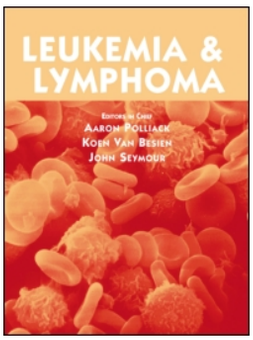

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Treatment facility volume and patient outcomes in Waldenstrom macroglobulinemia

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ABSTRACT

Waldenstrom macroglobulinemia (WM) has an annual incidence of 3–3.2 cases per million-person/year. National Cancer Data Base was used to identify newly diagnosed WM cases requiring initiation of therapy and their annual facility volume was used to divide the treatment facilities into four quartiles (Qs). Cox regression was used to analyze the association between facility volume and survival, adjusted by demographics, socioeconomic, geographic, comorbidity factors and year of diagnosis. A total of 3064 patients treated in 795 facilities were included. The unadjusted median overall survival (OS) by facility volume was: Q1:6.5 years (5-year OS 55%), Q2:7 years (5-year OS 60%), Q3:8 years (5-year OS 64%), and Q4: NR (5-year OS 71%), $p < 0.0001$. Our results demonstrated that a volume–outcome relationship exists in WM and is an independent predictor of overall survival in addition to the established risk factors as age and disease severity.

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Introduction

Waldenstrom macroglobulinemia (WM) is a rare and incurable non-Hodgkin lymphoma characterized by an indolent disease course and representing only 1–2% of all hematologic malignancies. The annual, age-adjusted incidence of 3.0–3.8 cases per million person years translates into approximately 1000–1500 new cases per year in the United States [1–3]. The American Society of Clinical Oncology (ASCO) Workforce Initiative and the National Census of Oncology Practices have estimated that the number of practicing hematologist/oncologist in the US are 12,000–13,000, with 81% being involved in direct patient care as their primary activity and 71% working in a general or combined hematology–oncology practice [4,5]. The low incidence of WM limits the clinical experience that any general hematologist/oncologist may have compared with more commonly seen malignancies.

Correlations between higher volume of care and patient outcomes has been previously described in both the surgical and medical management of various cancers [6–8]. Recently, Go et al. demonstrated an association between initial treatment at a high-volume facility and prolonged long-term survival among patients with multiple myeloma [9]. However, no such data assessing into whether treatment at high-volume centers portends better outcomes in patients with WM exists. The purpose of this study is to determine whether an association between treatment facility volume of new WM cases and survival outcomes exists in a population with this rare hematologic malignancy.

Methods

Patient level data from the National Cancer Database (NCBD) Participant-User File were used. The NCDB, a joint program of the American College of Surgeon's Commission on Cancer (CoC) and the American Cancer Society, is a nationwide, facility-based, cancer outcome data base of approximately 34 million patient records from more than 1500 CoC centers, which accounts for approximately 70% of all newly diagnosed cancer cases in the United States [10]. The

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study was conducted following the Mayo Clinic institutional review board approval.

The patients that are newly diagnosed with WM between the years 2004 and 2014 ($n = 6266$) were identified using the International Classification of Diseases for Onocology-3 code for WM (ICD-O 9761). Patients not requiring treatment (smoldering WM), not receiving at least the frontline treatment at the reporting facility, or with missing follow up date were excluded. This resulted in the final study population of 3064 patients with active WM. Overall survival (OS), which is the primary outcome of interest, was measured from the frontline therapy initiation date rather than time of diagnosis to further remove the impact of any smoldering (asymptomatic) period from the survival analysis.

The treatment facilities were stratified into quartiles (Qs) based on the volume of new WM patients seen annually averaged over the 10-year period of available data (2004–2014). Treatment facility data was extracted and facility type was classified as either academic or nonacademic. Academic medical facilities were defined as those with a postgraduate medical education in at least four program areas including internal medicine and general surgery, evaluating more than 500 newly diagnosed cancer cases each year, offering a full range of diagnostic and treatment services either on-site or by referral and participating in cancer-related clinical research.

