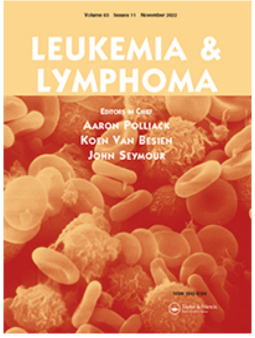

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ORIGINAL ARTICLE

Insurance-based disparities impact survival outcomes in Waldenström macroglobulinemia within the United States

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ABSTRACT

Considerable healthcare resource utilization and financial burden have been associated with the treatment of WM; however, the impact of health insurance status on outcomes has not been previously reported. We conducted a National Cancer Database analysis of newly diagnosed cases of active WM between 2004 and 2017 to evaluate the impact of insurance status on outcomes. For patients <65 years old ($n = 1249$, male sex: 62.4%, median age: 58 years), significant insurance-based survival differences were observed on multivariable analysis; patients who were uninsured [$n = 63$; HR 3.11 (95%CI, 1.77–5.45), $p < 0.001$], on Medicaid [$n = 87$; HR 1.88 (95% CI, 1.01–3.48), $p = 0.045$], or on Medicare [$n = 122$; HR 2.78 (95%CI, 1.76–4.38), $p < 0.001$], had inferior survival compared to patients with private insurance ($n = 977$; reference). In patients ≥65 years, no insurance-based survival differences were found ($p = 0.10$). Overall, significant insurance-based outcome disparities exist in WM. Further work is desperately needed to systematically uncover and address these disparities.

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Introduction

Waldenström macroglobulinemia (WM) is a rare non-Hodgkin lymphoma characterized by the presence of a lymphoplasmacytic infiltrate in the bone marrow associated with monoclonal immunoglobulin M (IgM) [1,2]. Currently, patients with WM are risk-stratified using the revised International Prognostic Scoring System (IPSS), which is based upon age, beta-2 microglobulin level, serum albumin, and LDH level [3]. Although these characteristics have been shown to be prognostic in WM, in oncologic care, socioeconomic-based disparities have gained increasing recognition as important factors associated with patient outcomes [1,4,5]. Previously, a Surveillance Epidemiology and End Results (SEER) database analysis identified significant ethnic disparities within WM survival, with significant interactions between overall survival (OS), gender, and race [6]. Additionally, previous work has shown an association between treatment facility volume and patient outcomes in WM [7].

Within both hematological and non-hematologic malignancies, insurance status has been shown to be significantly associated with patient outcomes [8–10]. Additionally, patients who are uninsured and Medicaid-insured have been previously shown to present with more advanced-stage cancers at diagnosis [11]. A significant economic burden has been identified to be associated with WM treatment; however, to date, the impact of insurance status on patient outcomes in WM has not been reported [12]. The primary aim of this study is to assess the impact of insurance status on survival outcomes in patients with WM, using a national patient cohort. We were particularly interested in assessing the insurance status-based disparities in younger (<65) patients, compared to older (≥65) patients due to Medicare eligibility differences. Our secondary aim was to assess the associations of insurance status with other socioeconomic disparities and the independent survival influence of these disparities.

Methodology

Patient cohort

The data used in this study was derived from the National Cancer Database (NCDB) Participant User

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Data File (PUF) for WM [13]. The NCDB is a joint program of the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society, with data representing more than 70% of newly diagnosed cases of cancer nationwide [14]. The PUF is a Health Insurance Portability and Accountability Act (HIPAA)-compliant data file that contains de-identified patient-level data submission to the CoC NCDB [13]. This data is available by application to investigators associated with CoC-accredited cancer programs to advance the quality of care for cancer patients. The PUF does not contain data regarding clinical trial participation at facilities.

Within our study, we included all available patients from the NCDB WM PUF data with newly diagnosed WM between 2004 and 2017 who received treatment, and had known insurance status (uninsured, Medicaid, Medicare, or private insurance) (Figure 1). We excluded patients who received no treatment, had unknown treatment status, or who received active surveillance. These exclusions were performed to control for patients with possible smoldering WM and account for lead-time. Based on the PUF data, "no treatment" was defined as patients who refused treatment, or the physician decided not to treat for any cause and "active surveillance" was defined as those undergoing watchful waiting. We further excluded patients with unspecified government, or unknown insurance, due to the heterogeneity of these insurance types.

Insurance status

Insurance status was recorded by assessing the primary payer at the time of diagnosis. Changes in the payer or insurance status were not available in the data. Patients were divided based upon insurance status: uninsured, Medicaid, Medicare, and private. Medicaid is a federal-state assistance insurance program available to patients who are of low-income status of all ages [15]. Medicare is a federal insurance program available for patients aged 65 or older of all income ranges, and in certain younger patients (<65) with disabilities or on dialysis [15]. To control for these age-based eligibility differences in Medicare, we grouped our study cohort based upon age (<65 and ≥65 years), as performed in previous studies [16].

