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The Unmet Need in Chronic Lymphocytic Leukemia: Impact of Comorbidity Burden on Treatment Patterns and Outcomes in Elderly Patients*

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ABSTRACT

Introduction: Chronic lymphocytic leukemia (CLL) is a disease of the elderly. Elderly patients often have increased comorbidity burden and loss of organ reserve that may impact their ability to tolerate cancer therapy. We described real-world characteristics of typical CLL patients and identified factors predictive of receiving treatment. **Methods:** A retrospective cohort analysis of 8343 first primary CLL patients was performed using the linked Surveillance, Epidemiology, and End Results-Medicare database. Patients were diagnosed from 1/1/1998 to 12/31/2007, >66 years, and continuously enrolled in Medicare Parts A and B in the year prior to diagnosis. Comorbidity was examined using the National Cancer Institute comorbidity index and the Cumulative Illness Rating Scale. Cox and Logistic regression modeling assessed patient characteristics predictive of receiving treatment within the first year after diagnosis. **Results:** Median follow-up time from diagnosis was 782 days. During the study time period, there were 3366 (40%) treated patients and 4977 (60%) untreated. Even among those diagnosed with advanced stage (n = 4213), 57% were not treated. Treated patients were younger at diagnosis compared to untreated (76 vs. 79; $p < 0.0001$). In general, as age increased, the incidence and severity of comorbidities increased. In multivariate regression analyses, the treatment rate was significantly lower among patients >80 years, females, and with early stage disease; and significantly decreased with increasing comorbidity burden. **Conclusions:** Age, gender, comorbidity and stage were predictive of receiving treatment. Among patients with advanced stage, 57% were not being treated possibly due to older age and/or higher comorbidity burden.

Keywords: Chronic Lymphocytic Leukemia; Elderly Patients; Comorbidities; Treatment; Survival

1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia diagnosed in older adults [1-3], with 68% of new cases diagnosed in individuals 65 years or older and median age at diagnosis of 72 years [3,4]. Elderly patients are frequently compromised by concurrent pathologic conditions and/or physiological decline of major organ systems; little is known about the spectrum or frequency of comorbidities in CLL patients. Loss of organ reserve and the comorbidities associated with aging are considered important determinants of patients' ability to tolerate the side effects of cancer therapy [5]. However, the majority of CLL clinical trials primarily enroll younger patients who are otherwise in good health and are better able to tolerate treatment-related adverse events [6-9], and this makes optimal treatment strategies and disease management unclear for typical patients.

Both age and comorbidities are significantly associated with the prognosis of patients with CLL, with older age being one of the most significant predictors of overall survival [6,10]. Fludarabine, cyclophosphamide, and rituximab (FCR) is considered the gold standard first-line treatment for physically fit CLL patients [6,11], but those with comorbid conditions may receive alternative therapies or a chemotherapy dose reduction in the FCR regimen [12-14].

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Given that elderly, unfit CLL patients have more limited treatment options, the goal of this study was to understand the unmet need in a real-world elderly (age-eligible for Medicare) cohort of patients. First, we characterized who received treatment in terms of demographic and clinical characteristics, including comorbidities. Second, we evaluated the patient factors associated with the likelihood of receiving treatment.

2. Methods

2.1. Data Sources

We utilized population-based claims data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Institutional review board approval was waived due to the absence of personal identifiers in the SEER-Medicare database. As described elsewhere [15], this database provides information on Medicare patients included in SEER, a nationally representative collection of 18 population-based registries of all incident cancers from diverse geographic areas covering approximately 26% of the United States population. All incident cancer patients who are reported to the SEER registries are cross-matched with a master file of Medicare enrollment [16]. Approximately 97% of individuals 65 years or older are eligible for Medicare and receive Part A coverage for inpatient care, skilled nursing care, home healthcare, and hospice care. Approximately 95% of beneficiaries also subscribe to Part B, which covers physician services and outpatient care [17]. The SEER-Medicare linkage includes all persons eligible for Medicare who were reported to the SEER database through 2007 and their Medicare claims for inpatient services covered under Part A and outpatient and physician services covered by Part B through 2009.

2.2. Study Population

Patients eligible for this study were 1) diagnosed with a first primary CLL from January 1, 1998 to December 31, 2007, 2) age 66 years or older at diagnosis, and 3) continuously enrolled in Medicare Part A and B during the 12 months prior to diagnosis. Patients were excluded if their date of death was recorded prior to or during the same month as the month of diagnosis, if they were enrolled in a health maintenance organization (HMO) at any time during the 12 months prior to diagnosis (because data were unavailable for these periods), and if there was documentation of 2 or more claims for chemotherapy prior to their diagnosis of CLL (to ensure that they were previously untreated).