The patient-level data regarding age, sex, race, comorbidities, residence, income, education level, distance from treatment facility and insurance status were extracted. Patients older than 90 years at the time of diagnosis of WM were recorded as being 90 years of age for Health Insurance Portability and Accountability Act (HIPPA) compliance. Comorbidity was measured by Charlson Comorbidity Index (CCI) and a summation of weighted scores associated with all the comorbidities were identified by using ICD-9-CM codes in a patient. For the definition of residence, rural was defined as counties with a population $<$ 2500; urban was defined as counties with a population between 2500 and 250,000, and metro as counties with a population of $>$ 250,000. Income was defined as a median household income for each patient's area of residence by matching zip code at time of diagnosis. The education level was defined as the proportion of people with at least a high school degree in the zip code of a patient's residence (Low, $<$79%; Middle-1, 79–87%; Middle-2, 88–93%; High, $\geq$93%). Patients with missing data or were recorded as unknown were removed from the multivariable analysis.

The patient and facility characteristics were described as median and range. The association between the treatment facility volume and survival was analyzed using a proportional hazard fit model and Pearson's Chi-square test adjusting for demographic (age, sex, race/ethnicity), socioeconomic (income, education, insurance type), geography (area of residence, treatment facility type, travel distance), comorbid (Charlson–Deyo score) factors, as well as year of diagnosis to calculate the hazard ratio of survival associated with each factor. Reverse Kaplan–Meier method was used to calculate the median follow-up of the cohorts. Time-to-event analysis from frontline therapy initiation date was analyzed using the Kaplan–Meier method and the log-rank test. Patients alive at the last follow up were censored. A p value of <0.05 was considered statistically significant.

Results

A total of 3064 patients with active WM treated in 795 facilities were identified. Out of 3064 patients, 152 (5%) patients were missing data in one or more risk factor variables and were excluded from the multivariable analysis.

The median age at diagnosis was 70 years (range, 26–90 years), the median overall survival (OS) for the entire cohort was 8 years (95% confidence interval (CI), 7.4–8.4 years) and the median follow-up time from frontline treatment was 4.7 years (95% CI, 4.5–5). The median time from diagnosis to treatment in each facility quartile were: Q1: 19.5 days, Q2: 20 days, Q3 20 days, and Q4 23 days ($p = 0.90$). The majority of the patients were Caucasian (90%), male (60%), lived in metro areas (82%), of moderate to high income (65% – median household income $>$ $48,000 annually), had health insurance (98%) and received treatment at non-academic facilities (50.2%). Seventy-four percent of patients were initially seen and treated within 20 miles of their residency zip-code.

The median patient volume across all facilities was 1 new WM patient per year (range 0.1–21.5). Q1 facilities treated $<$0.5 new WM cases/year ($<$1 new WM case every other year), Q2 facilities treated 0.5–1 new WM case/year, Q3 facilities treated between 1 and 2 new WM cases/year and Q4 facilities treated $>$ 2 new WM cases/year. High quartile facilities (Q3 & Q4) were more likely to be academic (71%) compared to lower quartile (Q1 &2) facilities (28%, $p < 0.001$). The patients seen at higher-quartile facilities were more likely to live in metro areas (85% versus 79%, $p < 0.001$), have

private insurance (55% versus 45%, $p = 0.001$), live in areas with higher median income (43% versus 32%, $p < 0.001$) and higher education level (37% versus 27%, $p < 0.001$) compared to the lower quartile facilities. The patients receiving care at high quartile facilities were more likely to travel >20 miles (32%) compared to patients seen at lower quartile facilities (20%, $p < 0.001$). There was no statistically significant difference among the different quartile facilities for racial/ethnic background or the age at diagnosis. The quartile specific patient characteristics are summarized in Table 1.

