



Primary therapy and relative survival in patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia: a population-based study in the Netherlands, 1989–2018

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Introduction

Lymphoplasmacytic lymphoma (LPL) is a rare, indolent B-cell non-Hodgkin lymphoma that predominantly infiltrates the bone marrow.¹ In >95% of LPL, increased serum levels of monoclonal immunoglobulin M (IgM) are present and

Summary

It is unclear how treatment advances impacted the population-level survival of patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia (LPL/WM). Therefore, we assessed trends in first-line therapy and relative survival (RS) among patients with LPL/WM diagnosed in the Netherlands between 1989 and 2018 ($N = 6232$; median age, 70 years; 61% males) using data from the nationwide Netherlands Cancer Registry. Patients were grouped into three age groups (<65, 66–75 and >75 years) and four calendar periods. Overall, treatment with anti-neoplastic agents within 1 year post-diagnosis gradually decreased over time, following a broader application of an initial watch-and-wait approach. Approximately 40% of patients received anti-neoplastic therapy during 2011–2018. Furthermore, use of chemotherapy alone decreased over time, following an increased application of chemoimmunotherapy. Detailed data among 1596 patients diagnosed during 2014–2018 revealed that dexamethasone-rituximab-cyclophosphamide was the most frequently applied regimen; its use increased from 14% to 39% between 2014 and 2018. The 5-year RS increased significantly over time, particularly since the introduction of rituximab in the early–mid 2000s. The 5-year RS during 1989–1995 was 75%, 65%, and 46% across the age groups compared to 93%, 85%, and 79% during 2011–2018. However, the survival improvement was less pronounced after 2011. Collectively, the impressive survival improvement may be accounted for by broader application of rituximab-containing therapy. The lack of survival improvement in the post-rituximab era warrants studies across multiple lines of therapy to further improve survival in LPL/WM.

Keywords: Waldenström macroglobulinaemia, lymphoplasmacytic lymphoma, population-based study, relative survival.

this IgM-secreting LPL is called Waldenström macroglobulinaemia (WM).² Both entities are hereafter collectively referred to as LPL/WM, a disease primarily affecting individuals aged >60 years.³ The annual age-standardised incidence rate (ASR) of LPL/WM is approximately three per million person-years in Western countries.^{4–6} The natural history of

LPL/WM is heterogeneous, with many patients remaining asymptomatic for years without need for treatment, while others require treatment early.⁷ Notwithstanding, the majority of patients will eventually require treatment at some stage during the disease course.

Before the turn of the 21st century, LPL/WM management often consisted of single-agent therapy using mainly alkylating agents such as chlorambucil and cyclophosphamide.⁸ However, in the 1990s, nucleoside analogues were shown to be more effective than alkylating agents. Consequently, the preferred treatment shifted towards fludarabine-based regimens.⁹ However, use of fludarabine was subsequently discouraged as first-line treatment due to significant toxicity and a possible increased risk of secondary primary malignancies and transformation.^{7,10,11} The introduction of rituximab in the early–mid 2000s altered the treatment paradigm in LPL/WM because of its ability to induce a response with low toxicity as a single agent.¹² Thereafter, a variety of rituximab-based regimens and novel targeted agents [e.g. proteasome inhibitors and Bruton tyrosine kinase (BTK) inhibitors] were added to the therapeutic arsenal in both upfront and relapsed settings.^{13–17}

Most data on LPL/WM management comes from phase II clinical trials and retrospective studies.^{9,14–16} The paucity of prospective intervention studies in LPL/WM, especially phase III clinical trials, complicates evidence-based treatment recommendations. Available studies report median overall survival (OS) rates varying from 7 to 10 years after treatment initiation.^{16,18} However, survival data derived from such studies should be extrapolated with caution to patients with LPL/WM managed in routine clinical practice due to the highly selected nature of patients enrolled in clinical trials based on stringent trial eligibility criteria.

Population-based studies can lend support to determine how therapeutic advances have impacted the outcomes of patients with LPL/WM at the population level. At present, large, population-based studies that assess the outcomes of patients with LPL/WM are scarce. Furthermore, these studies are mostly outdated and usually lack comprehensive information on incidence, therapy and survival.^{3,19–24} Therefore, it is unclear how contemporary treatment advances in LPL/WM have impacted the population-level survival.

Therefore, we conducted a large, comprehensive, nationwide, population-based study in >6000 patients diagnosed with LPL/WM in the Netherlands between 1989 and 2018. We aimed to assess trends in incidence, primary therapy and relative survival (RS).

