment have been published (Buske *et al*, 2009; Leblond *et al*, 2013; Rummel *et al*, 2013). Therefore, treatment guidelines are mostly based on results from phase II trials and retrospective data. Mostly the choice of first-line therapy is based on the individual patient's characteristic and disease symptoms and immunochemotherapy is currently the standard treatment for most WM patients (Buske *et al*, 2013; Treon, 2015; Leblond *et al*, 2016; Gertz, 2017).

Although WM remains an incurable disease, the median overall survival (OS) has improved, ranging from 6 years in the 1990s to 8 years in the first decade of the 2000s (Kristinsson *et al*, 2013; Castillo *et al*, 2015).

We present data from an analysis based on a nationwide prospective high-quality registry of the lymphoma population in Sweden with 15 years follow-up. Our study focuses on the incidence and outcome of WM in relation to clinical prognostic factors and primary systemic therapies.

The results from this unselected cohort of patients provide novel knowledge of this rare disease that can be applied to patients treated during routine clinical care.

Patients and methods

Swedish lymphoma registry

The Swedish Cancer Registry (SCR), established in 1958, is a compulsory registry for all newly diagnosed cancers in Sweden. All cancer subtypes are reported to the SCR both by the responsible pathologist and the treating physician. To obtain specific complementary information for lymphoma, such as clinical stage, prognostic factors and treatment, the Swedish Lymphoma Group (SLG) initiated a specific Swedish Lymphoma Registry (SLR) in 2000.

The coverage of SLR is high; >95% of the adult patients (>18 years of age) with a lymphoma diagnosis in the SCR are included also in the SLR (Swedish lymphoma register 2014; http://www.swedishlymphoma.se/rapporter). Between 2000 and 2006, data are incomplete regarding type of first-line treatment, but after 1 January 2007, when a more detailed web-based registry was introduced, most first-line therapies have been recorded in the registry.

Study population

From the SLR, we collected 1511 patients living in Sweden, a country with approximately 10 million inhabitants, who were diagnosed with WM/LPL between 1 January 2000 and 31 December 2014. A large proportion of the patients were reported to the registry as the broader diagnosis WM/LPL. To confirm WM diagnosis, data were extracted from the medical records of the 1511 patients registered in SLR. In total, 1139 of these (75%) had available serum protein electrophoresis, including immunofixation, and the pathology report of the bone marrow biopsy/aspiration and/or lymph node biopsy at the time of diagnosis and 981 (86·1%) fulfilled the criteria for WM (Fig 1). In Sweden, the World Health Organization (WHO) diagnostic criteria for WM are used, including morphological infiltration of LPL in the bone marrow (without a defined percentage of tumour cells) and an IgM MI of any concentration in serum (https://www.cancercentrum.se/samverkan/cancerdiagnoser/blod-lymfom-myelom/lymfom-lymfkortelcancer/vardprogram/gallande-vardprogram-waldenstroms-makroglobulinemi/). The definition of non-WM LPL included disease without a serum IgM MI. Also, patients with a lymph node infiltration with LPL cells but without a bone marrow infiltration and/or without IgM MI were defined as non-WM LPL.

In total, 124 patients (10·9%) fulfilled these LPL criteria (29 with IgG MI and 7 with IgA MI) and were analysed only for the total incidence of WM/LPL but excluded from other analyses. The non-WM LPL patients will be described elsewhere.

In addition, 16 (1·4%) patients were excluded because they were incorrectly registered as WM (Fig 1; Table SI) and 18 (1·6%) patients were excluded due to incomplete data on IgM MI in serum and/or bone marrow infiltration.

For the analysis of prognostic factors, we used the following data from the time point of diagnosis, collected from the SLR: age, lactate dehydrogenase (LDH) level, B-symptoms, WHO performance status (WHO PS; Oken *et al*, 1982), gender, haemoglobin, albumin, lymphocyte counts, time point for start of first-line treatment and time point for death. If these data were missing in the SLR, supplementary data were extracted from the medical records regarding haemoglobin, albumin, LDH, platelet count, beta-2 microglobulin (β2M), IgM MI level and immunoglobulin levels.

The analysis included the prognostic factors used in IPSSWM (Morel *et al*, 2009); age, haemoglobin (≤115 g/l), platelet count ($\leq 100 \times 10^9$/l), β2M (>3 mg/l) and IgM MI (>70 g/l). In addition, we used the median value of albumin for the cohort (≤35 g/l) and divided WHO PS into two groups; WHO PS 0 and WHO PS 1-4. (Oken *et al*, 1982). IgM MI was analysed both with continuous and dichotomous scales with three different cut-offs (30, 50 and 70 g/l). Hypogammaglobinaemia was defined as an immunoglobulin value below the lower level of the reference interval used by the individual laboratory.

The recommended workup in the Swedish national guidelines for patients with lymphoma include biopsy from bone marrow (and lymph node or other lymphoma involved site when applicable) as well as computed tomography (CT) scan of thorax, abdomen and pelvis and laboratory tests. In the registry, only 55% of the patients with WM/LPL had a complete recommended workup, and in most cases CT scan data and data on lymph node involvement were missing.

Date of start of first-line treatment and type of initial therapy were collected from the SLR. Between 2000 and 2006, data regarding type of first-line treatment was not a