The estimated unadjusted 5-year OS for Q4 to Q1 facilities were 71%, 64%, 60%, and 55% respectively ($p < 0.0001$). Figure 1(A) depicts the unadjusted OS by facility volume. A multivariable analysis including demographic, socioeconomic, geographic and comorbid factors, and the year of diagnosis demonstrated that facility volume was independently associated with all-cause mortality (Table 2). Compared with Q4 facilities, the adjusted hazard ratios (HR) for Q3 was 1.13 (95% CI, 0.92–1.38, $p = 0.25$), Q2 was 1.40 (95% CI, 1.17–1.72, $p = 0.001$) and Q1 was 1.50 (95% CI, 1.18–1.88, $p < 0.001$). The age at diagnosis, comorbidities and insurance status were also independently associated with all-cause mortality (Table 2).

To further explore the effect of the treatment facility volume on OS in a more homogenous patient population, we next analyzed the outcomes of patients treated only at the Q4 facilities. These patients were divided into two subgroups based on the treatment facility annual volume of new WM cases: top 10% facilities (or >90 percentile) versus top 25–10% (or percentile 75–90) facilities. Top 10% facilities were those treating >3.2 new WM cases/year, while the top 25% to >10% facilities were those treating between 2 and 3.2 new WM cases/year.

Table 1. Characteristics of patients according to treatment facility volume quartile.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-value
Patients/year, *n*	<0.5	0.5–1	1–2	>2	
Facilities, *n* (%)	391 (49)	246 (31)	110 (14)	48 (6)	
Age, median (range)	70 (30–90)	70 (28–90)	71 (26–90)	70 (28–90)	0.38
Sex, male (%)	57	61	62	60	0.18
Race (%)					0.08
White	92	92	93	94	
African-American	7	6	6	3.5	
Native-American	0.2	0	0.1	0.3	
Asian	1.8	2	0.9	2.2	
Comorbidity index (%)					0.02
Charlson Score 0	78	79	79	83	
Charlson Score 1	16	16	16	14	
Charlson Score ≥2	6	5	5	3	
Residence (%)					<0.001
Metro	76	80	85	86	
Urban	22	17	14	13	
Rural	2	3	1	1	
Median annual household income (%)					<0.001
≥$63,000	27	36	39	46	
$48,000–$62,999	31	27	26	28	
$38,000–$47,999	25	25	21	18	
<$38,000	17	12	14	8	
Education (%)					<0.001
High	20	31	34	41	
Middle-2	36	37	35	35	
Middle-1	28	21	20	18	
Low	16	11	11	6	
Insurance status (%)					<0.001
Private insurance	27	34	34	41	
Government insurance	66	62	62	56	
No insurance	4	2	2	2	
Other	3	2	3	1	
Treatment facility (%)					<0.001
Academic	18	36	58	84	
Nonacademic	82	64	42	16	
Distance to treatment facility (%)					<0.001
>20 miles	18	21	26	39	
9–20 miles	26	26	29	24	
4–9 miles	25	26	23	21	
< 4 miles	31	27	22	16	
Year of diagnosis (%)					0.13
2004–2008	34	36	40	39	
2009–2011	30	29	28	25	
2011–2014	36	35	32	36	