Methods

Registry and study population

The nationwide Netherlands Cancer Registry (NCR), which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL), covers >95% of all newly

diagnosed malignancies in the Netherlands since its establishment in 1989.²⁵ The NCR relies on comprehensive case notification through the Nationwide Histopathology and Cytopathology Data Network and the Nationwide Registry of Hospital Discharges (i.e. inpatient and outpatient discharges). Information on birth and diagnosis dates, sex, disease stage, topography, and morphology, and primary therapy is routinely recorded in the NCR by trained registrars of the NCR through retrospective medical records review. This basic information is relevant for cancer surveillance activities. Additional, more detailed, information on clinical (e.g. performance score), disease [e.g. International Prognostic Scoring System (IPSS)], and treatment characteristics (e.g. exact therapeutic regimen) is routinely ascertained in the NCR for all haematological malignancies diagnosed from 1 January 2014 onwards. Topography and morphology are coded in the NCR according to the International Classification of Diseases for Oncology (ICD-O). Information on the last known vital status for all patients (i.e. alive, death or emigration) is obtained through annual linkage with the Nationwide Population Registries Network that holds vital statistics on all residents in the Netherlands.

We selected all patients diagnosed with LPL/WM between 1 January 1989 and 31 December 2018, with follow-up for survival until 1 January 2020 from the NCR using ICD-O morphology codes 9671 and 9761. We only included LPL/WM cases diagnosed through bone marrow examination. IgM monoclonal gammopathy of undetermined significance (MGUS) is not ascertained in the NCR. A total of 28 patients diagnosed through autopsy were excluded from the survival analysis. However, these patients were included in analysing the overall and sex-specific ASRs. This analysis method conforms with international standards for calculating and comparing overall incidence rates.

According to the Central Committee on Research involving Human Subjects, this type of observational study does not require approval from an ethics committee in the Netherlands. The use of anonymous data for this study was approved by the Privacy Review Board of the NCR.

Primary therapy

The NCR records information on primary therapy initiated within 12 months post-diagnosis. Primary therapy was initially grouped into two broad categories, namely (i) no anti-neoplastic therapy and (ii) anti-neoplastic therapy and presented for three age groups at diagnosis (≤ 65 , 66–75 and >75 years), stratified by four calendar periods (i.e. 1989–1995, 1996–2002, 2003–2010 and 2011–2018). The first and last two calendar periods represent the pre- and post-rituximab era respectively. The NCR ascertains information on the use of rituximab, with or without chemotherapy, for patients diagnosed as of 1 January 2007. Trends in the application of rituximab, with or without chemotherapy, were presented from 2007 onward according to the three

abovementioned age groups, stratified by calendar year of diagnosis (i.e. from 2007 to 2018).

As noted earlier, information on the exact therapeutic regimen was registered in the NCR for patients diagnosed as of 1 January 2014. These regimens were defined as DRC (dex-amethasone, rituximab, and cyclophosphamide), R-CP (rituximab, cyclophosphamide, and prednisone), R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), R-Chl (rituximab and chlorambucil), rituximab monotherapy, rituximab in combination with other less commonly used agents, and other less frequently applied therapeutic approaches. The exact therapeutic regimens are presented separately for patients with asymptomatic and symptomatic disease. Symptomatic disease is indicated by the presence of disease-related symptoms such as anaemia (haemoglobin value of ≤ 100 g/l), a platelet count $< 100 \times 10^9/l$, lymphadenopathy, B-symptoms, lymphadenopathy, and/or hepatosplenomegaly.²⁶

Furthermore, this information is presented for patients with symptomatic disease, stratified by year of diagnosis and the three age groups. Finally, exact therapeutic regimens for patients with symptomatic disease are presented according to IPSS risk groups (i.e. low, intermediate, high, and unknown), stratified by the three age groups.²⁷ The revised IPSS could not be calculated because the NCR does not ascertain information on serum albumin and the absolute value of serum lactate dehydrogenase.²⁸

Statistical analysis

Descriptive statistics were used to present patient and treatment characteristics across the four calendar periods. The Pearson chi-square test was used to compare categorical covariates, and the Kruskal–Wallis test was used to compare nonnormally distributed continuous covariates. Trends in the application of primary therapy over the calendar periods were tested using non-parametric tests of trend across ordered groups.

Overall and sex-specific incidence rates were computed per 100 000 person-years using the annual mid-year population size obtained from Statistics Netherlands. These rates were age-standardised as per the European standard population. The use of ASR eliminates the effect of different age structures in a population when crude incidence rates for different time periods are compared. Furthermore, incidence rates were computed according to the calendar period of diagnosis, stratified by age (i.e. 0–59, 60–69 and ≥ 70 years). The present age categories somewhat differ from the age categories defined earlier, as incidence rates are commonly calculated per quinquennial years of age. This manner of categorisation allows an international comparison of incident rates. Lastly, age-specific incidence rates were calculated per 5-year age groupings of 0–4 years to ≥ 85 years.