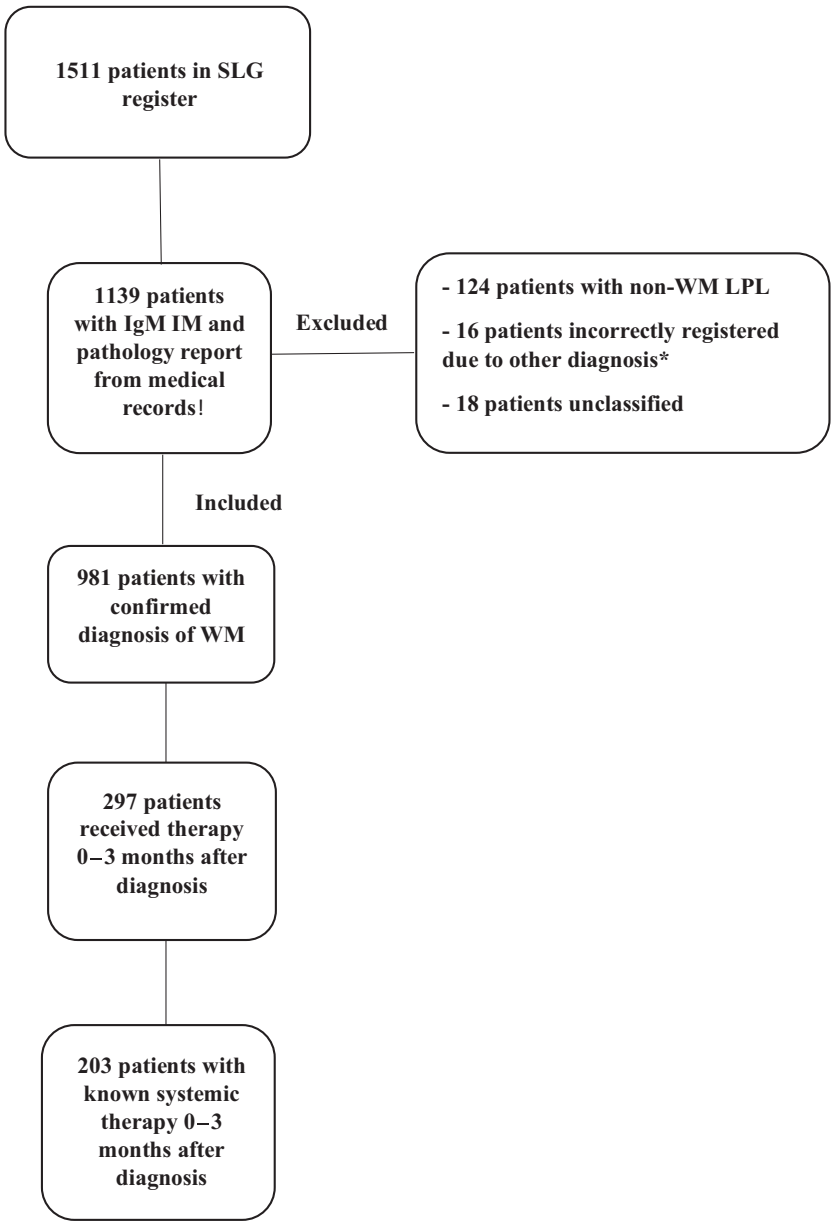


Fig 1. Flowchart of patient selection process. LPL, lymphoplasmocytic lymphoma; MI, monoclonal immunoglobulin; SLG, Swedish Lymphoma Group; WM, Waldenström macroglobulinaemia.

mandatory reporting requirement for the SLG and was missing in 94/144 patients. After 1 January 2007, when a more detailed web-based registry was introduced, most first-line therapies have been recorded in the registry**.** In the cohort reported 2007–2014 only 26·6% of the patients required first-line treatment within 0–3 months after diagnosis.

Because data on treatment outcome, relapses, and second-line treatment were missing for many patients, these data were excluded from further analysis.

In summary, of the 1511 patients registered in the SLR, 981 were confirmed as WM patients and were analysed in more detail (Fig 1). Therapy was initiated within 0–3 months after diagnosis in 297 patients, and the type of systemic therapy was reported in 203 of these patients.

This study was approved by the regional ethics committee of Umeå (2011-44-31M). A specific informed consent from the patients was not required as the study was mainly based on registry data. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

All statistical analyses were performed in the free software environment R version 3.0.2 (some analyses were performed in version 3.3.2) and the packages "survival" (Pohar Perme, 2013; Gerds, 2014; Therneau, 2015). Incidence calculation was done by age-adjusting (i.e., a weighted average of all the age-specific incidences), using the "European Standard

population 2013" (http://www.isdscotland.org/Products-and-Services/GPD-Support/Population/Standard-Populations/ (downloaded 7 May 2018) as a standard population. The Hazard ratios (HRs) for prognostic factors were calculated both by univariate and multiple Cox-regression. In the multiple Cox regression analysis, no exclusion procedure was performed, thus all considered factors were entered at the start and all remained at the end of analysis. The Pearson Chi-square test was used for frequency tabulation.

Survival analysis was performed by both ordinary overall survival (OS) and relative survival (RS) methods. The Kaplan–Meier method was used to estimate OS and the subsequent curves were compared using log-rank test (Harrington & Fleming, 1982). RS was estimated by the Pohar-Perme estimator (Pohar Perme, 2013) and the subsequent survival curves were compared using a log-rank type test (Graffeo *et al*, 2016). Life tables (of the population of Sweden) required for RS analysis were downloaded from the Human Mortality Database (https://www.mortality.org/). The median follow-up time was estimated using reverse Kaplan–Meier (Schemper & Smith, 1996).

Results

Incidence for WM/LPL

Using data collected from the SLR (1511 patients) between 1 January and 31 December 2014 the age-adjusted incidence for WM/LPL was 11·5 per million persons per year. The age-adjusted incidence for males during the same period was 15·5 per million males per year and the corresponding figure for females was 8·5. There were no significant changes in incidence rates over time for the two different genders. Incidence increased with age: <65 years, 3·4; 65–75 years, 32·7; >75 years, 45·5 per million persons per year, respectively. For the patients receiving therapy 0–3 months after diagnosis the age-adjusted incidence was 2·3 per million persons per year.

The age-adjusted incidence for WM/LPL varies between the different counties in Sweden (Fig 2).

Incidence for WM

The overall age-adjusted incidence for WM in Sweden could not be calculated because of incomplete data of the specific diagnosis in 372 patients. However, in the cohort of 1139 patients with a confirmed diagnosis, 981 (86·1%) were classified as WM. If the proportion of WM patients and the age distribution of WM patients is the same in the WM/LPL population as in the smaller cohort with confirmed WM diagnosis, the overall age-adjusted incidence for WM can be estimated. Per the assumptions outlined above, the estimated incidence for WM would be 86·1% of the calculated incidence for the whole WM/LPL cohort, i.e., 9·9 per million persons per year. In Norrbotten and Västerbotten, the two counties with complete diagnostic data, the true age-adjusted incidences for WM were 17·6 and 14·3 per million persons per year, respectively.