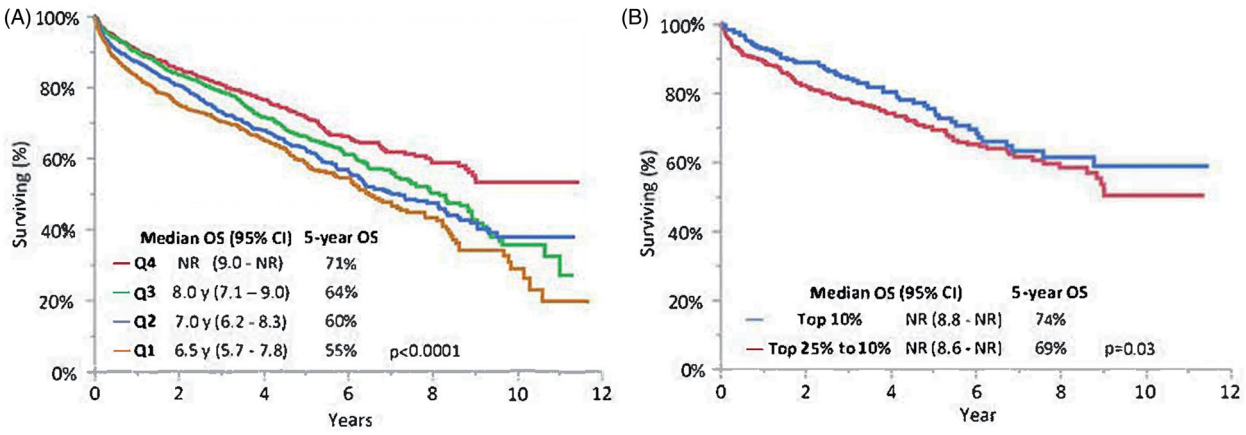

Figure 1. (A) Unadjusted overall survival change by facility volume. The estimated 5-year OS was 71%, 64%, 60%, and 55% for Q4–Q1 facilities, respectively ($p < 0.0001$). (B) Q4 subgroup analysis demonstrating the unadjusted overall survival by facility volume. The estimated 5-year OS was 74% for the top 10% compared to 69% for the top 25–10% ($p = 0.03$).

Table 2. Variables included in the multivariable analysis for survival for Q1–Q4 facilities.

Variables	Hazard ratio	95% CI	*p*-value
Facility volume (reference: quartile 4)			0.001
-Quartile 1	1.5	1.18–1.88	
-Quartile 2	1.4	1.17–1.72	
-Quartile 3	1.13	0.92–1.38	
Age			<0.001
-Per year	1.05	1.04–1.06	
Sex (reference: male)			0.05
-Female	0.87	0.76–0.99	
Race (reference: White)			0.08
-African-American	1.06	0.78–1.44	
-Native-American	2.15	0.52–8.81	
-Asian	1.98	1.17–3.33	
Comorbidity index (reference: score of 0)			<0.001
-Score 1	1.73	1.46–2.04	
-Score ≥ 2	2.01	1.56–2.58	
Residence area (reference: metro)			0.77
-Urban	1.07	0.87–1.32	
-Rural	1.05	0.64–1.72	
Median annual household income (reference: ≥$63,000)			0.21
-$48,000–$62,999	1.19	0.98–1.44	
-$38,000–$47,999	1.21	0.98–1.51	
-<$38,000	1.25	0.96–1.63	
Education (reference: high)			0.12
-Middle-2	1.16	0.96–1.4	
-Middle-1	1.30	1.04–1.63	
-Low	1.28	0.97–1.69	
Insurance status (reference: private insurance)			0.01
-Government insurance	1.31	1.07–1.59	
-No insurance	1.50	0.91–1.47	
-Other	1.76	1.16–2.67	
Facility type (reference: academic)			0.19
-Nonacademic	0.90	0.77–1.05	
Distance to treatment facility (reference: >20 miles)			0.16
−9–20 miles	1.02	0.83–1.26	
−4–9 miles	1.10	0.89–1.36	
-< 4 miles	1.23	0.99–1.52	
Year of diagnosis (reference: 2004–2008)			0.05
−2009–2011	0.93	0.77–1.12	
−2011–2014	0.75	0.62–0.91	

When comparing the top 10% facilities with the top 25–10% facilities, there was a higher proportion of academic facilities in the top 10% group (88% versus 80%, $p = 0.0009$). Patient treated at a top 10% facility were more likely to travel farther, with 48% living >20 miles from the treatment facility compared to 31%, $p < 0.001$ and more likely to be at the top tier of median household income (51% versus 42%, $p = 0.01$). There were no differences related to patients' age, sex, race, comorbidity index, area of residency, education level, insurance status or the year of diagnosis.

Table 3. Variables included in the multivariable analysis for survival for top 10% and top 25–10% facilities.