We calculated RS to estimate the disease-specific survival in the absence of information on the cause of death.²⁹ RS is

defined as the ratio of the OS of the patient cohort to the expected OS of an equivalent group from the general population, matched to the patients by age, sex and calendar year. As such, RS portrays the overall excess mortality associated with an LPL/WM diagnosis. The expected OS was estimated as per the Ederer II methodology using Dutch population life tables, stratified by age, sex and calendar year. RS was calculated up to 15 years post-diagnosis for three age groups at diagnosis (i.e. ≤ 65 , 66–75 and > 75 years), stratified by four calendar periods (i.e. 1989–1995, 1996–2002, 2003–2010 and 2011–2018), and measured from the time of diagnosis until death, emigration or end of follow-up (1 January 2020), whichever came first. RS was also calculated according to IPSS risk groups for patients diagnosed during 2014–2018.

Using a generalised linear model (GLM) that assumes a Poisson distribution for the observed number of deaths, we modelled the excess mortality over the calendar periods studied during the first 10 years after LPL/WM diagnosis, stratified by age at diagnosis (i.e. ≤ 65 , 66–75 and > 75 years). The GLMs produce excess mortality rate ratios (EMRRs), with associated 95% confidence intervals (CIs), and were simultaneously adjusted for years of follow-up, sex, calendar period of diagnosis and a prior malignancy before LPL/WM diagnosis.³⁰ The follow-up years were split into 1-year time bands for the initial 2 years of follow-up. The remaining 8 years of follow-up were split into 2-year time bands. The calendar period 2003–2010 was selected as the reference, as it was clinically relevant to assess the EMRR in the most recent calendar period (2011–2018); that is, in an era where rituximab-containing therapy was regarded as the standard first-line treatment for patients with LPL/WM.

A $P < 0.05$ was considered statistically significant. All analyses were performed using STATA/SE 16-1 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

A total of 6232 patients with LPL/WM were diagnosed in the Netherlands between 1989 and 2018, and included in the study. Baseline characteristics, according to the calendar period of diagnosis, are presented in Table I. The majority of the patients were male (61%). The male predominance persisted throughout the calendar periods studied and increased over the calendar periods studied ($P < 0.0001$). The median (range) age at diagnosis was 70 (19–96) years, with no significant differences over the calendar periods ($P = 0.213$). The proportion of patients with a prior malignancy increased over time from 6% to 15% between 1989 and 1995 and 2011–2018 ($P < 0.0001$).

For 1596 patients diagnosed during 2014–2018, data on IPSS risk group and performance score are summarised in Table II. In this population, symptomatic disease at diagnosis was established in 60% of patients, and 19%, 17%, and 15%

Table I. Patient characteristics, 1989–2018.

Characteristics	Calendar period of diagnosis										P
	1989–1995		1996–2002		2003–2010		2011–2018		Total		
	N (%)	IR	N (%)	IR	N (%)	IR	N (%)	IR	N (%)	IR	
Total number of patients	1153	1.11	1123	0.98	1605	1.05	2351	1.27	6232	1.11	
Sex											<0.0001
Male	653 (57)	1.45	637 (57)	1.24	985 (61)	1.38	1506 (64)	1.68	3781 (61)	1.44	
Female	500 (43)	0.78	486 (43)	0.72	620 (39)	0.72	845 (36)	0.85	2451 (39)	0.77	
Age, years											0.213
Median (IQR)	71 (62–78)		70 (62–77)		70 (61–78)		70 (62–77)		70 (62–77)		
≤65	383 (33)	0.39	404 (36)	0.39	607 (38)	0.51	807 (34)	0.67	2201 (35)	0.49	
66–75	384 (33)	5.24	371 (33)	4.70	467 (29)	4.55	859 (37)	6.37	2081 (33)	5.23	
>75	386 (33)	9.04	348 (31)	7.43	531 (33)	8.23	685 (29)	8.61	1950 (31)	8.33	
Prior malignancy											<0.0001
No	1085 (94)	–	1006 (90)	–	1419 (88)	–	1999 (85)	–	5509 (88)	–	
Yes	68 (6)	–	117 (10)	–	186 (12)	–	352 (15)	–	723 (12)	–	
Vital status											<0.0001
Alive	46 (4)	–	152 (14)	–	622 (39)	–	1767 (75)	–	2587 (42)	–	
Death	1107 (96)	–	971 (86)	–	983 (61)	–	584 (25)	–	3645 (58)	–	

IQR, interquartile range; IR, incidence rate.

All overall and sex-specific IRs are adjusted for age structure as per the European standard population.

IRs are presented per 100 000 person-years.

of patients were categorised as low-, intermediate-, and high-risk as per the IPSS. In 49% of patients, the IPSS could not be determined due to the absence of β_2 -microglobulin levels.