WM patient clinical characteristics

The diagnosis of WM was confirmed in 981 patients (86·1%) based on LPL infiltration in bone marrow and serum IgM

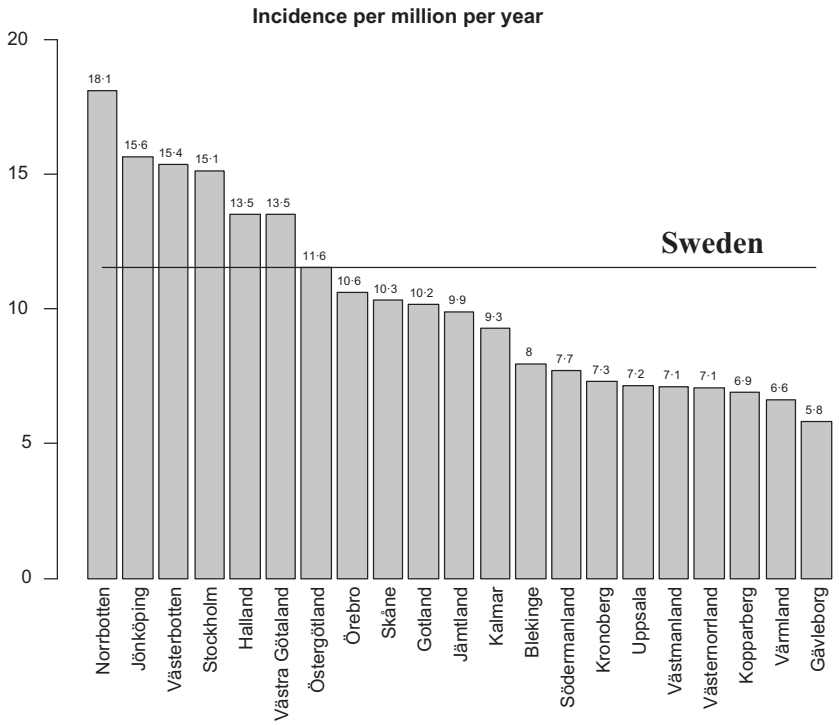


Fig 2. Incidence of Waldenström macroglobulinaemia in different counties in Sweden.

MI. Patient characteristics regarding age, gender and prognostic factors are described in Table I. Only 26 patients (2·7%) were diagnosed before 50 years of age and 721 (73·5%) patients were older than 65 years. The median follow-up time from diagnosis for survival for all patients was 79·9 months. By the end of the observation period (7 October 2015), 449 (45·8%) patients had died.

B-symptoms were present at diagnosis in 143 (14·6%) of the patients; the most frequent B-symptom was weight loss (89 patients, 9·1%), followed by night sweats (73 patients, 7·4%) and fever (24 patients, 2·4%) (Table II). This table also presents data on patients receiving therapy 0–3 months after diagnosis (n = 297) and on "watch and wait" patients (n = 684).

WM survival

The median OS of all WM patients (2000–2014) was 96 months and the three-year and five-year survival was 78% and 66%, respectively. The OS was worse for WM patients receiving therapy 0–3 months after diagnosis compared with "watch and wait" patients, with a five-year survival of 61% and 68%, respectively (see Figure S1). Kaplan–Meier and RS curves for the two periods (2000–2006 and 2007–2014, respectively) are shown in Fig 3. The median follow-up time for survival for the patients diagnosed 2000–2006 was 151 months and for 2007–2014 cohort it was 55·5 months. In univariate analyses, patients diagnosed between 2000 and 2006 showed a higher mortality rate with a HR of 1·445 (95% confidence interval [CI] 1·171–1·783, $P < 0·001$) compared with patients diagnosed between 2007 and 2014. The HR remained stable when adjusted for significant prognostic factors (HR 1·412, (95% Cl 1·061–1·879, $P = 0·019$).

The OS increased in the three cohorts between the time periods 2000–2006 and 2007–2014 (Fig 3).

Age was a strong prognostic factor (Fig 4). Compared to the younger patients, the elderly had worse OS ($P < 0·001$) and RS, although the OS was improved in all age groups between 2000–2006 and 2007–2014 (data not shown).

Kaplan–Meier curves showed no difference in survival between male and females ($P = 0·18$ and $P = 0·46$, respectively).

WM prognostic factors

Univariate and multivariable analysis in all WM patients. In univariate analysis, significant prognostic factors evaluated at the time of diagnosis in all WM patients (n = 981) were: age, WHO PS, elevated LDH, B-symptoms, time of diagnosis (2000–2006 or 2007–2014), albumin ≤35 g/l, haemoglobin ≤115 g/l, platelet count $\leq 100 \times 10^9$/l, lymphocytosis $\geq 5 \times 10^9$/l and β2M >3 mg/l (Table II).

β2M data was not required in the SLR and β2M data could be extracted for only 200 (20·4%) patients from the medical records. Lymphocyte and platelet counts were not registered in SLG until 2007, and we could extract data for 614 (62·6%) and 643 (65·5%) patients respectively.

β2M level, platelet count and lymphocyte count were significant prognostic factors according to univariate analysis; however, these variables were not included in the multivariable analysis due to the many missing values.

The serum level of the IgM MI at diagnosis was not a significant prognostic factor in univariate analysis, calculated with both continuous and dichotomous scales with different cut-off values, 30 and 50 g/l, respectively**.** In addition, the cut-off used in the IPSSWM (70 g/l) showed no prognostic value in univariate analysis. However, in total only 33 (3·5%) of the WM patients had an IgM MI >70 g/l at diagnosis. Hypogammaglobinaemia and type of light chain (kappa or lambda) were of no prognostic value.

The multivariable analysis revealed that age, WHO PS, LDH level and haemoglobin ≤115 g/l were still significant prognostic factors. Female sex was not a significant prognostic factor in the univariate analysis but emerged as a positive prognostic factor in the multivariable analysis (Table II).

Univariate and multivariable analysis of prognostic factors in WM patients receiving therapy 0–3 months after diagnosis and "watch and wait" WM patients. Univariate and multivariable analyses of prognostic factors for OS were performed separately for the patients whose therapy was initiated 0–3 months after diagnosis (n = 297) and for "watch and wait "patients (n = 684) (Table II). The univariate analysis showed the same prognostic factors as for all WM patients, except that albumin ≤35 g/l, for the cohort that received early therapy, and gender and B-symptoms, for the "watch and wait" cohort, were not significant prognostic factors. In the multivariable analysis, age, haemoglobin ≤115 g/l and elevated LDH remained significant prognostic factors in the cohort that received therapy at diagnosis, and age, female sex, WHO PS and haemoglobin ≤115 g/l remained significant prognostic factors for the "watch and wait" cohort. Neither the level of the IgM MI calculated with continuous scale nor IgM MI >70 g/l was a significant prognostic factor in any of the patient groups (Table II). However, only 13/684 (1·9%) of the "watch and wait" patients and 20/297 (6·7%) of the patients receiving early therapy (0–3 months after diagnosis) had an IgM MI >70 g/l.

