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Overall survival and competing risks of death in patients with Waldenström macroglobulinaemia: an analysis of the Surveillance, Epidemiology and End Results database

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Summary

Waldenström macroglobulinaemia (WM) is a rare and incurable lymphoma. Given that the survival of WM patients can be prolonged, our objective was to describe trends in overall survival (OS) and analyse competing risks of death in patients with WM. The analysis included 5784 patients diagnosed with WM between 1991 and 2010 from the Surveillance, Epidemiology and End Results (SEER) database. Multivariate hazard models for OS and cumulative incidence of death were fitted according to epoch of diagnosis (1991–2000 vs. 2001–10) while adjusting for age, sex, race, histology, site of involvement and registry. Median OS for the 1991–2000 and the 2001–10 cohorts was 6 and 8 years, respectively ($P < 0{\cdot}001$). In the multivariate analysis, better OS [hazard ratio (HR) 0·73, 95% confidence interval (CI) 0·67–0·79; $P < 0{\cdot}001$] was seen in the 2001–10 cohort. Survival benefits were identified, for the 2001–10 cohort, in almost every stratum analysed, with the exception of patients aged <50 years and blacks. In the multivariate competing-risk analysis, the 2001–10 cohort experienced lower rates of WM-related (HR 0·57, 95% CI 0·49–0·66; $P < 0{\cdot}001$) and non-WM-related deaths (HR 0·72, 95% CI 0·66–0·79; $P < 0{\cdot}001$). In conclusion, there have been significant improvements in OS, WM-related and non-WM-related mortality in patients with WM diagnosed in the last decade.

Keywords: Waldenström macroglobulinaemia, survival, competing risks, epidemiology, outcomes.

Waldenström Macroglobulinaemia (WM) is a rare indolent B-cell non-Hodgkin lymphoma (NHL) characterized by the accumulation of malignant lymphoplasmacytic and plasma cells in the bone marrow, lymph nodes, spleen and/or liver consistent with infiltration by a lymphoplasmacytic lymphoma (LPL) and the presence of an immunoglobulin M (IgM) monoclonal spike in the serum protein electrophoresis (Swerdlow *et al*, 2008). According to the Surveillance, Epidemiology and End Results (SEER) database, approximately 1000–1500 new cases of WM are diagnosed every year in the US (Sekhar *et al*, 2012). Some patients do not need treatment at diagnosis but most require systemic treatment at some time during the course of their disease. Although no clear standard of care for the therapy of WM has emerged, alkylating agents, nucleoside analogues, anti-CD20 monoclonal antibodies and proteasome inhibitors can be used with high response rates (Treon, 2009). WM, however, remains incurable.

Previous epidemiological studies suggested that survival of WM patients could be prolonged and sometimes measured in decades (Castillo *et al*, 2014). It is unclear, however, if survival of patients with WM has improved with the advent of novel therapies. Recent studies from Europe have shown mixed results (Kastritis *et al*, 2011; Kristinsson *et al*, 2013). As the majority of WM patients are diagnosed in the sixth decade of life and the disease-specific mortality is low, competing risks for mortality might bias any attempt to identify an overall survival (OS) benefit on these patients. We have previously showed improvements in relative survival (RS) in patients with WM within the last decade (Castillo *et al*, 2014); however, OS trends in the context of competing risks of death characteristic of older

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age groups have not been extensively evaluated in these patients.

Therefore, our objective was to perform a comprehensive population-based analysis to investigate trends in OS rates and competing risks for mortality in patients diagnosed with WM.

Methods

Data source and cohort selection

Our study was based on data from the SEER program database (http://www.seer.cancer.gov/seerstat/). SEER collects cancer incidence (with a mandated case ascertainment of 98%), characteristics, treatment and outcome information from 18 geographic areas in the United States, representing 28% of the population. We used direct case listings extracted by SEER*STAT software, version 8.0.2 (http://www.seer.cancer.gov/data/seerstat/nov2011/). Our query included all patients with a diagnosis of LPL or WM between 1 January 1980 and 31 December 2010, based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) histology codes 9671 (Lymphoplasmacytic lymphoma) and 9761 (Waldenström Macroglobulinaemia), recorded between 1980 and 2010 ($n = 7744$). We excluded patients diagnosed before 1991 ($n = 447$) to minimize classification bias. Patients younger than 20 years of age at diagnosis ($n = 9$), patients in whom WM was not the first malignancy ($n = 1422$) and patients diagnosed only by autopsy ($n = 82$) were also excluded.