Variables	Hazard ratio	95% CI	*p*-value
Facility volume (reference: top 10%)			0.04
-Top 25–10%	1.37	1.0–1.87	
Age			<0.001
-Per year	1.06	1.04–1.07	
Sex (reference: male)			0.49
-Female	1.10	0.82–1.48	
Race (reference: White)			0.46
-African-American	1.04	0.39–2.7	
-Native-American	4.99	0.6–41.3	
-Asian	2.17	0.84–5.6	
Comorbidity index (reference: score of 0)			<0.001
-Score 1	1.84	1.24–2.74	
-Score ≥ 2	3.34	1.7–6.54	
Residence area (reference: metro)			0.52
-Urban	1.35	0.81–2.25	
-Rural	1.21	0.35–4.16	
Median annual household income (reference: ≥$63,000)			0.49
-$48,000–$62,999	0.79	0.53–1.17	
-$38,000–$47,999	0.80	0.5–1.3	
-<$38,000	0.64	0.33–1.22	
Education (reference: high)			0.009
-Middle-2	1.57	1.08–2.28	
-Middle-1	2.30	1.39–3.79	
-Low	1.98	1.02–3.85	
Insurance status (reference: private insurance)			0.07
-Government insurance	1.23	0.85–1.79	
-No insurance	0.60	0.13–2.61	
-Other	3.96	1.49–10.4	
Facility type (reference: academic)			0.20
-Nonacademic	1.26	0.88–1.83	
Distance to treatment facility (reference: >20 miles)			0.33
−9–20 miles	1.05	0.67–1.64	
−4–9 miles	1.15	0.73–1.79	
-< 4 miles	1.48	0.94–2.33	
Year of diagnosis (reference: 2004–2008)			0.01
−2009–2011	0.62	0.45–0.86	
−2011–2014	0.62	0.32–1.2	

In the subgroup analysis comparing the top 10% versus top 25–10% of facilities, the estimated 5-year OS was 74% for the top 10% compared to 69% for the top 25–10% ($p = 0.03$). Figure 1(B) illustrates the unadjusted overall survival of the top 10% facilities compared to top 25–10% facilities. The multivariable analysis including the same variables as above demonstrated that facility volume remained independently associated with all-cause mortality. The adjusted HR for the top 25–10% of facilities was 1.37 (95% CI, 1.0–1.87, $p = 0.04$) as compared to the top 10% facilities (Table 3).

Discussion

Our study identified a volume–outcome relationship between a facility's annual median volume of new WM patients and all-cause mortality. Compared to the patients treated at high-volume treatment facilities, those treated at lower-volume facilities had a higher incremental risk of death, even after adjusting for socioeconomic and geographic factors, comorbidities, and the year of diagnosis. The risk of death was 50% higher in the lowest quartile facilities (<0.5 new WM cases/year) compared to the top quartile facilities (>2 new WM cases/year). Even when considering only the top quartile facilities, an increased risk of death was noted in the subgroup analysis comparing the Top 10% facilities (>3.2 new WM cases/year) to remaining facilities (2–3.2 new WM cases/year), suggesting the lack of an obvious plateau in the volume-outcome relationship.

These findings are in agreement with that of similar studies conducted for other uncommon hematological malignancies such as non-Hodgkin lymphoma (NHL) and chronic myeloid leukemia (CML) [11,12]. A study by Goa et al. on patients with NHL has demonstrated that OS could vary significantly; 61.8–83.6 months from the lowest volume facilities to higher volume facilities ($p < 0.001$) [11]. This facility volume effect has been well studied in oncologic surgery as reported in a systematic analysis showing that one additional volume-associated perioperative death per year can be prevented by moving 10–50 patients from 'low'

volume to 'high' volume facilities depending on the cancer type [13]. Furthermore, a subgroup analysis in our study considering the top quartile (Q4) facilities has further demonstrated that differences exist even among high-volume facilities.

The median OS of 8 years and the median age at diagnosis of 70 years found in our study were in line with that reported in the current literature [3,14]. Importantly, the disease course of WM is such that those with smoldering (asymptomatic) disease have mortality similar to that of the general population while those with active (symptomatic) disease have mortality approximately five times higher [15,16]. Therefore, survival in WM is best measured from the time of initiation of treatment which is limited to the symptomatic patients, denoting a more active disease status. In addition, we demonstrated that similar time period from diagnosis to treatment initiation was seen among facility quartiles, hence, significantly minimizing the impact of lead-time bias. The similar overall outcomes seen in our cohort in comparison with other published studies of active WM outcomes suggests that the influence of smoldering WM in our study, if any, was greatly minimized by using initiation of therapy for survival analysis [3,14].