*Systemic therapies (*n = *203).* In Sweden, rituximab was introduced as a routine treatment for WM patients in a population-based setting as late as 2008. Data on 111 patients treated with rituximab 0–3 months after diagnosis are available; 32 of these patients received rituximab monotherapy.

Table III lists the distribution of the most commonly used chemotherapies. When comparing OS and RS in patients treated with single rituximab, rituximab-containing chemotherapies and chemotherapies alone, patients treated with rituximab-containing therapies had the longest survival ($P < 0·001$) (Fig 5).

Table I. Patient characteristics in all WM patients (n = 981), WM patients with first line treatment 0–3 months after diagnosis (n = 297) and "watch and wait" WM patients (n = 684), diagnosed in Sweden 2000–2014.

	All patients with diagnosis of WM (n = 981)	WM patients with first line treatment 0–3 months after diagnosis (n = 297)	WM patients with no treatment within 3 months of diagnosis, "watch and wait" (n = 684)
Median age, years	73 (range 29–94)	73 (range 40–94)	73 (range 29–92)
Age >65 years	721 (73·5%)	210 (71·0%)	510 (74·6%)
Gender			
Male	596 (60·8%)	186 (62·6%)	410 (59·9%)
Female	385 (39·2%)	111 (37·4%)	274 (40·1%)
WHO PS (n = 948)			
0	620 (64·0%)	149 (50·7%)	471 (69·8%)
1–4	349 (36·0%)	145 (49·3%)	204 (30·2%)
WHO PS 1–4 ≤ 65 years	51 (19·8%)	25 (29·4%)	26 (15·1%)
WHO PS 1–4 66–75 years	101 (32·6%)	41 (31·5%)	60 (27·8%)
WHO PS 1–4 ≥76 years	197 (40·0%)	79 (68·7%)	118 (41·1%)
LDH – elevated (n = 863)	118 (13·7%)	59 (21·5%)	59 (10·0%)
B-symptoms – yes (n = 914)	143 (15·6%)	83 (30·1%)	60 (9·4%)
Haemoglobin ≤115 g/l (n = 815)	393 (48·2%)	172 (76·1%)	221 (37·5%)
Platelet count ≤100 × 10^9/l (n = 643)	50 (7·8%)	31 (18·1%)	19 (4·0%)
Lymphocytosis ≥5 × 10^9/l (n = 614)	40 (6·5%)	14 (8·5%)	26 (5·8%)
Albumin level, median (n = 777)	35	33	36
Albumin ≤35 g/l (n = 793)	405 (51·1%)	144 (65·2%)	261 (45·6%)
β2M >3 mg/l (n = 200)	71 (35·5%)	30 (62·5%)	41 (27·0%)
Median IgM MI (n = 936)	19 (range 1–127)	25 (range 2–127)	17 (range 1–118)
IgM MI >70 g/l	33 (3·5%)	20 (6·7%)	13 (1·9%)
Light chain (n = 794)			
kappa	642 (80·9%)	185 (78·7%)	457 (81·8%)
Subnormal IgG (n = 754)	324 (43·0%)	100 (48·3%)	224 (41·0%)
Subnormal IgA (n = 741)	411 (55·5%)	125 (61·0%)	286 (53·4%)
Subnormal IgG and IgA (n = 733)	264 (36·0%)	81 (39·7%)	283 (34·6%)
Subnormal IgG or IgA (n = 733)	453 (61·9%)	141 (69·1%)	312 (59·1%)
Biclonal MI	26 (2·8%)		
IgG MI	23		
IgA MI	3		
Medium follow-up time (months)	79·9	93·3	78·0
Dead at the end of observation period	449 (45·8%)	153 (51·5%)	295 (43·3%)

β2M, β2-microglobulin; LDH, lactate dehydrogenase; MI, monoclonal immunoglobulin; WHO PS, Word Health Organization performance status; WM, Waldenström macroglobulinaemia.

Both the univariate (HR 4·268, 95% CI 2·521–7·667, $P < 0·001$) and multivariable analysis showed that patients treated with rituximab-containing therapies had significant improved OS compared to patients treated with chemotherapy alone. When adjusting for age, WHO PS, sex, haemoglobin ≤115 g/l and LDH, the HR was 0·405 (95% CI 0·223–0·738, $P = 0·003$) for rituximab-containing therapies compared with chemotherapies alone.

Gender and choice of systemic therapies. The choice of treatment with different chemotherapies tended to differ between males and females, but the treatment groups were generally too small for significance testing. However, females were more often treated with chlorambucil than males (60% vs. 30%, $P < 0·001$). In general, patients treated with chlorambucil were older and had more adverse prognostic factors, but there was no age difference between males and females (Table III). The overall use of rituximab ($P = 0·259$) did not differ between the genders, nor did the prognostic factors, such as age, LDH and haemoglobin ≤115 g/l, except that females had WHO PS 1–4 more often than males (62% vs. 41%).