Incidence

The overall ASR of LPL/WM remained relatively stable throughout the entire study period (1.11 per 100 000 person-years during 1989–2018; Table I). The overall ASR was consistently higher among males than females (1.44 vs. 0.77 per 100 000 person-years during 1989–2018; Table I). Interestingly, before the age of 50 years, no difference in sex-specific incidence rate was found (Figure S1). The age-specific incidence in males and females was the highest in the age group 80–84 years (13.25 per 100 000 person-years during 2011–2018) and 75–79 years (6.67 per 100 000 person-years during 2011–2018) respectively (Figure S1).

Primary therapy

Information on primary treatment according to age at diagnosis and calendar period of diagnosis is presented in Fig 1A. The up-front application of anti-neoplastic therapy decreased gradually over time across all age groups, following a broader application of an initial watch-and-wait approach. However, this trend was not statistically significant for patients aged >75 years ($P = 0.062$). The proportion of patients receiving anti-neoplastic therapy within 1 year post-diagnosis was 42%, 38%, and 41% across the three age groups during 2011–2018.

Figure 1B shows trends in first-line immunotherapy, with or without chemotherapy, for patients diagnosed from 2007 onwards. The application of chemoimmunotherapy increased over time, following a decreased application of chemotherapy only. Application of chemoimmunotherapy increased from 18% to 33%, 8% to 32%, and 11% to 33% across three age groups between 2007 and 2018.

Detailed data on primary therapy among the 1596 patients diagnosed during 2014–2018 are presented for patients with asymptomatic and symptomatic disease in Fig 1C. As expected, asymptomatic patients were less likely to receive treatment than patients with symptomatic disease (6% vs. 64%). For patients with symptomatic disease, treatments are stratified by age at diagnosis, year of diagnosis and IPSS risk groups in Fig 1D. DRC was the most frequently applied regimen across all age groups, of which its overall use increased from 14% to 39% between 2014 and 2018. Consequently, the use of R-C(V)P decreased from 12% to 2% between 2014 and 2018. For patients aged >75 years, R-Chl was the second most applied regimen after DRC in 15% of patients compared to 1.2% and 4.5% in patients aged ≤65 and 66–75 years respectively. The use of anti-neoplastic therapy increased with higher IPSS risk group (46%, 65%, and 80% in patients with low-, intermediate-, and high-risk IPSS). R-Chl was primarily applied in the high-risk IPSS group compared to the low- and intermediate-risk groups due to the increased portion of elderly patients in the high-risk IPSS group. The regimens in the 'other therapy' group ($n = 47$) were very heterogeneous and are presented in Table SI.

Table II. Patient characteristics, 2014–2018.

Characteristics	N (%)
Total number of patients	1596
Sex	
Male	1030 (65)
Female	566 (35)
Symptomatic disease	
No	536 (34)
Yes	960 (60)
Unknown	100 (6)
WHO Performance Status	
0	459 (29)
1	235 (15)
2	43 (3)
3	10 (0.6)
4	3 (0.2)
Unknown	843 (53)
IPSS	
Low	310 (19)
Intermediate	264 (17)
High	234 (15)
Unknown	788 (49)
Age, years	
Median (range)	70 (21–75)
≤65	537 (34)
66–75	595 (37)
>75	464 (29)
Prior malignancy	
No	1339 (84)
Yes	257 (16)
Vital status	
Alive	1310 (82)
Death	286 (18)

WHO, World Health Organisation; IPSS, International Prognostic Scoring System.

Relative survival

Figure 2A shows RS according to age at diagnosis and calendar period of diagnosis. The 5-year RS increased significantly over time across all age groups. More specifically, patients across the three age groups diagnosed during 2011–2018, as compared to those diagnosed during 1989–1995, had higher 5-year RS rates of 93% (95% CI 90–95%) *versus* 75% (95% CI 69–79%), 85% (95% CI 81–89%) *versus* 65% (95% CI 59–71%), and 79% (95% CI 73–86%) *versus* 46% (CI 39–53%). RS decreased with older age group across all calendar periods studied ($P < 0.05$ for all comparisons). Furthermore, 10- and 15-year RS rates also improved significantly between 1989 and 1995 and 2003–2010. The improvement in 5- and 10-year RS was most conspicuous for patients aged >75 years, whereas the improvement in 15-year RS was most notable among patients aged ≤65 years.

The age-stratified multivariable model of RS, which was adjusted for sex, a prior malignancy before LPL/WM diagnosis and years of follow-up, demonstrated that RS between

2003 and 2010 and 2011–2018 did not improve further. This model also demonstrates that male sex and a prior malignancy were independent predictors of poor prognosis (Table III).

Figure 3 shows RS according to the IPSS risk score. The 5-year RS was significantly higher among patients classified as low-risk compared to the high-risk group ($P < 0.05$).