Patient and Treatment-Related variables

Patient-level data were extracted including the year of diagnosis, age, sex, race, comorbidities, income range, education status, distance from the treatment center, and type of treatment center. For patients above 90 years of age, the age was presented as 90 years for compliance with HIPAA privacy requirements. The race was categorized as White, Black, or other race. Comorbidities were presented in the database using the Charlson Comorbidity Scoring system [17,18]. Income was estimated using the median

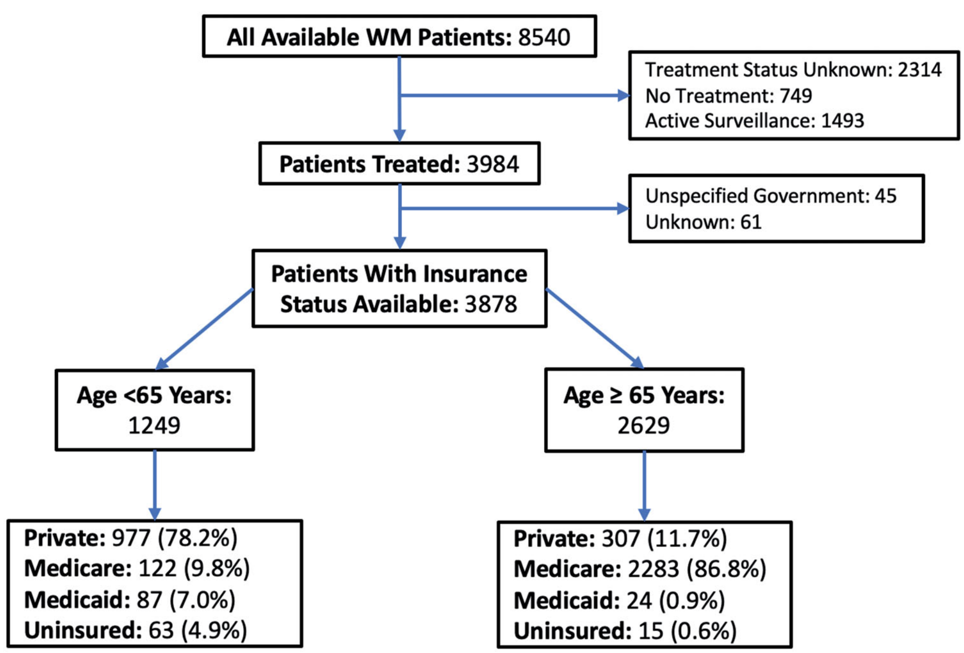

Figure 1. Diagram representing total available patients, the reason for exclusion, and final cohort within the study divided by age group and insurance status.

household income in the area of residence based on the patients' zip code using the 2016 American Community Survey Data [19]. High income was defined as ≥$63,333, medium-1 as $50,354–63,332, medium-2 as $40,227–50,353 and low was <$40,227. The education level was estimated based on the percentage of adults aged 25 or older in the patient's zip code who did not graduate from high school, using the 2016 American Community Survey Data [19]. High education was defined as <6.3%, medium-1 as 6.3–10.8%, medium-2 as 10.9–17.5%, and low education was defined as ≥17.6% education attainment. Urban, metro, or rural status was determined using the typology published by the United States Department of Agriculture Economic Research Service. Facility type was categorized into community or academic center. The community programs included both the community cancer and the comprehensive community cancer programs, and the academic programs include both academic/research and integrated network cancer programs. Distance from the treatment center was determined using the distance in miles from the patient's residence and the hospital that reported the case. The treatment start was determined using the number of days between the initial diagnosis and the start of systemic therapy (chemotherapy, immunotherapy, etc.), the time ranges used were based upon previous literature assessing insurance-based disparities in other hematological malignancies [9,10,16]. Chemotherapy administration included patients who received chemotherapy within the first course of treatment at any facility. Immunotherapy administration included patients who received immunotherapy within the first course of treatment at any facility.

Statistical analysis

Whole cohort and stratified analyses were conducted based upon patient age, <65 and ≥65 years. Continuous and categorical variables were described using median (range), frequencies (n), and percentages where applicable. Patients with missing data were recorded as unknown and the corresponding value was removed from the analysis. The association between insurance status (uninsured, Medicaid, Medicare, private) and covariates was evaluated using Pearson's Chi-Square tests. Univariate and multivariate analyses were conducted using the Cox proportional hazards model. Overall survival (OS) was calculated from the date of diagnosis to the date of the last follow-up. Patients alive at last contact were censored. The Kaplan-Meier method using log-rank testing was used to assess the survival differences based on the insurance status. The 5-year OS, with the corresponding 95% confidence intervals (CIs) was determined using the Kaplan-Meier estimates. The Reverse Kaplan-Meier method was used to estimate median follow-up time. A p value of <0.05 was considered statistically significant for all analyses. All statistical analyses were performed using IBM SPSS v27.

Results

Cohort-Related data

Among a total of 8,540 patients identified, 3,878 patients were analyzed after applying the inclusion and exclusion criteria (Figure 1). The median age was 70 years (range, 28–90) with 2,372 (61.2%) males. The insurance status amongst the cohort ranked by the number of patients (highest to lowest) was Medicare ($n = 2{,}405$, 62.0%), private ($n = 1{,}284$, 33.1%), Medicaid ($n = 111$, 2.9%), and Uninsured ($n = 78$, 2.0%). The baseline characteristics for the whole cohort and association of covariates with the insurance status are demonstrated in Supplemental Table 1. We further assessed the association between distance to the treatment center, in relation to key socioeconomic markers (race, income and education) (Supplemental Table 2). A significant association was found between distance to the treatment center and education level ($p < 0.001$) and household income ($p < 0.001$), but no significant association was found when assessing patient race ($p = 0.55$).

Excluded from the cohort: among patients who received no treatment ($n = 727$), the distribution of insurance status from highest to lowest was: 71.5% ($n = 520$) Medicare, 25.6% ($n = 186$) private, 2.3% ($n = 17$) Medicaid, and 0.6% ($n = 4$) uninsured. Additionally, in those who received active surveillance ($n = 1453$), the distribution of insurance status from highest to lowest was: 64.0% ($n = 930$) Medicare, 32.5% ($n = 472$) private, 2.5% ($n = 37$) Medicaid and 1.0% ($n = 14$) uninsured.