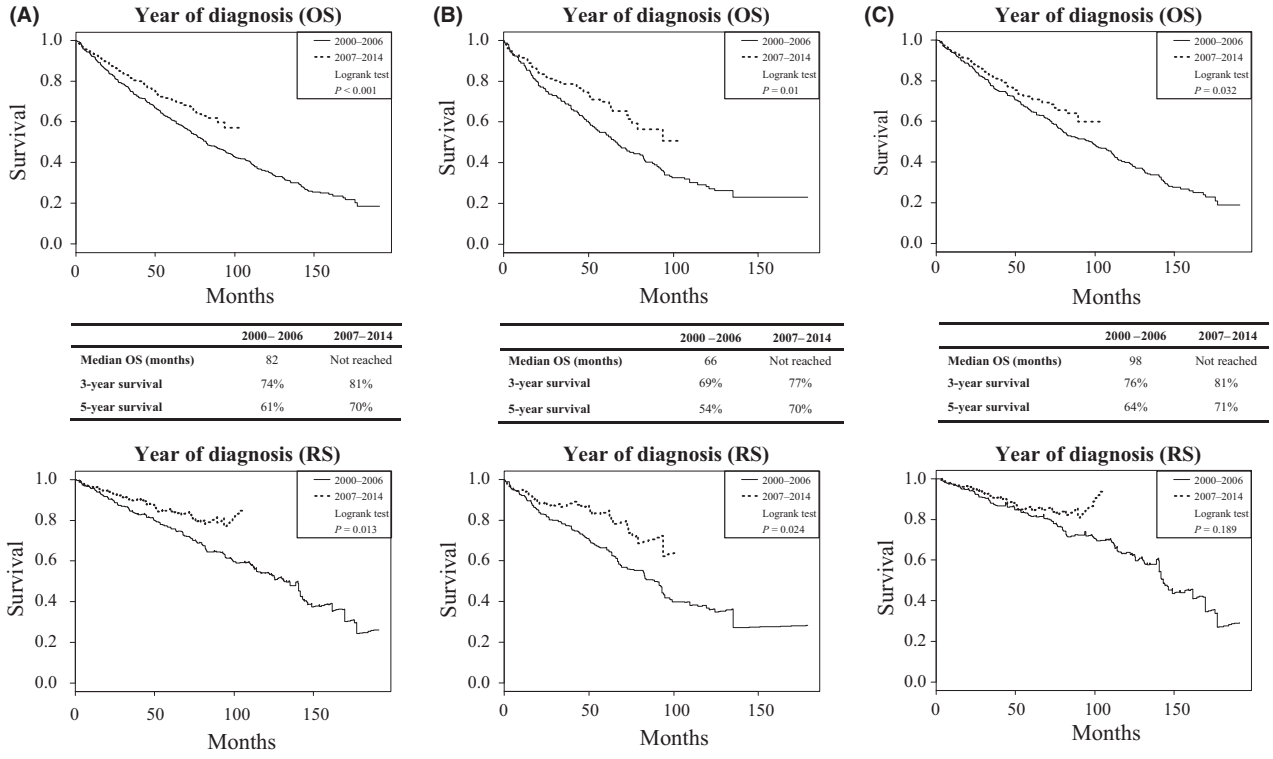
Discussion

Waldenström macroglobulinaemia is a rare disease with a worldwide incidence of 3–4 million persons per year and this rate varies between geographical areas: US = 3·8

Table II. Cox analysis (univariate and multivariable) of prognostic factors in WM patients for the years 2000–2014 in all patients (n = 981), patients with first line treatment 0–3 months after diagnosis (n = 297) and "watch and wait" patients.

	Univariate			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
All patients						
Time period 2000–2006	1·445	1·171–1·783	<0·001	1·412	1·061–1·879	0·018
Age (per year)	1·086	1·074–1·098	<0·001	1·079	1·062–1·097	<0·001
Age >65 years	4·146	3·104–5·538	<0·001			
Gender – male	1·140	0·941–1·380	0·180	1·431	1·084–1·888	0·011
WHO PS 1–4	2·678	2·215–3·238	<0·001	1·403	1·057–1·863	0·015
LDH elevated	1·658	1·272–2·162	<0·001	1·527	1·063–2·193	0·022
B-symptoms	1·553	1·210–1·994	<0·001	1·186	0·841–1·673	0·331
Albumin ≤35 g/l	1·751	1·403–2·187	<0·001	1·206	0·906–1·604	0·199
Haemoglobin ≤115 g/l	2·106	1·694–2·616	<0·001	1·696	1·260–2·282	<0·001
Platelet count ≤100 × 10^9/l	2·942	1·993–4·344	<0·001			
Lymphocytes ≥5 × 10^9/l	2·470	1·627–3·747	<0·001			
β2M >3 mg/l	2·669	1·693–4·205	<0·001			
IgM MI >70 g/l	0·835	0·470–1·482	0·538			
IgM MI per g/l	1·002	0·997–1·007	0·389	1·002	0·995–1·009	0·636
IgM MI >30 g/l	1·020	0·825–1·261	0·856			
Early therapy						
Time period 2000–2006	1·594	1·116–2·275	0·01	1·525	0·936–2·485	0·091
Age (per year)	1·086	1·066–1·106	<0·001	1·089	1·054–1·124	<0·001
Age >65 years	4·309	2·699–6·880	<0·001			
Gender – male	0·866	0·627–1·195	0·381	1·297	0·773–2·177	0·324
WHO PS 1–4	2·787	1·994–3·897	<0·001	1·130	0·659–1·937	0·657
LDH elevated	1·638	1·129–2·377	0·009	2·017	1·114–3·651	0·020
B-symptoms	1·472	1·040–2·083	0·029	1·303	0·771–2·203	0·323
Albumin ≤35 g/l	1·450	0·954–2·204	0·082	1·039	0·608–1·774	0·889
Haemoglobin ≤115 g/l	1·820	1·105–3·000	0·019	1·874	1·002–3·504	0·049
Platelet count ≤100 × 10^9/l	3·169	1·878–5·346	<0·001			
Lymphocytes ≥5 × 10^9/l	2·674	1·318–6·551	0·006			
β2M >3 mg/l	2·677	1·094–6·551	0·031			
IgM MI >70 g/l	0·858	0·437–1·685	0·657			
IgM MI per g/l	1·997	0·990–1·004	0·380	1·003	0·992–1·014	0·647
IgM MI >30 g/l	0·829	0·594–1·156	0·268			
Watch and wait						
Time period 2000–2006	1·332	1·024–1·733	0·032	1·405	0·979–2·017	0·065
Age (per year)	1·088	1·073–1·104	<0·001	1·076	1·055–1·096	<0·001
Age >65 years	4·164	2·878–6·027	<0·001			
Gender – male	1·282	1·010–1·627	0·041	1·499	1·072–2·095	0·018
WHO PS 1–4	2·527	1·994–3·202	<0·001	1·586	1·123–2·233	0·009
LDH elevated	1·503	1·013–2·230	0·043	1·164	0·705–1·922	0·554
B-symptoms	1·460	0·980–2·176	0·063	1·020	0·610–1·703	0·941
Albumin ≤35 g/l	1·831	1·405–2·386	<0·001	1·235	0·878–1·738	0·226
Haemoglobin ≤115 g/l	2·264	1·750–2·928	<0·001	1·801	1·258–2·578	0·001
Platelet count ≤100 × 10^9/l	2·298	1·173–4·500	0·015			
Lymphocytes ≥5 × 10^9/l	2·311	1·376–3·880	0·002			
β2M >3 mg/l	2·429	1·393–4·237	0·002			
IgM MI >70 g/l	0·636	0·204–1·984	0·435			
IgM MI per g/l	1·005	0·998–1·012	0·168	1·005	0·996–1·015	0·296
IgM MI >30 g/l	1·078	0·812–1·433	0·603			

β2M, β2-microglobulin; CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; MI, monoclonal immunoglobulin; WHO PS, Word Health Organization performance status; WM, Waldenström macroglobulinaemia.