Definition of variables

The database contained variables indicating age at diagnosis, year of diagnosis, sex, race, primary site of involvement, marital status, outcome, survival time and cause of death. Age was categorized into age groups of 20–49, 50–59, 60–69, 70–79 and ≥80 years. Race was categorized as white, black, other and unknown based on the SEER record. Primary anatomical sites were categorized as bone marrow, extramedullary and unrecorded sites according to the ICD-O-3 topography code. Lymph nodes and other organs were considered extramedullary disease. Lymphoma subtype was categorized as LPL and WM according to SEER ICD-O-3 coding. Geographical regions were designated as Northeast, West, South and Midwest according to the location of the SEER registry. The analytical cohort was divided in two cohorts according to the epoch of diagnosis, 1991–2000 and 2001–10, to indirectly reflect the adoption of novel therapies in the management of WM in the last decade. OS time was calculated between the date of diagnosis and the date of death, date last known to be alive, or date of the study cut-off (31 December 2010). For the competing-risk of death analysis, any death from leukaemia, lymphoma or myeloma was considered WM-related. All other causes of death were considered non-WM-related. This definition may overcome misattribution of causes on death certificates.

Statistical analysis

Descriptive statistics were used to report population characteristics. OS estimates were calculated using the Kaplan–Meier method (Kaplan & Meier, 1958), and curves were compared using the log rank method (Mantel, 1966). Multivariate Cox proportional-hazards regression models were also fitted to evaluate variables associated with OS (Cox, 1972). We did not find evidence of interactions between the predictor variables and therefore did not include any interaction terms in the models. The proportional-hazard assumption was assessed by studying interaction of all variables with time. For the competing risk analysis, cumulative incidence function (CIF) curves were plotted. Rates of WM-related and non-WM-related death were evaluated using Fine and Gray multivariate regression models (Fine & Gray, 1999). Outcomes are reported as percentages or hazard ratios (HR) with 95% confidence interval (CI). P-values < 0·05 were considered statistically significant. Calculations and graphs were obtained using STATA, version 13.1 (StataCorp LP, College Station, TX, USA).

Results

Our analytical cohort included 5784 patients with WM. The median age at diagnosis was 70 years (range: 20–98 years). There was a male predominance with a male-to-female ratio of 1·4. Eighty-one percent of patients were white. In 62% of patients, the primary site of involvement was the bone marrow. Based on year of diagnosis, 1877 patients (32·5%) were diagnosed between 1991 and 2000, and 3907 (67·5%) between 2001 and 2010. No major differences in the characteristics of patients between epochs were identified (Table I). Given the large sample size, statistical comparisons between epochs of diagnosis were not performed to avoid reporting statistically but not clinically relevant differences.

Overall survival

After a median follow-up time of 7 years, median OS for the entire cohort was 7 years, and the 5- and 10-year OS rates were 62% and 39%, respectively (Fig 1A). For the 1991–2000 cohort, the median follow-up time was 13 years, and the median OS was 6 years, and for the 2001–10 cohort, the median follow-up time was 5 years, and the median OS was estimated at 8·2 years (Fig 1B). This difference was statistically significant (log-rank $P < 0·001$). There were statistical differences in OS based on age. The median OS for patients aged 20–49, 50–59, 60–69, 70–79 and ≥80 years were not reached, 13, 10, 6 and 4 years, respectively (log-rank $P < 0·001$). For the 1991–2000 cohort, the median OS times were not reached, 12, 7, 5 and 3 years, respectively (log-rank

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Table I. Selected characteristics of patients with Waldenström macroglobulinaemia from the SEER database according to epoch of diagnosis, 1991–2010.