Patients <65 years old

There were 1,249 patients below the age of 65 years; the median age was 58 years (range, 28–64), with 779 (62.4%) males. The race distribution in this age group was: 86.1% ($n = 1076$) White, 9.0% ($n = 113$) Black and 4.8% ($n = 60$) other races. Insurance status ranked by

Table 1. Baseline characteristics of patients <65 years old and association with insurance status.

Characteristics	All patients < 65 ($n = 1249$)	Insurance status: Uninsured $N = 63$ (4.9%)	Private $N = 977$ (78.2%)	Medicaid $N = 87$ (7.0%)	Medicare $N = 122$ (9.8%)	P-value
Age (years) – no (%)						**<0.001**
<55	369 (29.5%)	22 (34.9%)	301 (30.8%)	27 (31.0%)	19 (15.6%)	
55–60	465 (37.2%)	24 (38.1%)	368 (37.7%)	35 (40.2%)	38 (31.1%)	
61–64	415 (33.2%)	17 (27.0%)	308 (31.5%)	25 (28.7%)	65 (53.3%)	
Male sex – no (%)	779 (62.4%)	40 (63.5%)	603 (61.7%)	55 (63.2%)	81 (66.4%)	0.78
Comorbidity index – no (%)						**<0.001**
0	1051 (84.1%)	54 (85.7%)	847 (86.7%)	65 (74.7%)	85 (69.7%)	
1	138 (11.0%)	6 (9.5%)	98 (10.0%)	11 (12.6%)	23 (18.9%)	
2	40 (3.2%)	0	26 (2.7%)	5 (5.7%)	9 (7.4%)	
≥3	20 (1.6%)	3 (4.8%)	6 (0.6%)	6 (6.9%)	5 (4.1%)	
Race – no (%)						**<0.001**
White	1076 (86.1%)	47 (74.6%)	868 (88.8%)	60 (69.0%)	101 (82.8%)	
Black	113 (9.0%)	12 (19.0%)	64 (6.6%)	20 (23.0%)	17 (13.9%)	
Other	60 (4.8%)	4 (6.3%)	45 (4.6%)	7 (8.0%)	4 (3.3%)	
Residence – no (%)						0.09
Metro	1029 (85.5%)	47 (75.8%)	809 (86.4%)	73 (83.9%)	100 (84.0%)	
Urban	156 (13.0%)	11 (17.7%)	114 (12.2%)	13 (14.9%)	18 (15.1%)	
Rural	20 (1.6%)	5 (6.5%)	13 (1.4%)	1 (1.1%)	1 (0.8%)	
Household income – no (%)						**<0.001**
Low	158 (14.6%)	15 (25.0%)	100 (11.9%)	19 (25.0%)	24 (21.6%)	
Medium-2	249 (23.0%)	15 (25.0%)	181 (21.6%)	24 (31.6%)	29 (26.1%)	
Medium-1	325 (30.0%)	12 (20.0%)	259 (30.9%)	18 (23.7%)	36 (32.4%)	
High	352 (32.5%)	18 (30.0%)	297 (35.5%)	15 (19.7%)	22 (19.8%)	
Education level – no (%)						**<0.001**
Low	159 (14.7%)	17 (28.3%)	99 (11.9%)	19 (25.0%)	24 (22.0%)	
Medium-2	196 (18.1%)	8 (13.3%)	142 (17.0%)	21 (27.6%)	25 (22.9%)	
Medium-1	267 (24.7%)	13 (21.7%)	212 (25.4%)	18 (23.7%)	24 (22.0%)	
High	458 (42.4%)	22 (36.7%)	382 (45.7%)	18 (23.7%)	36 (33.0%)	
Year of diagnosis – no (%)						0.07
2010–2014	557 (44.6%)	33 (52.4%)	442 (45.2%)	28 (32.2%)	54 (44.2%)	
2014–2017	692 (55.4%)	30 (47.6%)	535 (54.8%)	59 (67.8%)	68 (55.7%)	
Institution- no (%)						0.14
Non-academic	487 (39.8%)	33 (52.4%)	370 (38.7%)	31 (37.3%)	53 (43.3%)	
Academic	736 (60.2%)	30 (47.6%)	585 (61.3%)	52 (62.7%)	69 (56.6%)	
Distance to reporting center (miles)- no (%)						**<0.001**
<10	520 (47.4%)	22 (36.7%)	398 (47.0%)	54 (70.1%)	46 (41.1%)	
10–25	290 (26.5%)	22 (36.7%)	221 (26.1%)	10 (13.0%)	37 (33.0%)	
≥25	286 (26.1%)	16 (26.7%)	228 (26.9%)	13 (16.9%)	29 (25.9%)	
Treatment start (days) – no (%)						**0.03**
0–14	419 (35.9%)	31 (50.8%)	309 (34.0%)	39 (48.1%)	40 (34.5%)	
15–30	318 (27.2%)	15 (24.6%)	258 (28.4%)	17 (21.0%)	28 (24.1%)	
≥31	430 (36.8%)	15 (24.6%)	342 (37.6%)	25 (30.9%)	48 (41.4%)	
Chemotherapy as first course- no (%)						0.31
No	170 (13.9%)	7 (11.1%)	141 (14.7%)	7 (8.1%)	15 (12.5%)	
Yes	1056 (86.1%)	56 (88.9%)	816 (85.3%)	79 (91.9%)	105 (87.5%)	
Immunotherapy as first course – no (%)						0.84
No	601 (48.4%)	28 (44.4%)	468 (48.2%)	43 (49.4%)	62 (51.2%)	
Yes	641 (51.6%)	35 (55.6%)	503 (51.8%)	44 (50.6%)	59 (48.8%)	