	2000–2006	2007–2014
Median OS (months)	82	Not reached
3-year survival	74%	81%
5-year survival	61%	70%

	2000–2006	2007–2014
Median OS (months)	66	Not reached
3-year survival	69%	77%
5-year survival	54%	70%

	2000–2006	2007–2014
Median OS (months)	98	Not reached
3-year survival	76%	81%
5-year survival	64%	71%

Fig 3. Kaplan–Meier overall survival (OS) and relative survival (RS) curves in Waldenström macroglobulinaemia patients for the years 2000–2006 and 2007–2014, respectively, for (A) all patients (n = 981), (B) patients receiving therapies 0–3 months after diagnosis (n = 297) and (C) "Watch and wait" patients (n = 684).

(Wang *et al*, 2012), South East England = 5·5 (Phekoo *et al*, 2008) and Japan = 0·43 (Iwanaga *et al*, 2014). We observed a three times higher incidence of WM in Sweden (11·5 per million persons per year) and an even higher incidence in northern Sweden (Brandefors *et al*, 2016). Contributing factors to this could be that Sweden has a mandatory cancer registry and a high proportion of WM patients with asymptomatic disease at diagnosis are followed with a "watch and wait" policy (73·4%), while the corresponding figure in the literature is approximately one-quarter of the patients (Pophali *et al*, 2018). Counties with a low incidence (≤0·7) had more symptomatic patients requiring therapy at diagnosis than counties with a high incidence (≥1·2), 31% and 15%, respectively, and inferior survival (P < 0·001). On the other hand, Norrbotten, the county with the highest incidence, had the same frequency of patients requiring therapy as counties with low incidence. Generally, Sweden follows the 2nd International Workshop recommendations for initiating therapy (Kyle *et al*, 2003). The differences in incidences between the counties in Sweden may partly reflect different organization of healthcare, availability to haematologists and haematopathologists, and local practices regarding the time at which to bone marrow biopsies are performed.

Another factor is different diagnostic criteria: one example is the Mayo Clinic criteria, which require an infiltration of >10% LPL cells in the bone marrow (Kapoor *et al*, 2017). Moreover, all of the above-mentioned incidence studies used different standard populations (2000 US standard population, European standard population and WHO standard population) when calculating the age-adjusted incidence. It is known that the WHO standard population has a comparable young population structure and thus will, in the case of a disease of elderly, yield lower incidence rates. In this article we therefore chose to use European 2013 standard population.

The incidence of WM has geographical, ethnic and gender differences and there are associations with immune conditions and family history of haematological malignancy for the development of WM (Ekström Smedby *et al*, 2008; Kristinsson *et al*, 2008, 2010). We have observed aggregations of families with WM and a co-occurrence with autoimmune diseases in the northern Sweden (Brandefors *et al*, 2016), a region with a small but stable and, in some areas, isolated population. This suggests that both genetic and environmental factors can influence the incidence of disease. This part of Sweden also has low sun exposure, especially in the winter, and several studies indicate an increased risk of lymphoma with decreased sun exposure (Kricker *et al*, 2008). In addition, WM incidence is higher in males. Being male is a well-known risk factor for many subtypes of lymphomas and haematological malignancies, but the underlying causes of

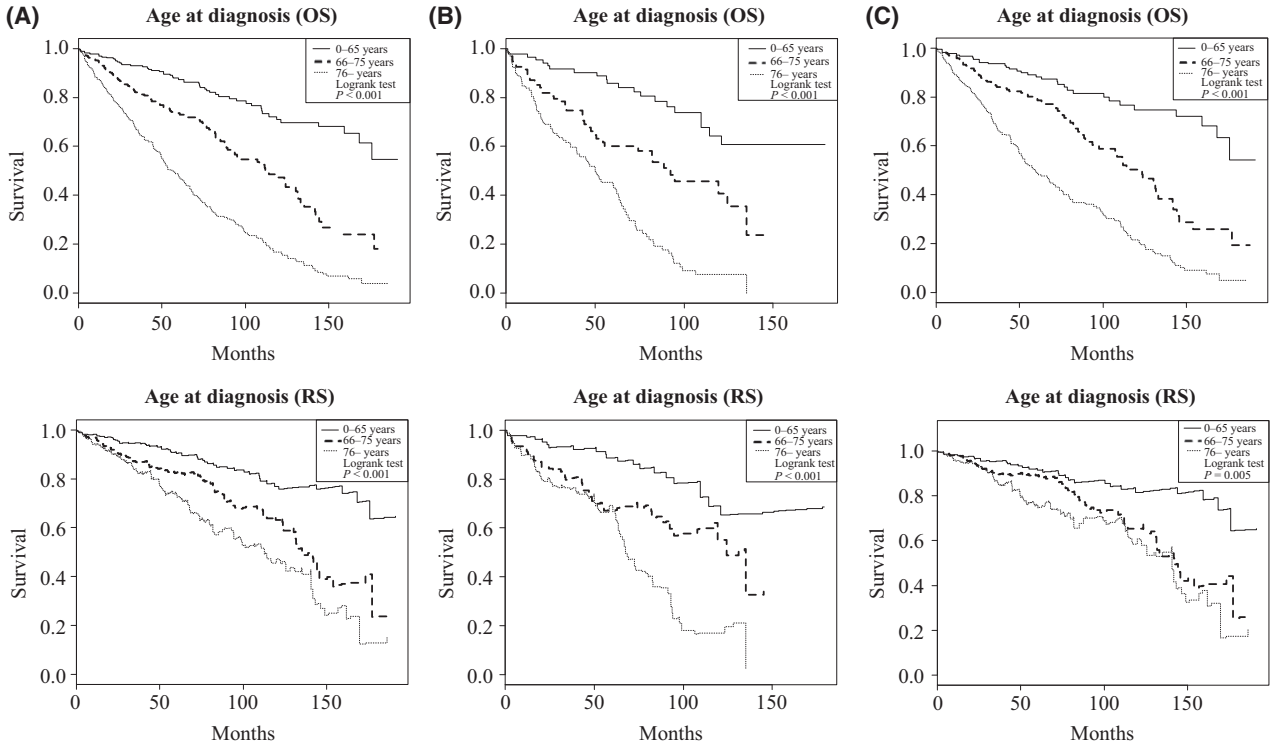


Fig 4. Kaplan–Meier overall survival (OS) and relative survival (RS) curves in Waldenström macroglobulinaemia patients in the age groups: ≤65, 66–75 and ≥76 years. (A) All patients. (B) patients receiving therapy 0–3 months after diagnosis. (C) "Watch and wait" patients.