Numerous factors could influence the volume–outcome relationship observed. With an incidence as low as 0.03 per 100,000 persons per year [1], physician familiarity with this disease management could be limited. A survey carried out in The Netherlands among hematologist/oncologist found several disparities in the treatment of WM as well as identifying and preventing 'IgM flares' [17]. Similarly, physician familiarity of the disease and physician specialization has been demonstrated to influence the patient outcome in many conditions. Newly diagnosed chronic lymphocytic leukemia (CLL) patients were studied by Shanafelt et al. who showed that those patients treated by CLL-specialized hematologists had longer time-to-first-treatment (TTFT) and a better OS than those treated by non-CLL-specialized hematologist even after adjustment for age, sex, stage of the disease and lymphocyte count at diagnosis (median TTFT 9.2 versus 6.1 years; $p < .001$ and OS 10.5 years versus 8.8 years; $p < 0.001$) [18].

Another element that may impact the superior outcomes seen in higher volume facilities is the likelihood that these are comprehensive or academic centers where patients have access to more practice disciplines that can positively contribute to the multidisciplinary management of WM. Due to the indolent nature of the disease, patients with WM are more likely to have a non-WM related death than WM related death [14,19]. Therefore, the management of the comorbidities and complications likely plays an important role in the overall survival of these patients. The importance of a multidisciplinary approach in such situations has been well demonstrated [20,21].

Several socioeconomic factors (i.e. private insurance and estimated higher median household income and education level) were associated with higher-volume facilities in our study, with an overall incremental change from Q1 to Q4 facilities. These factors have been previously shown to influence cancer patients' outcomes as they have an increased access to health care as the common denominator [22,23]. However, the volume–outcome relationship remains an independently associated variable to mortality in our study after adjustment for these factors. In addition to that, our study is strengthened by having a rather large cohort of a rare disease using patient-level data from a nation-wide registry. Furthermore, our study incorporates heterogeneous treatment strategies that are used in the US, thereby resembling the real world practice.

Our study is not without limitations. The NCDB does not include data related to subsequent treatments; therefore the referral patterns after initial therapy cannot be evaluated. However, the outcome of each patient is tied to the facility of initial reporting/patient encounter and only patients treated at the reporting facility were included in our analysis. Therefore, even if a patient was later referred to a high-volume treatment facility for subsequent management, that patient's outcome would be tied to the initial low-volume facility, only minimizing the significant difference reported in our study. Additionally, the impact of the treating-physician's experience with WM could not be assessed, but only facilities as a whole. Underlying disease biological factors, such as laboratory parameters at the time of diagnosis or treatment as the level of hemoglobin, platelet count, M protein level or LDH level, and those included in the International Prognostic Scoring System for WM, known to be associated with outcomes in WM could not be evaluated [24]. Hence, this is a limitation of our study. However, notwithstanding these limitations, with the same follow-up time, our study showed a survival difference among facility quartiles and facility volume as an independent risk factor in predicting survival. Furthermore, an insight in to the exact treatment regimens used would have shed light on the disparities of treatment among facilities. The evaluation of the patterns of disease complications and

treatment along with the specific cause of death could also have demonstrated areas for improvement.

Conclusion

Our results demonstrated that a volume–outcomes relationship does exist in WM as patients initially treated at higher-volume facilities had a lower risk of mortality. Even though WM shares some similarities with other hematologic malignancies, its evaluation and management is not only unique, but has changed significantly over the last several years [25]. As with other rare malignancies, a collaborative co-management between the treating physician and a WM-specialized hematologist may yield better patient outcomes.

Author contributions

Conceptualization and methodology: JP; Data curation and analysis: MDSKG, AJS, JPA; Writing- original draft: MDSKG, AJS, JP; Writing- review and editing: JPA, SMA, MAG, PK, AP, SA, CBR, TEW, TMH, AJN, MQL, RAK, RSG.

Disclosure statement

The authors report no conflict of Interest.

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