no or n.
Significant p-values are in bold

the number of patients (highest to lowest) was private ($n = 977$, 78.2%), Medicare ($n = 122$, 9.8%), Medicaid ($n = 87$, 7.0%), and uninsured ($n = 63$, 4.9%). The baseline characteristics for the <65 years cohort and the association of covariates with insurance status are demonstrated in Table 1. A significant association between the insurance status and the patient's age ($p < 0.001$), comorbidity index ($p < 0.001$), race ($p < 0.001$), household income ($p < 0.001$), an education level ($p < 0.001$), distance to the reporting site ($p < 0.001$) and the timing of treatment initiation ($p = 0.03$) was observed.

Patients ≥65 years old

There were 2,629 patients aged 65 years and older, the median age was 75 years (range, 65–90), with 1,593 (60.6%) males. The race distribution in this age group was: 92.7% ($n = 2436$) White, 3.8% ($n = 100$) Black and 3.5% ($n = 93$) of other races. The insurance status ranked by the number of patients (highest to lowest) was, Medicare ($n = 2,283$, 86.8%), private ($n = 307$, 11.7%), Medicaid ($n = 24$, 0.9%) and uninsured ($n = 15$, 0.6%). The baseline characteristics for the cohort ≥65 years of age and the association of covariates with insurance status are demonstrated in Table 2. A significant association

Table 2. Baseline characteristics of patients ≥ 65 years old and association with insurance status.

Characteristics	Patients ≥ 65 Years ($n = 2629$)	Insurance status: Uninsured $n = 15$ (0.6%)	Private $n = 307$ (11.7%)	Medicaid $n = 24$ (0.9%)	Medicare $n = 2283$ (86.8%)	*P*-value
Age (years) – no (%)						**<0.001**
65–70	760 (28.9%)	6 (40.0%)	139 (45.3%)	7 (29.2%)	608 (26.6%)	
71–80	1146 (43.6%)	5 (33.0%)	113 (36.8%)	14 (58.3%)	1014 (44.4%)	
≥81	723 (27.5%)	4 (26.7%)	55 (17.9%)	3 (12.5%)	661 (29.0%)	
Male sex – no (%)	1593 (60.6%)	10 (66.7%)	198 (64.5%)	15 (62.5%)	1370 (60.0%)	0.47
Comorbidity index – no (%)						**0.005**
0	2023 (76.9%)	10 (66.7%)	246 (80.1%)	11 (45.8%)	1756 (76.9%)	
1	393 (14.9%)	4 (26.7%)	43 (14.0%)	9 (37.5%)	337 (14.8%)	
2	137 (5.2%)	1 (6.7%)	12 (3.9%)	1 (4.2%)	123 (5.4%)	
≥3	76 (2.9%)	0	6 (2.0%)	3 (12.5%)	67 (2.9%)	
Race – no (%)						**<0.001**
White	2436 (92.7%)	11 (73.3%)	274 (89.3%)	18 (75.0%)	2133 (93.4%)	
Black	100 (3.8%)	3 (20.0%)	13 (4.3%)	3 (12.5%)	81 (3.5%)	
Other	93 (3.5%)	1 (6.7%)	20 (6.5%)	3 (12.5%)	69 (3.0%)	
Residence – no (%)						**0.044**
Metro	2143 (84.1%)	15 (100.0%)	267 (89.3%)	23 (95.8%)	1838 (83.2%)	
Urban	364 (14.3%)	0	28 (9.4%)	1 (4.2%)	335 (15.2%)	
Rural	41 (1.6%)	0	4 (1.3%)	0	37 (1.7%)	
Household income – no (%)						**0.048**
Low	246 (10.6%)	0	27 (9.9%)	3 (13.0%)	216 (10.8%)	
Medium-2	485 (21.0%)	1 (7.1%)	42 (15.3%)	3 (13.0%)	439 (22.0%)	
Medium-1	564 (24.4%)	6 (42.9%)	61 (22.3%)	7 (30.4%)	490 (24.5%)	
High	1016 (44.0%)	7 (50.0%)	144 (52.6%)	10 (43.5%)	855 (42.8%)	
Education level – no (%)						0.20
Low	274 (11.8%)	2 (14.3%)	41 (15.0%)	3 (13.0%)	228 (11.4%)	
Medium-2	500 (21.6%)	4 (28.6%)	42 (15.3%)	7 (30.4%)	447 (22.3%)	
Medium-1	717 (31.0%)	2 (14.3%)	85 (31.0%)	5 (21.7%)	625 (31.2%)	
High	823 (35.6%)	6 (42.9%)	106 (38.7%)	8 (34.8%)	703 (35.1%)	
Year of diagnosis mean (SD) – no (%)						0.42
2010–2014	1087 (41.3%)	9 (60.0%)	126 (41.0%)	8 (33.3%)	944 (41.3%)	
2014–2017	1542 (58.7%)	6 (40.0%)	181 (59.0%)	16 (66.7%)	1339 (58.7%)	
Institution- no (%)						0.12
Non-academic	1210 (46.0%)	6 (40.0%)	128 (41.7%)	7 (29.2%)	1069 (46.8%)	
Academic	1419 (54.0%)	9 (60.0%)	179 (58.3%)	17 (70.8%)	1214 (53.2%)	
Distance to center (miles)- no (%)						0.69
<10	1236 (53.0%)	10 (71.4%)	154 (55.8%)	14 (60.9%)	1058 (52.4%)	
10–25	617 (26.4%)	2 (14.3%)	72 (26.1%)	6 (26.1%)	537 (26.6%)	
≥25	481 (20.6%)	2 (14.3%)	50 (18.1%)	3 (13.0%)	426 (21.1%)	
Treatment start (days) – no (%)						0.44
0–14	765 (31.1%)	4 (33.3%)	90 (30.9%)	11 (52.4%)	660 (30.9%)	
15–30	744 (30.3%)	4 (33.3%)	81 (27.8%)	4 (19.0%)	655 (30.7%)	
≥31	950 (38.6%)	4 (33.3%)	120 (41.2%)	6 (28.6%)	820 (38.4%)	
Chemotherapy as first course- no (%)						0.71
No	1293 (49.7%)	9 (60.0%)	156 (51.8%)	11 (45.8%)	1117 (49.4%)	
Yes	1310 (50.3%)	6 (40.0%)	145 (48.2%)	13 (54.2%)	1146 (50.6%)	
Immunotherapy as first course – no (%)						0.70
No	1293 (49.7%)	9 (60.0%)	156 (51.8%)	11 (45.8%)	1117 (49.4%)	
Yes	1310 (50.3%)	6 (40.0%)	145 (48.2%)	13 (54.2%)	1146 (50.6%)	