these associations remain unknown (Abrahamsson *et al*, 2014; Ellin *et al*, 2014). Occupational and environmental exposure are potential risk factors, but there are no convincing data to confirm that relationship; only a few studies have been conducted, and these studies report mixed results (Linet *et al*, 1993; Royer *et al*, 2010; Vajdic *et al*, 2014).

The literature indicates that about 5% of the WM/LPL patients fulfil the diagnostic criteria for non-WM LPL (Swerdlow *et al*, 2008). In our study the proportion is higher. One explanation is that we have included patients with an IgM MI but without bone marrow involvement in the non-WM LPL group. Further, there are known diagnostic difficulties in the diagnosis of WM/LPL and a review of the diagnosis in patients not fulfilling the WM criteria (non-WM LPL) by a haematopathologist is ongoing.

We confirmed that most of the established prognostic factors used at time of first therapy were also relevant at diagnosis in univariate and multivariable analysis. However, the level of the IgM MI was of no prognostic value neither in the whole cohort nor in the patients receiving first-line therapies at diagnosis. The IgM MI level as a prognostic factor is controversial as some studies indicate a correlation between the level of the IgM and survival (Morel *et al*, 2000; Garcia-Sanz *et al*, 2001; Dhodapkar *et al*, 2009) One explanation could be that IgM levels correlate more to the differentiation of plasma cells than to the overall tumour burden in the bone marrow (Treon, 2015).

We included all patients (patients with treatment at diagnosis and "watch and wait" patients) in the analysis because the need for a prognostic index for all patients at the time of diagnosis is important. Other prognostic indexes for indolent lymphomas (such as the Follicular Lymphoma International Prognostic Index for follicular lymphomas and Rai-Binet for chronic lymphocytic leukaemia) are used for all patients at diagnosis. The most established prognostic index for WM (i.e., the IPSSWM) is only validated at the time for the first line treatment, while a large proportion of WM patients are asymptomatic ("wait and watch" patients) at diagnosis. In addition, we also analysed prognostic factors for patients receiving first line therapy at diagnosis and "watch and wait" patients, separately. As in the data from the Greek Myeloma Study Group (Kastritis *et al*, 2010), elevated LDH emerged as a significant prognostic factor in the cohort receiving therapy 0–3 months after diagnosis, this was not seen in the "watch and wait" cohort. LDH is a prognostic factor in many other subtypes of lymphomas, but it is not included in the IPSSWM.

Waldenström macroglobulinaemia is a disease of the elderly with a median age of 73 years at diagnosis and age was one of the strongest prognostic factors in the present study. Unrelated WM mortality is significant in this mostly elderly cohort and should be considered when choosing treatment and estimating survival (Castillo *et al*, 2015; Kastritis *et al*, 2015). RS better reflects the disease-specific

Table III. Chemotherapy regimens for 203 patients with WM and first line treatment 0–3 month after diagnosis.

	Chlorambucil	Cyclophosphamide containing *	Fludarabine containing	Bendamustine	CHOP-like	Rituximab – monotherapy	Other	Total
Patients	68 (34%)	34 (17%)	42 (21%)	11 (5%)	10 (5%)	32 (16%)	6 (3%)	203
Rituximab – yes	10 (15%)	31 (91%)	15 (36%)	11 (100%)	10 (100%)	32	2 (33%)	111
Median age, years	78·5	67	69·5	65	74	67·5		73
Gender								
Male	34 (30%)	26 (23%)	32 (28%)	9 (8%)	7 (6%)	18 (14%)	6 (5%)	132
Female	34 (60%)	8 (14%)	10 (18%)	2 (4%)	3 (5%)	14 (20%)	0	71
Year of diagnosis								
2000–2006	27 (54%)	1 (2%)	17 (34%)	0	0	3 (6%)	2 (33%)	50
2007–2014	41 (27%)	33 (22%)	25 (16%)	11 (7%)	10 (6%)	29 (19%)	4 (66%)	153
WHO PS 1–4	46 (68%)	10 (29%)	16 (38%)	6 (54%)	6 (60%)	14 (44%)	4 (60%)	102 (8 missing)
LDH – elevated	16 (24%)	7 (21%)	6 (14%)	3 (27%)	0 (0%)	4 (12%)	0	36 (15 missing)
Haemoglobin ≤ 115 g/l	44 (65%)	29 (85%)	29 (69%)	10 (91%)	6 (60%)	17 (53%)	4 (80%)	139 (28 missing)

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; LDH, lactate dehydrogenase; WHO PS, Word Health Organization performance status; WM, Waldenström macroglobulinaemia.
*CVP (cyclophosphamide, vincristine, prednisone) = 10 patients, DRC (dexamethasone, rituximab, cyclophosphamide) = 24 patients.

mortality and the differences between the older and younger cohorts have decreased during the last several years. Competing risk survival analysis is another useful tool for evaluating long-term outcome of WM; however, this approach was unavailable to us because we did not have access to data on competing causes of death.

Both the OS and the RS improved between the two periods (2000–2006 and 2007–2014), a finding that agrees with other recent studies. Most of the earlier registry studies included LPL/WM; however, our study included only WM (Kristinsson *et al*, 2013; Castillo *et al*, 2014). Data from previous studies (Kristinsson *et al*, 2013) as well as preliminary data from the SLR (unpublished observations) suggest that WM has better survival than LPL.