Characteristic	1991–2000 (%)	2001–10 (%)	Total (%)
Total	1877 (32·5)	3907 (67·5)	5784 (100)
Age, years			
Median (range)	70 (23–97)	71 (20–98)	70 (20–98)
20–49	185 (9·9)	259 (6·6)	444 (7·7)
50–59	270 (14·4)	640 (16·4)	910 (15·7)
60–69	447 (23·8)	962 (24·6)	1409 (24·4)
70–79	602 (32·1)	1164 (29·8)	1766 (30·5)
80+	373 (19·9)	882 (22·6)	1255 (21·7)
Sex			
Male	1110 (59·1)	2246 (57·5)	3356 (58·0)
Female	767 (40·9)	1661 (42·5)	2428 (42·0)
Race			
White	1540 (82·1)	3170 (81·1)	4710 (81·4)
Black	111 (5·9)	207 (5·3)	318 (5·5)
Other	101 (5·4)	228 (5·8)	329 (5·7)
Unknown	125 (6·7)	302 (7·7)	427 (7·4)
Subtype recode			
Lymphoplasmacytic lymphoma	761 (40·5)	1718 (44·0)	2479 (42·9)
Waldenström macroglobulinaemia	1116 (59·5)	2189 (56·0)	3305 (57·1)
Sites of involvement			
Bone marrow	1181 (62·9)	2419 (61·9)	3600 (62·2)
Extramedullary disease	695 (37·0)	1481 (37·9)	2176 (37·6)
Unknown	1 (0·05)	7 (0·18)	8 (0·14)
Region			
Northeast	226 (12·0)	725 (18·6)	951 (16·4)
West	1154 (61·5)	2305 (59·0)	3459 (59·8)
South	96 (5·1)	441 (11·3)	537 (9·3)
Midwest	401 (21·4)	436 (11·2)	837 (14·5)

$P < 0·001$; Fig 1C). For the 2001–10 cohort, the median OS times were not reached, not reached, not reached, 7 and 4 years, respectively (log-rank $P < 0·001$; Fig 1D). There were no significant differences in OS rates based on sex, race, site of involvement, histological subtype and region of registry.

In the multivariate analysis for OS (Table II), factors associated with a worse OS rate were older age, male sex and black race. Better outcomes were observed in patients in the 2001–10 cohort. In the stratified multivariate analysis (Table III), there was a significant improvement in OS in patients diagnosed in the 2001–10 epoch when compared with patients from the 1991 to 2000 epoch in almost every stratum except in patients aged 20–49 years, blacks and patients of other races, in whom confidence intervals were wide due to the small number of patients. However, when evaluating all non-whites (blacks, other races and unknown), there was better OS rate in the 2001–10 cohort when compared with the 1991–2000 cohort (HR 0·71, 95% CI 0·58–0·88, $P = 0·001$).

Causes of death and competing risk analysis

There were 2786 deaths in the entire cohort (48% of patients), including 1436 deaths (77% of patients) in the 1991–2000 cohort and 1350 deaths (35% of patients) in the 2001–10 cohort. The most common causes of death were undefined (29%), lymphoma (23%), solid tumours (20%) and cardiac causes (15%) (Table IV). In the 1991–2000 cohort, 403 (28%) and 1033 deaths (72%) were considered WM-related and non-WM-related deaths respectively, while in the 2001–10 cohort, 369 (27%) and 981 (73%) events were considered WM-related and non-WM-related.

The 5-year cumulative incidence rates of WM-related death were 13% in the 1991–2000 cohort and 10% in the 2001–10 cohort (Fig 2A). The 5-year cumulative incidence rates on non-WM-related death were 30% and 25%, respectively (Fig 2B). Our multivariate competing-risk analysis showed that the 2001–10 cohort had lower WM-related (HR 0·57, 95% CI 0·49–0·66; $P < 0·001$) as well as non-WM-related mortality (HR 0·72, 95% CI 0·66–0·79; $P < 0·001$) than the 1991–2000 cohort. Our analysis showed that age influenced WM-related and non-WM related mortality. The 5-year cumulative incidence rates of WM-related death in patients aged 20–49, 50–59, 60–69, 70–79 and 80+ years was 6%, 6%, 10%, 11% and 16%, respectively (Fig 2C), and the 5-year cumulative incidence rates of non-WM-related death was 11%, 13%, 17%, 33% and 48%, respectively (Fig 2D). In the multivariate analysis, the adjusted HR for WM-related death in patients aged 50–59, 60–69, 70–79 and 80+ years compared with patients 20–49 years was 1·44 (95% CI 0·99–2·10; $P = 0·06$), 2·23 (95% CI 1·57–3·15; $P < 0·001$), 2·17 (95% CI 1·54–3·06; $P < 0·001$) and 2·65 (95% CI 1·86–3·77; $P < 0·001$), respectively. The HR for non-WM-related death was 1·32 (95% CI 1·00–1·76; $P = 0·05$), 1·83 (95% CI 1·41–2·39; $P < 0·001$), 3·53 (95% CI 2·74–4·55; $P < 0·001$) and 6·17 (95% CI 4·76–7·99; $P < 0·001$), respectively.