no or n, number.
Significant *p*-values are in bold

between the insurance status and the patient's age ($p < 0.001$), comorbidity index ($p = 0.005$), race (<0.001), residence ($p = 0.044$), and household income ($p = 0.048$) was found.

Overall survival

The median follow-up times were 54.6 months (95% CI, 53.1–56.1) for the whole cohort, 56.3 months (95% CI, 53.2–59.4) for patients <65 years of age, and 53.6 months (95% CI, 51.9-55.3) for patients ≥65 years old. For the whole cohort, univariate and multivariate OS analysis controlling for all covariates listed is shown in Supplemental Table 3. A significant OS difference was seen (Supplemental Figure 1) based on the insurance status (log-rank $p < 0.001$). OS analysis based on patient age ranges ($p < 0.001$) is demonstrated in Supplemental Figure 2.

For patients, less than 65 years of age, univariate, and multivariate analyses, with corresponding hazard ratios (HR) are demonstrated in Table 3. All variables listed were entered into the multivariable analysis, in which significant associations between age, comorbidity index, race, insurance status, and year of diagnosis

Table 3. Univariate and multivariate overall survival analysis in patients <65 and ≥ 65 years old.

	<65 years old				≥ 65 years old			
Characteristics	Unadjusted	*P*-value	Adjusted	*P*-value	Unadjusted	*P*-value	Adjusted	*P*-value
Insurance status– HR (95% CI)								
Private	Ref		Ref		Ref		Ref	
Uninsured	3.38 (2.06–5.53)	**<0.001**	3.11 (1.77–5.45)	**<0.001**	0.58 (0.18–1.83)	0.35	0.25 (0.03–1.77)	0.16
Medicaid	2.64 (1.59–4.37)	**<0.001**	1.88 (1.01–3.48)	**0.045**	1.20 (0.56–2.59)	0.64	1.05 (0.45–2.43)	0.91
Medicare	3.96 (2.72–5.75)	**<0.001**	2.78 (1.76–4.38)	**<0.001**	1.26 (1.02–1.55)	0.03	1.08 (0.85–1.36)	0.53
Age – HR (95% CI)								
<55	Ref		Ref					
55–60	1.38 (0.91–2.09)	0.13	1.40 (0.85–2.31)	0.18				
61–64	2.14 (1.44–3.18)	**<0.001**	2.32 (1.43–3.78)	**<0.001**				
65–70					Ref		Ref	
71–80					1.46 (1.22–1.74)	**<0.001**	1.30 (1.07–1.58)	**0.009**
≥81					3.19 (2.67–3.81)	**<0.001**	2.77 (2.27–3.38)	**<0.001**
Female sex– HR (95% CI)	1.12 (0.82–1.53)	0.47	1.29 (0.90–1.83)	0.17	0.96 (0.84–1.09)	0.51	0.84 (0.72–0.97)	**0.02**
Comorbidity index – HR (95% CI)								
0	Ref		Ref		Ref		Ref	
1	1.61 (1.05–2.47)	**0.03**	1.23 (0.76–2.02)	0.40	1.53 (1.29–1.80)	**<0.001**	1.42 (1.17–1.71)	**<0.001**
2	2.11 (1.07–4.15)	**0.03**	1.60 (0.71–3.60)	0.25	1.92 (1.50–2.46)	**<0.001**	1.65 (1.23–2.20)	**<0.001**
≥3	4.96 (2.42–10.17)	**<0.001**	2.41 (1.10–5.28)	**0.03**	1.87 (1.32–2.65)	**<0.001**	1.48 (1.01–2.19)	**0.047**
Race – HR (95% CI)								
White	Ref		Ref		Ref		Ref	
Black	2.03 (1.34–3.07)	**<0.001**	2.00 (1.20–3.32)	**0.008**	1.21 (0.88–1.68)	0.25	1.07 (0.72–1.61)	0.73
Other	0.51 (0.20–1.44)	0.21	0.51 (0.16–1.65)	0.26	0.76 (0.52–1.12)	0.16	0.71 (0.46–1.10)	0.12
Residence– HR (95% CI)								
Metro	Ref		Ref		Ref		Ref	
Urban	1.22 (0.78–1.89)	0.39	0.97 (0.54–1.74)	0.92	1.03 (0.86–1.23)	0.76	0.97 (0.76–1.23)	0.77
Rural	2.95 (1.21–7.22)	**0.02**	1.74 (0.63–4.84)	0.29	0.77 (0.44–1.36)	0.37	0.56 (0.26–1.21)	0.14