One possible reason for the improved survival is the introduction of better chemo- and immunotherapies, such as rituximab-containing therapies. In Sweden, different chemotherapy regimens have been used at different time periods. For example, fludarabine was used in younger patients until 2010, when fludarabine was mostly replaced by bendamustine. Recently, the use of dexamethasone, rituximab and cyclophosphamide (DRC) has increased as first-line therapy, especially after 2013 when the national guidelines recommended this combination. Chlorambucil was used during the entire study period, often as treatment in older patients with comorbidity.

Rituximab has improved the survival for WM patients (Fig 5; Table II). When rituximab is used in combination with chemotherapy, the overall response rate (ORR) is between 80% and 95% (Buske *et al*, 2009; Leblond *et al*, 2016). Rituximab used without chemotherapy has a lower ORR, between 30% and 50% (Dimopoulos *et al*, 2002; Gertz *et al*, 2004; Treon *et al*, 2005), and is mostly used in patients with low tumour burden and in some fragile patients. Improvements in supportive care, for example, prophylactic treatment of infections, may also partly explain the improved OS in recent years.

Treatment choice for males and females tended to differ. Females more often received chlorambucil, which is an older and relatively inexpensive therapy, and single rituximab, which is considered a milder treatment. Males, on the other hand, received more intensive therapies, such as fludarabine and bendamustine, which are considered more modern therapies but with more side-effects. That is, males more often than females received more intensive treatments (fludarabine, bendamustine and CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone]) ($P = 0{\cdot}014$). These results must be interpreted with caution as the sample size is small. Little is known about gender difference in the treatment of haematological malignancies, especially lymphomas; as a result, more research is needed to investigate how gender influences choice of therapy. Gender imbalances with respect to medical treatment in general is well known and have been discussed, as equal care is a goal in health care (Hamberg *et al*, 2002; Borkhoff *et al*, 2009; Sharma *et al*, 2015). Gender and socioeconomic imbalances could be improved by developing and

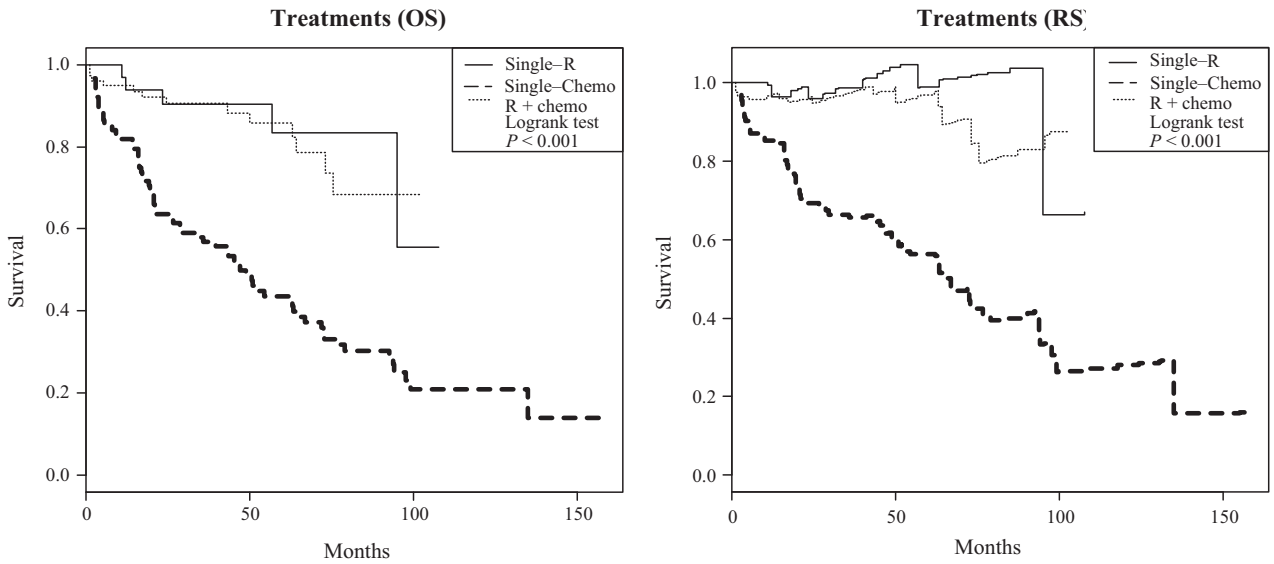


Fig 5. Kaplan–Meier overall survival (OS) and relative survival (RS) curves for patients treated with rituximab (R) monotherapy, rituximab-chemotherapy and chemotherapy alone (n = 203).

implementing national guidelines for both diagnostic criteria and treatment.

Our study has several strengths. Sweden has a long tradition of high quality population-based registries. The SLR covers approximately 95% of the population, which is high compared to other studies without the possibility to linkage through registries.

This study is a large population-based study of a rare disease, based on the entire Swedish population diagnosed over 15 years, with access to clinical data, such as exact lymphoma subtype, prognostic factors and detailed treatment, so selection bias is minimized. These data provide important information about outcome, prognostic factors and treatments in this unselected cohort. Prognostic factors were only available at diagnoses and calculations on prognostic factors in relation to OS were made for all patients and for the cohort that needed treatment 0–3 month after diagnosis, thus lead-time bias was avoided.

The study also has some limitations. The following data were not available or were incomplete: type of treatment before 2007 and important prognostic factors for calculating the IPSSWM, such as platelet count and β2M, treatment outcome, number of relapses, second-line treatments, comorbidity and cause of death. The diagnosis of WM according to the 2008 WHO classification includes infiltration of LPL in the bone marrow and a MI of IgM type of any size (Swerdlow *et al*, 2008). In the 2016 revision of the WHO classifications, the disease-defining mutation *MYD88* L265P was added as this mutation is found in about 90% of WM and in a significant proportion of IgM MGUS patients (Swerdlow *et al*, 2016). A limitation in our study is the lack of pathology review and lack of data regarding the *MYD88* L265P mutation, which had not been performed in most cases.

In summary, our population-based study compared survival in a large unselected cohort of patients with WM in relation to clinical prognostic factors and therapies. Survival increased over time and established prognostic factors available at the time of diagnosis significantly influenced survival, except the IgM MI level. In addition, we provide support that rituximab is essential in the treatment of WM and is associated with improved survival.

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Authorship contributions

Contribution: L.B., E.K., K.L, B.M., and J.L. designed the research, analysed data and wrote the paper; L.B. collected data.

Conflict-of-interest disclosure

The authors declare no competing 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 for OS and RS curves in WM patients for the years 2000–2014.

Table SI. Patients incorrectly registered.

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