Discussion

WM is a rare B-cell lymphoproliferative disorder. Despite its incurability, patients with WM can enjoy prolonged survival with excellent quality of life. Based on the results of this large population-based study, we were able to identify an improvement in the OS rates in patients with WM in the last decade, independent of other important clinical variables, such as age, sex, race and site of involvement. In the multivariate analysis, patients diagnosed between 2001 and 2010 had 27% lower risk of dying from all causes and 43% lower risk of dying from WM-related causes when compared with those diagnosed between 1991 and 2000. Worse outcomes were seen in older patients, men and blacks when compared with younger patients, women and whites, respectively.

Previous studies have evaluated outcomes in patients with WM, particularly in Europe, with mixed results. A Greek study including 345 patients with WM, of whom 130

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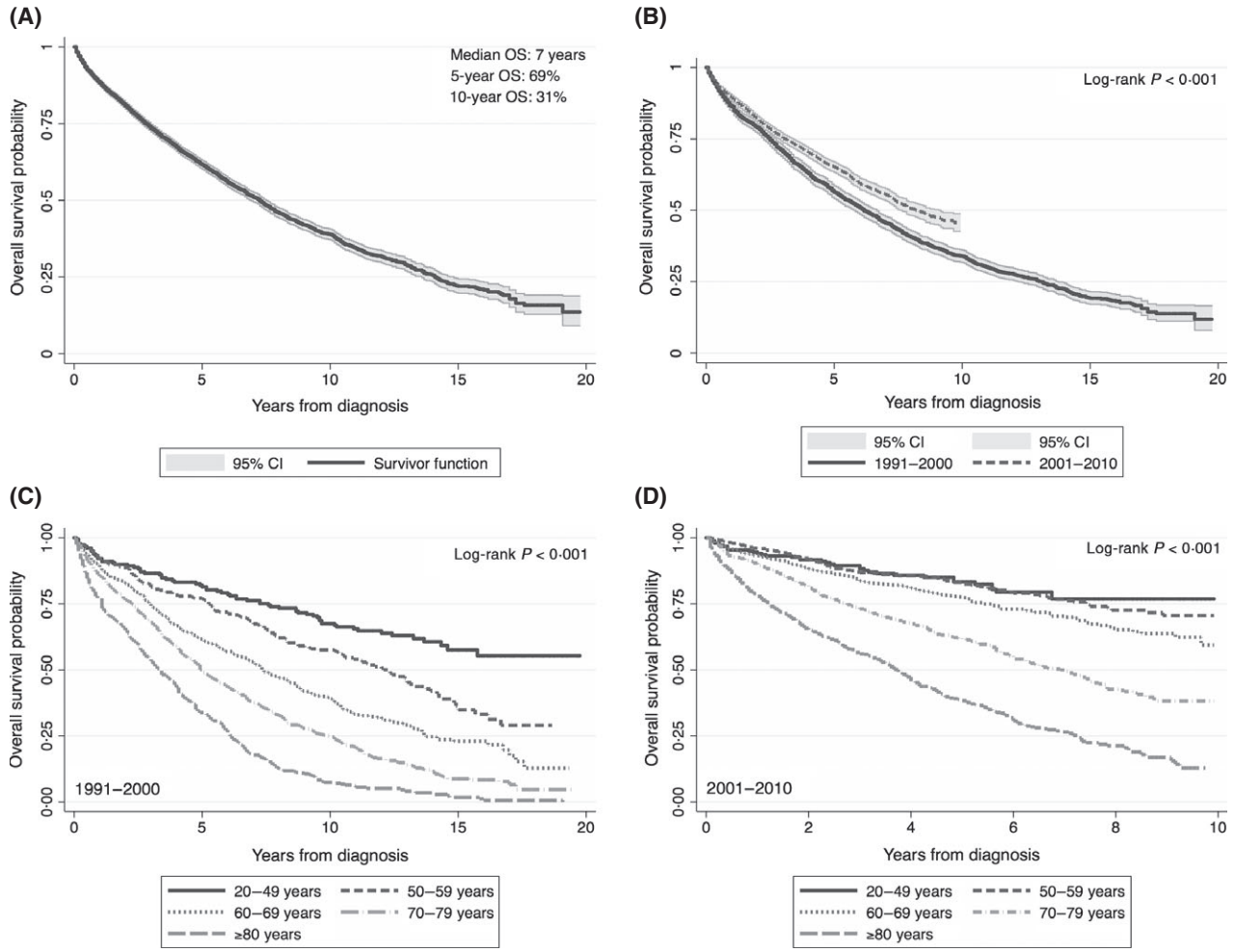