Discussion

In the present large, nationwide, population-based study among patients diagnosed with LPL/WM during a 30-year period in the Netherlands, we demonstrated trends in applying different first-line therapies over time and improving RS among all age groups after the introduction of rituximab. The present study complements and extends on the limited epidemiological studies performed in LPL/WM.^{3,19,21–24,31} Moreover, the present study is, to the best of our knowledge, the only population-based study to date that includes pathology confirmation in LPL/WM that offers comprehensive information on incidence, primary therapy and RS from a historical and contemporary perspective. The second-largest population based-study in the USA lacked pathology confirmation and did not report on primary therapy.¹⁹

The 30-year incidence rate of LPL/WM in the Netherlands was slightly higher compared to that of previous population-based studies in LPL/WM.^{3,21,22} In two other population-based studies, the incidence initially increases until the late 1990s/early 2000s, after which it stabilised.^{6,23} Unlike these studies, an increase in incidence was not observed in our present study. This difference could be due to stable registration and diagnostic practices in the Netherlands. Of note, the absolute number of patients with LPL/WM increased substantially over time due to the ageing population. Using the ASR, this effect is eliminated, thereby demonstrating that the incidence remains stable over time.

As mentioned earlier, the use of nucleoside analogues (e.g. fludarabine) are currently discouraged as first-line treatment in clinical practice, although our present data could not objectify this. Whether nucleoside analogues were more frequently applied before 2014 remains unknown, as detailed therapy data before 2014 is lacking in the NCR. The introduction of rituximab in the early 2000s demonstrated responses as a single agent with a favourable toxicity profile.¹² We observed that the use of chemotherapy alone in LPL/WM is almost entirely abandoned in contemporary clinical practice in the Netherlands and was replaced by chemoimmunotherapy. This phenomenon was also reported in a population-based analysis in the USA during 1994–2011 evaluating changes in management in 2666 patients with WM.³² Detailed data of our present study for patients diagnosed from 2014 showed that DRC was the preferred first-line regimen, while the use of R-CVP declined. This trend coincided with the publication of the first Dutch guideline for diagnosis and management of LPL/WM in 2012 that