Household income– HR (95% CI)								
Low	Ref		Ref		Ref		Ref	
Medium-2	0.77 (0.48–1.24)	0.28	1.16 (0.65–2.07)	0.61	0.98 (0.77–1.25)	0.90	1.02 (0.78–1.35)	0.87
Medium-1	0.60 (0.38–0.96)	**0.03**	0.97 (0.51–1.82)	0.91	0.84 (0.67–1.07)	0.17	0.93 (0.70–1.24)	0.61
High	0.55 (0.36–0.83)	**0.005**	1.12 (0.56–2.23)	0.75	0.76 (0.61–0.95)	**0.02**	0.90 (0.66–1.22)	0.51
Education level – HR (95% CI)								
Low	Ref		Ref		Ref		Ref	
Medium-2	0.90 (0.56–1.43)	0.64	1.02 (0.59–1.78)	0.94	0.86 (0.68–1.08)	0.20	0.97 (0.75–1.26)	0.84
Medium-1	0.81 (0.52–1.28)	0.37	1.02 (0.55–1.88)	0.96	0.81 (0.65–1.01)	0.06	0.98 (0.75–1.27)	0.85
High	0.58 (0.36–0.93)	**0.02**	0.86 (0.43–1.75)	0.68	0.69 (0.56–0.85)	**<0.001**	0.84 (0.72–0.97)	0.02
Year of diagnosis – HR (95% CI)								
2010–2014	Ref		Ref		Ref		Ref	
2014–2017	1.66 (1.16–2.36)	**0.005**	1.71 (1.08–2.72)	**0.02**	0.99 (0.86–1.14)	**0.90**	1.07 (0.89–1.28)	0.49
Academic institution – HR (95% CI)	0.81 (0.60–1.11)	0.19	0.90 (0.62–1.30)	0.58	0.86 (0.75–0.97)	**0.02**	0.93 (0.80–1.08)	0.32
Distance to center– HR (95% CI)								
<10	Ref		Ref		Ref		Ref	
10–25	0.92 (0.62–1.36)	0.68	0.92 (0.59–1.45)	0.72	0.89 (0.76–1.04)	0.15	0.97 (0.81–1.15)	0.97
≥25	1.41 (0.99–2.02)	0.06	1.49 (0.92–2.41)	0.10	0.82 (0.69–0.98)	**0.03**	0.95 (0.76–1.19)	0.95
Treatment start– HR (95% CI)								
0–14	Ref		Ref		Ref		Ref	
15–30	1.06 (0.72–1.56)	0.77	1.29 (0.84–1.99)	0.25	0.81 (0.68–0.95)	**0.009**	0.85 (0.71–1.01)	0.07
≥31	0.81 (0.55–1.18)	0.26	0.95 (0.62–1.44)	0.80	0.65 (0.56–0.77)	**<0.001**	0.66 (0.56–0.78)	<**0.001**
Chemotherapy – HR (95% CI)	1.01 (0.63–1.61)	0.98	1.21 (0.64–2.27)	0.56	1.04 (0.88–1.23)	0.62	1.01 (0.83–1.25)	0.88
Immunotherapy – HR (95% CI)	1.08 (0.78–1.49)	0.66	0.79 (0.51–1.22)	0.28	0.81 (0.71–0.93)	**0.002**	0.87 (0.72–1.05)	0.14

CI, confidence interval; Ref, reference; HR, hazard ratio.
Significant *p*-values are in bold

were seen (Table 3). Notably, in addition to the non-private insurance, older age in the 61–64 years range [HR 2.32 (95% CI, 1.43–3.78), $p < 0.001$], comorbidity index ≥3 [HR 2.41 (95% CI, 1.10–5.28), $p = 0.03$] and the Black race [HR 2.00 (95% CI, 1.20–3.32), $p = 0.008$] were independently associated with a shorter OS on the adjusted multivariable analysis. Looking specifically at the insurance status, compared to private insurance (reference), uninsured [HR 3.11 (95% CI, 1.77–5.45), $p < 0.001$], Medicaid [HR 1.88 (95% CI, 1.01–3.48), $p = 0.045$], and Medicare [2.78 (95% CI, 1.76–4.38), $p < 0.001$] based insurance led to substantially increased risk of mortality. Figure 2A shows the OS curves grouped by the patients' insurance status. The median survival time was only reached for Medicare insurance [92.2 months (95%CI, 80.5–103.8)]. Overall, there were significant survival differences (log-rank $p < 0.001$). At 5-year estimates, private insurance had the highest survival rate (91.2%, 95% CI, 89.2–93.2), as compared to Medicaid (79.8%, 95% CI, 70.0–89.6), uninsured (77.4%, 95% CI, 66.4–88.4), and Medicare (70.2%, 95% CI, 60.8–79.6).