Fig 1. Overall survival (OS) estimates with 95% confidence intervals (CI) in patients with Waldenström Macroglobulinaemia from the SEER database for (A) the entire cohort, and according to (B) epoch of diagnosis, and (C) age categories for 1991–2000 cohort and (D) age categories for 2001–10 cohort.

initiated therapy before the year 2000 and 215 who started after 2000, showed no evidence of OS or cause-specific survival improvement in the latter group (Kastritis *et al*, 2011). However, the group treated after the year 2000 was older and presented with higher risk disease. Also, the median follow-up for both groups was short, at 9 and 3 years for the groups before and after 2000, respectively. However, the proportion of patients who had died at the time of the analysis is similar to ours, at 76% and 33%, respectively. This latter point argues that given the small sample size, the study might have been underpowered to detect the expected benefit. Moreover, it was focused on patients eligible for systemic chemotherapy and thus does not reflect prognosis of patients at time of diagnosis.

The results of our analyses are consistent with a Swedish study, which included 1555 patients with WM diagnosed between 1980 and 2005 (Kristinsson *et al*, 2013). In this study, with 1187 patients diagnosed before 2000 and 368 after 2000, a continuous relative survival benefit was identified with improvements seen in the 1990s as well as the 2000s. In line with our results, older patients and men had worse outcomes. The authors evaluated lead-time bias (i.e. longer survival in patients diagnosed earlier in the course of the disease) as one of the factors associated with the improvement seen in the outcomes of patients with WM and did not find differences in the proportion of asymptomatic patients diagnosed before or after 2000.

Age is a strong factor for survival in patients with haematological malignancies. We found that there was no statistically significant outcome improvement in patients younger than 50 years diagnosed during 2001–10 when compared to patients of the same age diagnosed during 1991–2000. The likely explanation for this finding is the small sample size of patients younger than 50 years, comprising <8% of our cohort and rendering the analysis in this age group underpowered. Patients 80 years or older might have also experienced less benefit due to a high rate of co-morbidities, more aggressive disease or inability to tolerate more intensive

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Table II. Multivariate hazard analysis for overall survival in patients with Waldenström macroglobulinaemia from the SEER database, 1991–2010.

	Overall survival	
Variable	HR (95% CI)	*P*-value
Age, years		
20–49	Reference	
50–59	1·44 (1·15–1·81)	0·002
60–69	2·26 (1·83–2·80)	<0·001
70–79	3·76 (3·07–4·62)	<0·001
80+	6·99 (5·68–8·60)	<0·001
Sex		
Female	Reference	
Male	1·23 (1·14–1·34)	<0·001
Race		
White	Reference	
Black	1·38 (1·16–1·63)	<0·001
Other	1·02 (0·86–1·22)	0·79
Unknown	0·86 (0·72–1·01)	0·07
Primary site of involvement		
Bone marrow	Reference	
Extramedullary disease	0·97 (0·79–1·16)	0·58
Unknown	0·90 (0·33–2·44)	0·83
Subtype recode		
Lymphoplasmacytic lymphoma	Reference	
Waldenström macroglobulinaemia	0·92 (0·76–1·11)	0·38
Region		
Northeast	Reference	
West	1·03 (0·92–1·16)	0·58
South	1·18 (0·99–1·40)	0·06
Midwest	1·08 (0·94–1·24)	0·25
Epoch of diagnosis		
1991–2000	Reference	
2001–10	0·73 (0·67–0·79)	<0·001

HR, hazard ratio; CI, confidence interval.

Table III. Multivariate hazard analysis on the effect of epoch of diagnosis on overall survival, stratified according to age, sex, race, marital status, primary site of involvement and lymphoma subtype in patients with Waldenström macroglobulinaemia from the SEER database, 1991–2010.