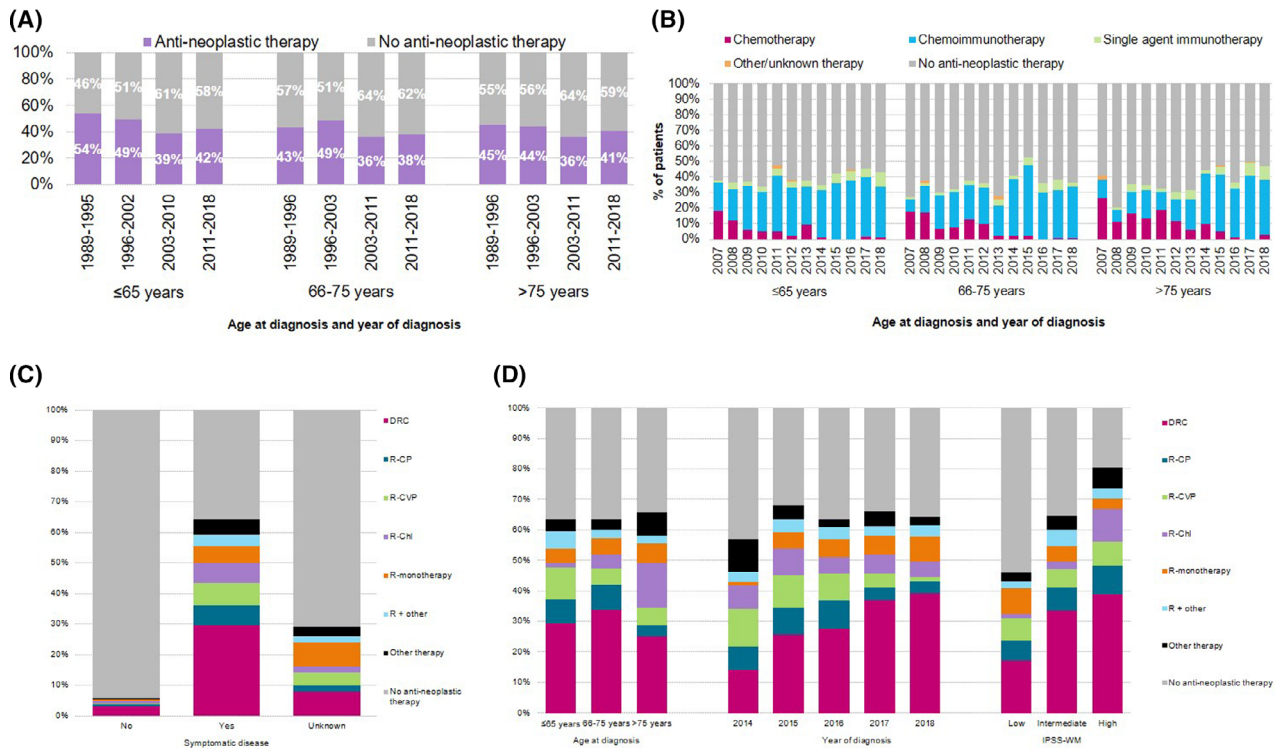


Fig 1. (A) Primary therapy of adult patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia (LPL/WM) in the Netherlands according to age at diagnosis and calendar period of diagnosis, 1989–2019. (B) Trends in applying first-line immunotherapy, with or without chemotherapy, for patients diagnosed from 2007 onwards. (C) Detailed data on primary therapy among 1596 patients diagnosed during 2014–2018 presented for patients with asymptomatic and symptomatic disease. (D) Detailed data on primary therapy stratified by age at diagnosis, year of diagnosis and International Prognostic Scoring System (IPSS) risk groups for symptomatic patients. [Colour figure can be viewed at wileyonlinelibrary.com]

suggested DRC or R-CP as a suitable first-line treatment and recommended omitting vincristine.² This guideline aligns with the consensus treatment recommendations from the 10th International Workshop for Waldenström Macroglobulinaemia. Nevertheless, some agents (e.g. carfilzomib and ofatumumab) are currently not implemented to treat LPL/WM in the Netherlands as they are not covered by health insurance.³³ Of note, ibrutinib was not routinely available in the Netherlands for the first-line treatment of LPL/WM during the study period.

We also report significant improvement in RS over time for all age groups. The 5-year RS in our present study followed similar patterns with comparable RS estimates in a Swedish study in 1555 patients with WM diagnosed between 1980 and 2005. Furthermore, the 10- and 15-year RS estimates from the same study were comparable to our present study and show that outcomes improve over time.³¹ This is also evident in the second-largest study in the USA with 6231 patients with WM diagnosed between 1980 and 2010 with comparable RS estimates.¹⁹ On the other hand, a Greek study with 345 patients with WM diagnosed over a 25-year period could not demonstrate overall or cause-specific survival improvement, possibly attributable to the smaller sample size. Several analyses have pointed out that novel agents

might have resulted in the survival improvement in LPL/WM.^{31,34} Collectively, our present study confirms that the addition of rituximab to the therapeutic arsenal of LPL/WM probably contributed to the survival improvement at the population level.

In our present study, excess mortality was most significant in patients aged >75 years. The prognostic effect of older age might be due to comorbid conditions being more abundantly present among elderly patients. Another explanation might be the lower application of chemoimmunotherapy in this age group due to concerns regarding therapy-related morbidity and mortality. Therefore, treatment strategies tailored to older patients are warranted. Excess mortality was also significantly increased in males and patients who had a prior malignancy in our present study. It is known that sex influences cancer mortality rates, as men are more likely to die from cancer, especially haematological malignancies, partly due to genetic or hormonal differences influencing response to chemotherapy.³⁵ Excess mortality in patients with a history of a prior malignancy is potentially attributed to the malignancy itself, the long-term carcinogenic effects of systemic therapy, a potential long-term immune dysfunction related to cancer treatment and genetic susceptibility to cancer.³⁶