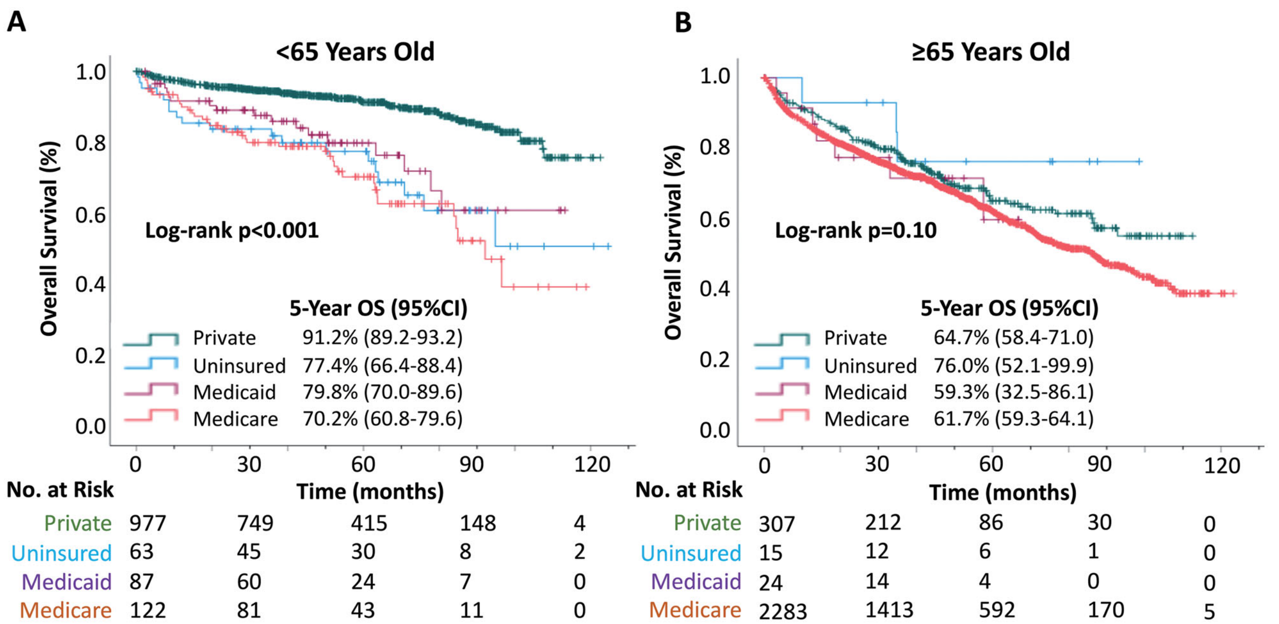

Figure 2. Overall survival analysis comparing insurance status for patients <65 and ≥65 years of age. Kaplan-Meier overall survival (OS) analysis assessed from the date of diagnosis comparing private insurance, Medicare, Medicaid, and uninsured status. (A) <65 and (B) ≥65 years old. CI, confidence interval.

For patients 65 years or greater, univariate, and multivariate analyses of OS, with the corresponding hazard ratios are demonstrated in Table 3. All listed variables were entered into the multivariable analysis, with evidence of significant associations between age, comorbidity index, and days to the treatment initiation. Notably, older age, ≥81 years [HR 2.77 (95% CI, 2.27–3.38), $p < 0.001$], and comorbidity index ≥3 [HR 1.48 (95% CI, 1.01–2.19), $p = 0.047$] were independently associated with reduced survival on the adjusted multivariable analysis. Looking specifically at the insurance status, compared to private insurance (reference), there were no significant risk differences in uninsured patients ($p = 0.16$), and those on Medicaid ($p = 0.91$) or Medicare ($p = 0.53$). The survival curves grouped by the patients' insurance status are shown in Figure 2B. The median OS was only reached for the cohort on Medicare [85.6 months (95% CI, 78.6–92.7)], and the entire cohort of patients who were 65 years or greater [87.1 months (95% CI, 79.9–94.3)]. There were no significant differences between the insurance status (log-rank = 0.10), with the estimated 5-year OS shown in Figure 2B.

Discussion

Previous literature has demonstrated the importance of socioeconomic disparities in cancer care; however, there is limited literature assessing the impact of these disparities in WM. In our NCDB analysis, we found a significant impact of the insurance status on OS of patients with WM. For patients below the age of 65 years, no insurance, Medicaid, or Medicare-based insurance led to increased risk for mortality compared to those with private insurance. However, these insurance-based survival differences were not seen amongst those aged 65 years and greater.

Our findings are in accordance with the previous studies assessing hematological malignancies and the impact of insurance status on patient survival [10,20,21]. In an NCDB analysis assessing 45,777 patients with Hodgkin lymphoma, those who were uninsured or on Medicaid had a lower 5-year OS (54% vs 87%, $p < 0.01$) compared to those with private insurance or on Medicare [10]. Furthermore, on multivariable analysis, patients with uninsured or on Medicaid had a significantly increased risk of mortality (HR 1.60; 95% CI, 1.34–1.91, $p < 0.01$) [10]. In another study assessing patients with multiple myeloma, compared to patients with private insurance, those with Medicaid had a significantly lower 5-year survival (HR 1.44, 95% CI 1.36–1.53), and uninsured patients had a 26% (95% CI 1.04–1.53) increased mortality hazard [21].