	Overall survival	
Stratum	HR for epoch 2001–10 (95% CI)	*P*-value
Age, years		
20–49	0·87 (0·56–1·35)	0·54
50–59	0·67 (0·51–0·88)	0·004
60–69	0·55 (0·45–0·66)	<0·001
70–79	0·74 (0·65–0·86)	<0·001
80+	0·85 (0·73–0·98)	0·03
Sex		
Male	0·68 (0·61–0·75)	<0·001
Female	0·82 (0·72–0·93)	0·003
Race		
White	0·72 (0·66–0·79)	<0·001
Black	0·83 (0·57–1·20)	0·32
Other	0·86 (0·59–1·25)	0·42
Unknown	0·56 (0·39–0·79)	0·001
Primary site		
Bone marrow	0·73 (0·66–0·81)	<0·001
Extramedullary disease	0·73 (0·63–0·83)	<0·001
Subtype		
Lymphoplasmacytic lymphoma	0·71 (0·62–0·81)	<0·001
Waldenström macroglobulinaemia	0·74 (0·67–0·82)	<0·001
Region		
Northeast	0·77 (0·61–0·95)	0·01
West	0·72 (0·65–0·80)	<0·001
South	0·68 (0·49–0·93)	0·01
Midwest	0·76 (0·61–0·93)	0·009

HR, hazard ratio; CI, confidence interval.

regimens that incorporate alkylating agents or nucleoside analogues. However, there was a significant improvement in OS in this age group.

Our study also showed that blacks had worse outcomes. Blacks have had consistently worse outcomes than whites in previous epidemiological studies of various lymphoproliferative disorders (Shenoy *et al*, 2011a,b; Castillo *et al*, 2013; Nabhan *et al*, 2014a,b). This disparity in outcomes seen in blacks has been ascribed to differences in socioeconomical status, health insurance coverage and patients' or providers' attitudes towards therapy. For example, black patients are less likely to receive rituximab as part of treatment for NHL (Flowers *et al*, 2012), although they appear to derive survival benefits when treated with chemoimmunotherapy (Flowers *et al*, 2013). Biological factors may also play a role considering the recognized racial differences in the incidence of monoclonal gammopathy of unknown significance (MGUS) in blacks compared to whites (Landgren & Weiss, 2009). Blacks have increased incidence of IgG and IgA MGUS, which might explain the increased incidence of myeloma seen in blacks. In contrast, the incidence of IgM MGUS is decreased. It is unclear, however, if this difference is responsible for the worse outcomes seen in black patients with WM.

Our competing-risk analysis shows that, in the last decade, there have been statistically significant relative improvements in WM-related as well as non-WM-related deaths. The absolute improvement, however, can be considered clinically small, as the 5-year cumulative incidence rate of WM-related and non-WM-related deaths decreased by 3% and 5%, respectively. However, we believe these differences are expected to widen as patients' survival gets longer. Expectedly, age seems to affect the rates of non-WM-related death. An interesting finding is that WM-related deaths might account for approximately one quarter of the causes of death in our cohort, with the remaining three quarters associated with other processes. These findings argue in favour of the thoughtful and personalized approach needed when making recommendations not only on the type but also the timing

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of treatment. We cannot, however, dismiss the likelihood that many of the non-WM-related deaths might have been directly or indirectly related to complications of the disease or therapy.

Table IV. Causes of death according to epoch of diagnosis in patients with Waldenström macroglobulinaemia from the SEER database, 1991–2010.

Cause of death	1991–2000 (%)	2001–10 (%)	Total (%)
Lymphoma	329 (22·9)	298 (22·1)	627 (22·5)
Solid tumours	263 (18·3)	296 (21·9)	559 (20·1)
Cardiac causes	205 (14·3)	198 (14·7)	403 (14·5)
Infections	77 (5·4)	57 (4·2)	134 (4·8)
Central nervous system	67 (4·7)	55 (4·1)	122 (4·4)
Myeloma	42 (2·9)	40 (3·0)	82 (2·9)
Leukaemia	32 (2·2)	31 (2·3)	63 (2·3)
Other causes	421 (29·3)	375 (27·9)	796 (28·6)
Total	1436 (100·0)	1350 (100·0)	2786 (100·0)

The significant decrease in non-WM mortality between the 1990s and 2000s (HR 0·72) probably reflects improvements in mortality rates in the general US population. According to the National Center for Health Statistics (Arias, 2014), the yearly mortality rate for a white man in the US decreased from 3·6% in 1990 to 2·6% in 2005 (rate ratio 0·72), and for a black man, from 5·3% to 4% (rate ratio 0·75). These notable improvements reflect advances in the management of cardiovascular disease and other medical aspects, and underscore the necessity for competing risk analyses when comparing survival between historical cohorts in malignancies with a low disease-specific mortality rate such as WM.