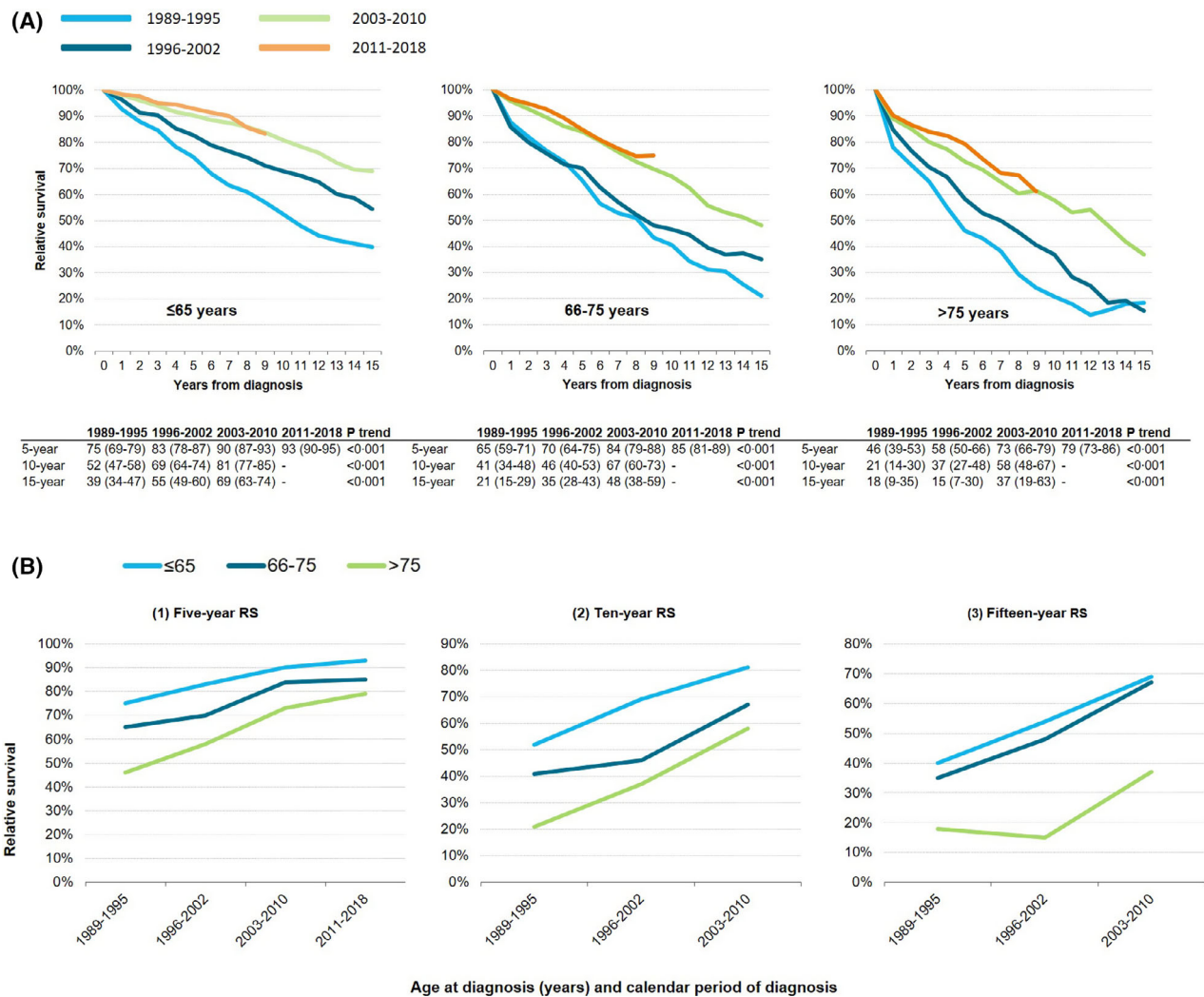


Fig 2. (A) Relative survival of patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia (LPL/WM) in the Netherlands according to age at diagnosis and calendar period of diagnosis, 1989–2018. (B) 5-year, 10-year and 15-year relative survival of patients with LPL/WM in the Netherlands according to age at diagnosis and calendar period of diagnosis, 1989–2018. [Colour figure can be viewed at wileyonlinelibrary.com]

Table III. Excess mortality ratio during the first 10 years after Waldenström macroglobulinaemia diagnosis according to age at diagnosis.

Covariate	≤65 years			66–75 years			>75 years		
	EMR*	95% CI	P	EMR*	95% CI	P	EMR*	95% CI	P
1989–1995	3.11	2.37–4.08	<0.001	2.36	1.79–3.12	<0.001	2.46	1.88–3.22	<0.001
1996–2002	1.76	1.31–2.37	<0.001	2.11	1.59–2.79	<0.001	1.65	1.22–2.22	0.001
2003–2010	1	(ref)		1	(ref)		1	(ref)	
2011–2018	0.74	0.51–1.09	0.126	0.78	0.56–1.10	0.154	0.81	0.58–1.12	0.203
Male	1	(ref)		1	(ref)		1	(ref)	
Female	0.73	0.59–0.90	0.004	0.80	0.66–0.98	0.029	0.77	0.63–0.94	0.011
No	1	(ref)		1	(ref)		1	(ref)	
Yes	1.90	1.33–2.71	<0.001	1.35	1.03–1.78	0.032	1.39	1.07–1.80	0.013

CI, confidence interval; EMR, excess mortality ratio.

*Each covariate is simultaneously adjusted for all other covariates in the table, along with 5 years of follow-up.