Within our study, the improved outcome with private insurance can possibly be explained by a multitude of facility-, treatment-, and patient-related factors. First, significant differences were seen in terms of distance to the reporting center. In a previous review of literature containing 27 studies, comprising 716,153 patients, travel burden was associated with advanced disease at diagnosis, inappropriate treatment, lower adherence to treatment, worse prognosis, and worse quality of life [22]. Given that most patients with private insurance lived less than 10 miles away from the reporting center, they likely benefited from access to care closer to their residence. In terms of treatment-related characteristics, within WM, treatment is typically initiated only at the onset of patient symptoms, and there were significant differences between treatment start times [23,24]. Over half of the uninsured patients received treatment within 0–14 days, compared to only about a third of patients with private insurance. It is possible that patients with private insurance presented earlier in the disease course, with a lower likelihood of WM-related end-organ damage, requiring less prompt initiation of therapy. Furthermore, in terms of patient-related characteristics, significant comorbidity differences were present among the insurance categories, and a lower rate of comorbidities was seen in patients with private insurance. The degree of comorbidities has been previously associated with poorer outcomes, which may explain the worse outcomes seen in patients with non-private or no insurance [25,26]. Additionally, based upon eligibility criteria, most patients within this age range with Medicare insurance likely had significant disabilities or were dialysis-dependent, further contributing to their inferior survival. Overall, it is not possible to pinpoint which factors led to the insurance-based survival outcome differences. However, it is likely that there was a contribution of multiple covariates included in this study, and beyond, which played an interlinked role.

The significant survival differences seen amongst patients younger than 65 were not observed amongst patients 65 years or older. All patients 65 years or greater are Medicare-eligible, and previous studies which have assessed patients grouped by age, have noted a similar lack of significant survival differences [16,20,27]. In an NCDB study of patients less than 65 years with Burkitt lymphoma, those who were uninsured (HR 1.44; 95% CI 1.2–1.7; $p = 0.0003$), Medicaid (HR 1.22; 1–1.4 95% CI; $p = 0.02$), or Medicare (HR 1.53; 95% CI 1.2–1.9; $p < 0.0001$) insured had overall worse survival on multivariable analysis comparison to patients with private insurance [16]. However, amongst patients 65 years and older, in comparison to patients with private insurance, on multivariable survival analysis, no significant differences were seen with Medicaid ($p = 0.53$) or Medicare ($p = 0.12$), but uninsured patients had lower survival (HR 8.38; 95% CI 2.5–28.3; $p = 0.0006$) [16]. Assessing chronic myeloid leukemia, a SEER database study found that among patients less than 65 years, being Medicaid insured or uninsured was associated with worse survival as compared to patients with other insurances ($p < 0.001$) [20]. However, in the 2,142 patients who were 65 years and older, there were no significant insurance-based survival differences seen ($p = 0.07$) [20]. Within our cohort of patients who were 65 years and older, we observed that most patients were Medicare insured, and very few patients were uninsured or Medicaid insured (1.5% total). Furthermore, some of the important insurance-based associations in education status, treatment start time, and distance to the treating center seen in the younger cohort, were not observed amongst this older Medicare-eligible cohort. Additionally, in patients surviving beyond 65 years, there is likely a less wide distribution of serious comorbidities that favor earlier death, leading to a more homogenous cohort. Overall, the non-significant survival differences in this age group may be due to most patients having similar insurance status (Medicare), and a lack of significant differences in other socioeconomic factors, leading to relatively equivalent outcomes.

In addition to the insurance status, independent survival associations were found with other important covariates including age, sex, race, and comorbidities. Notably, in patients less than 65 years old, the Black race was associated with significantly higher mortality as compared to the White race. This association has been previously demonstrated in a SEER analysis, in which significant interaction between median OS, gender, and race ($p = 0.007$) was observed, and worse OS was seen in African-American patients, aged <65 years [6]. In terms of other independent survival associations, in another NCDB study from our group, a volume-outcomes relationship was seen in WM [7]. Of a total of 3,064 patients treated at 795 facilities, using quartile cutoffs, patients treated at the highest quartile volume facilities (Q4) had a higher 5-year overall survival (Q4: 71% vs Q1: 55%, $p < 0.0001$) as compared to patients treated at lowest quartile volume facilities (Q1) [7]. Overall, within the limited body of literature assessing disparities in WM, there have been several independent disparities identified that impact patient outcomes. These observations highlight that careful systemic exploration should be undertaken to understand and effectively reduce these disparities in care to improve outcomes for patients.

There are several limitations within our work to highlight. Firstly, with regards to the patient factors, there is a lack of granular information on important prognostic markers in WM, such as serum beta-2 microglobulin, serum albumin, and serum LDH level available in the NCDB PUF. Thus, we were unable to risk-stratify patients and control for these factors in our analysis. Secondly, although we only included patients who were treated for WM, it's possible that some inappropriately treated patients with smoldering WM were included in our analyses, thereby potentially confounding the results. In addition, given data limitations, we cannot determine which patients presented earlier or later in the disease course, thus there may be an element of lead-time bias that should be considered. Thirdly, we did not have data regarding what specific treatment regimens were utilized and which patients received Bruton tyrosine kinase (BTK) inhibitors within our cohort. Lastly, some of the PUF data, such as education and income, is based on Zip codes. Although these are important socioeconomic markers, it does not assess the individual patient characteristics, which could be different from the surrounding area.

Conclusion

Our results demonstrate that in patients less than 65 years, significant insurance-based disparities exist among patients with WM, and without private insurance, patients have a higher risk of mortality. Attempts should be made to assess how to assure all patients receive the best possible care regardless of their insurance status. Further work is needed to uncover and address such disparities among patients with Waldenström macroglobulinemia.

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Authors contributions

K.L.C and J.P designed this study, analyzed/interpreted the data, and wrote the manuscript. J.P.A, S.M.A, M.A.G, P.K, A.P, S.A., C.B.R, T.E.W, T.M.H, M.Q.L, R.A.K and R.S.G, made significant contributions in interpreting the data and writing the manuscript. All authors provided final approval of the manuscript and are accountable for all aspects of the work.

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