There are several possible causes for the decreased WM-related mortality in the 2000s compared with the 1990s. One is the application of efficacious systemic therapy. A randomized study in WM patients demonstrated improved OS with fludarabine compared with chlorambucil (Leblond *et al*, 2013), and a trend towards improved OS with addition of rituximab to chemotherapy (Buske *et al*, 2009). Other hypothetical factors

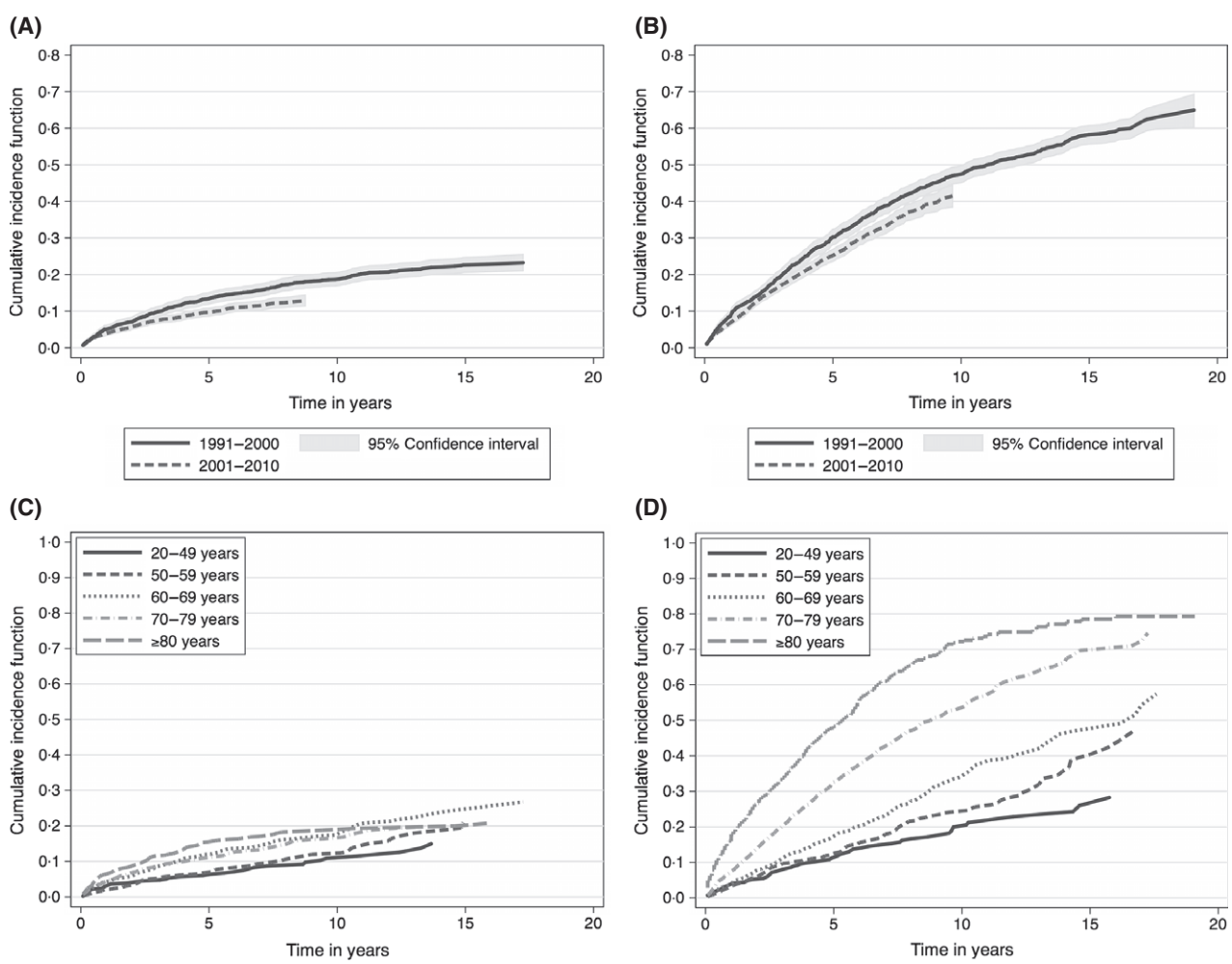

Fig 2. Cumulative incidence function curves evaluating the effect of epoch of diagnosis in (A) Waldenström Macroglobulinaemia (WM)-related deaths and (B) non-WM-related deaths, and the effect of age in (C) WM-related deaths and (D) non-WM-related deaths.