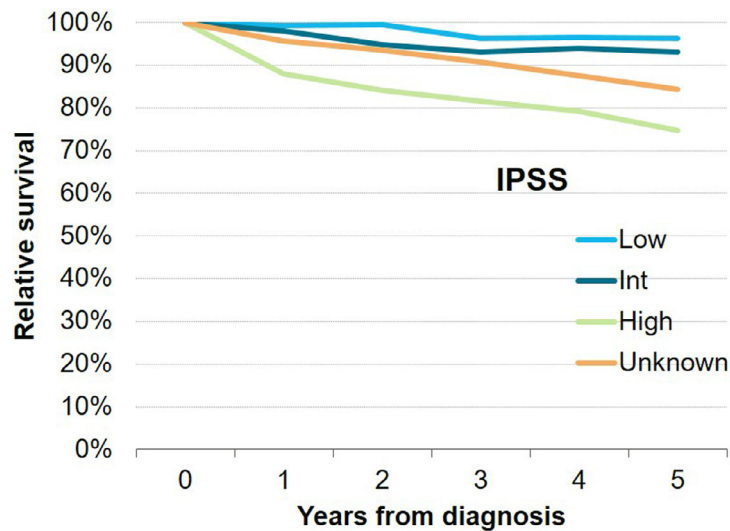


Fig 3. Relative survival of patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia (LPL/WM) in the Netherlands according to International Prognostic Scoring System (IPSS) risk groups. [Colour figure can be viewed at wileyonlinelibrary.com]

	Low	Intermediate	High	Unknown	P trend
1-year	99 (97-100)	98 (95-100)	88 (82-92)	96 (94-97)	<0.001
5-year	96 (92-99)	93 (84-100)	75 (64-84)	84 (79-89)	<0.001

Interestingly, a lack of survival improvement in the most recent calendar period (2011–2018) was seen. During this time, the LPL/WM therapeutic arsenal was further expanded with agents like the proteasome inhibitor bortezomib, bendamustine, and the BTK inhibitor ibrutinib. Although these agents likely contribute to improved survival, it is probably still too early to notice their effects at the population-level. Therefore, a longer follow-up of our present cohort is warranted.³⁷ Furthermore, randomised controlled trials in WM evaluating the efficacy of novel agents like acalabrutinib, zanubrutinib and venetoclax are being conducted. Population-based studies in the future can therefore be used to evaluate the effects of the introduction of these novel, often expensive regimens across various lines of therapy.^{16,38}

Our present study is also the first to present RS stratified for the IPSS risk groups. We demonstrate that patients within the low-risk group experience minimal excess mortality. Furthermore, a clear prognostic effect between the low- and intermediate-risk group could not be observed in the present study, which could be attributed to the decreased prognostic ability of the IPSS-WM in the rituximab era.

Limitations of the present population-based study are the lack of detailed data on the type of therapy before 2014 and data on the treatments that were given beyond 1 year post-diagnosis. As particular novel agents are only prescribed for patients with relapsed/refractory LPL/WM in the Netherlands, we could not determine how these agents affected the RS in recent years. Another limitation is the absence of data on the revised IPSS. These data could have been used to identify how subsets of patients benefit from the used

treatment options and evaluate its prognostic ability on a population-level.

A great strength of the present study is the use of a nationwide population-based cancer registry with high coverage of >95% of all cases in the Netherlands to represent the general population of LPL/WM and based on pathology results rather than diagnostic codes only. Availability of information on patient characteristics and primary therapy and adequate survival follow-up for all patients also contributed to this study's strength.

Conclusions

In the present nationwide, population-based study, the impressive survival improvement over time may be accounted for by the introduction and broader application of rituximab-containing therapy since its introduction in the early–mid 2000s. The lack of survival improvement in the post-rituximab era warrant longer follow-up of this cohort after introduction of novel therapies and should bolster clinical studies to improve survival in LPL/WM further.

Declarations

Ethics approval and consent to participate

According to the Central Committee on Research involving Human Subjects, this type of observational study does not require approval from an ethics committee in the Netherlands. The use of anonymous data for this study was approved by the Privacy Review Board of the NCR.

Consent for publication

All authors approved this manuscript and its submission to Journal of Haematology and Oncology.

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Author contributions

Avinash G. Dinmohamed, Karima Amaador, and Marie José Kersten designed the study; Karima Amaador analysed the data; Avinash G. Dinmohamed provided statistical support; Otto Visser was responsible for the collected data; Karima Amaador wrote the manuscript with contributions from all authors, who also interpreted the data, and read, commented on, and approved the final version of the manuscript.

Conflict of interest

There is no financial support for this work that could have influenced the outcomes described in the manuscript. However, particular authors report a potential conflict of interest, which is described below. All remaining authors have declared no competing financial interests.

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Data availability statement

Data that underlie the results reported in this study are available on request from the corresponding author Karima Amaador.

Supporting Information

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

Table SI. Age-specific incidence rates according to sex and calendar period of diagnosis.

Table SII. Overview of primary therapy included in the 'Other therapy' category of LPL/WM patients in the Netherlands.

Fig S1. Age-specific incidence rates of patients with Waldenström's Macroglobulinemia in the Netherlands according to sex. The age-specific incidence rates are presented per 100,000 person-years.

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