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include improved supportive care, particularly with regard to management of infections and WM-related comorbidities, such as hyperviscosity. We also cannot rule out an apparent improvement related to evolving classification and better distinction of WM from other B-cell malignancies.

Our study carries several limitations. First, the lack of pathological confirmation could have introduced classification bias. Other low-grade lymphoma subtypes, such as marginal zone lymphoma and small lymphocytic lymphoma, can present with monoclonal paraproteinaemia and plasmacytic differentiation (Pangalis *et al*, 2005). With the improvements in classification through the years, misclassification might have impacted cases diagnosed in the 1991–2000 epoch. The period of our analysis encompassed the application of the Working Formulation (The Non-Hodgkin's Lymphoma Pathologic Classification Project, 1982), Harris *et al* (1994) and the Jaffe *et al* (2001) classification of lymphoid neoplasms, although the diagnostic criteria for WM have been fairly uniform. Second, the SEER database does not report utilization of chemotherapy or immunotherapy, and reported an increased coverage from 13% to 26% of the US population since 2001. Hence, lead-time bias has probably been introduced in our analysis, as the time from diagnosis to therapy was not recorded, and a larger number of WM patients have been included in the database since 2001 that might have been mostly asymptomatic. Research efforts directed at evaluating this issue using the SEER-Medicare database are ongoing. Third, the SEER database does not provide information on prognostic laboratory data such as IgM, beta-2-microglobulin, haemoglobin and M-protein levels (Morel *et al*, 2009), precluding adjustment for those factors in our analysis. Finally, the SEER data is reflective of the multi-ethnic nature of the US population, which might not be applicable to other regions of the world. As an example, hepatitis C infection has been linked to an increased risk of WM in an Italian study (Mussini *et al*, 1995); however, this finding was not confirmed in a study from our institution (Leleu *et al*, 2007). Finally, there is a possibility of misclassification on the causes of death registered in the death certificates. However, such misclassification, being non-systematic, would be unlikely to favour one cohort over the other. Despite these limitations, we were able to identify, in the largest population-based study to date, an improvement in OS in patients with WM during the last decade, which can provide patients and clinicians with more reliable data to conduct discussions on survival.

Two recent studies have evaluated outcomes in patients with WM using the SEER database (Sekhar *et al*, 2012; Ailawadhi *et al*, 2014). Both of these studies analysed a significantly smaller sample than our study, including only patients with WM (ICD-9 code 9761). In our study, we have also included patients with LPL (ICD-9 code 9671). WM is, by definition, an IgM-secreting LPL, and accounts for approximately 95% of all LPL cases (Swerdlow *et al*, 2008). Therefore, it is reasonable to consider most LPL patients as WM patients for this analysis. Although bias might have been introduced due to the inclusion of IgA and IgG LPL cases, we would not expect such bias to be sizable enough to alter the results of our study. On the other hand, our analysis provides additional insights and is more powerful at identifying outcome disparities, specifically in the competing-risk analysis.

Moving forward, we believe there are reasons to be optimistic with regard to the outcomes in patients with WM thanks to the advent of highly effective, easy-to-administer and less toxic therapies. Novel agents include proteasome inhibitors and B-cell receptor inhibitors, which offer excellent response rates and even molecular remissions (Treon *et al*, 2009, 2013, 2014). The identification of the *MYD88* L265P gene mutation, detected in 90% of patients with WM (Treon *et al*, 2012), might lead to targeted interventions contributing to further survival advantage, although this remains to be demonstrated in future clinical trials.

In conclusion, there has been an improvement in the survival of US patients with WM over the last decade. These improvements were less apparent in patients younger than 50 years and blacks, probably due to underpowered sample size. Additional research, however, is needed to address the source of these disparities. As the therapy of patients with WM continues to advance at a fast pace with the advent of targeted agents, we believe the outcomes of patients with WM will continue to improve.

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Authors contribution

JJC designed the research and wrote the manuscript. JJC and AJO performed the statistical analysis. All the authors analysed the data and critically reviewed and approved the manuscript.

Disclosure

The authors have no conflict of interest to disclose.

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