2.3. Study Variables

Registries reporting to the SEER program routinely collect data on: patient demographics (age, race/ethnicity, residence, and socioeconomic status based on income and education per census tract); primary tumor site, tumor morphology, and stage at diagnosis; first course of treatment; and follow-up for vital status. Median annual household income at the census tract level and the percentage of the population who completed specific levels of education at the ZIP code level were used as a proxy for socioeconomic status. The SEER site code was used to identify patients with a diagnosis of CLL. The SEER database does not provide stage at diagnosis for CLL. Based on the Rai and Binet staging systems for CLL [18, 19], we created a proxy for stage at diagnosis by classifying patients as "advanced stage disease" if anemia and/or thrombocytopenia were present in the claims database [20].

To identify treated patients, claims for chemotherapy and immunotherapy administration [21], data were abstracted from 5 merged SEER-Medicare files including Medicare provider analysis and review (MEDPAR), carrier claims (NCH), outpatient claims (OUTSAF), durable medical equipment (DME), and prescription drug event (PDE) files. In July 2006, Medicare coverage was expanded to include prescription drugs under Medicare Part D. Chlorambucil is covered by Medicare Part D and data for its use were only available from 2007 to 2009 in the PDE file. Chemotherapy and immunotherapy was characterized and quantified using International Classification of Disease (ICD) diagnosis codes, ICD procedural codes, Current Procedural Terminology (CPT) codes, Healthcare Common Procedure Coding System (HCPCS) codes, and revenue center codes. We searched claims for specific drug codes to identify the type of chemotherapy or immunotherapy used. The absence of these claims was interpreted as lack of treatment while the first chemotherapy/immunotherapy claim following the date of diagnosis indicated the start of therapy.

The National Cancer Institute (NCI) comorbidity index [22] was calculated for each patient using diagnosis and procedure codes in the Medicare Parts A and B claims files to identify the 15 non-cancer comorbidities from the Charlson Comorbidity Index (CCI) [23]. A weight is assigned to each condition based on its potential influence on 2-year mortality, and the weights are summed to obtain a comorbidity index for each patient. The CCI accounts for the number and severity of the conditions with higher scores indicating a greater burden of comorbid disease.

Comorbidity was also examined using the organ systems in the Cumulative Illness Rating Scale (CIRS) [24, 25]. The CIRS uses physician ratings of the degree of pathology and impairment in 14 major organ groups. Disease severity data were not available in this claims-based analysis to calculate the total CIRS score. There-

fore, we used diagnosis codes in the Medicare Parts A and B claims files to identify specific conditions that belong to each organ system category, and calculated the "number of involved organ systems" (CIRS-SYS) for each patient.

The CCI and the CIRS are among the most valid and reliable measures of multi-morbidity [26]. For both co-morbidity definitions, Medicare claims during the year prior to diagnosis were used to determine the baseline comorbidity burden for each patient. Specific conditions must have appeared on at least 2 different claims that were more than 30 days apart to ensure that "rule out" diagnoses were not counted as comorbid conditions.

The date of death was assigned by using the Medicare date or SEER date of death if the Medicare date was missing. All other patients were assumed to be alive at the end of the follow-up period on December 31, 2009, although they may have been censored earlier for other reasons such as development of a second primary cancer or Medicare claims data no longer available.

2.4. Statistical Analysis

All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc., Cary, North Carolina). Using the frequency procedure in SAS, we examined the distribution of patient demographic and clinical characteristics by treatment status for all CLL patients and a subset of patients diagnosed at advanced stage. Differences by treatment status were assessed using Chi-square tests for categorical variables and analysis of variance (ANOVA) or t-tests for continuous variables. We used two methods to determine the predictors of receiving treatment within the first year after diagnosis. The Cox Proportional Hazards regression modeled time to treatment and the logistic regression modeled the odds of receiving treatment. Predictor variables in the models were selected from demographic and clinical characteristics. Kaplan-Meier survival curves and corresponding log-rank tests were generated to determine unadjusted OS by comorbidity burden. Follow-up was calculated from the date of diagnosis up until the first occurrence of a censoring event including date of death, development of a second primary tumor, the last date for which Medicare claims were available, or the end of the follow-up period (December 31, 2009). Differences with a probability of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Demographic & Clinical Characteristics

Of the 8343 CLL patients who met all the study eligibility criteria, the mean age at diagnosis was 78, with 57% of the cohort age 75 years or older. The majority were male (54%) and white (92%). There were 3366 (40%) patients who received treatment and 4977 (60%) who never received treatment during follow-up. The mean age at diagnosis was 76 for those administered treatment compared with 79 in the untreated group ($p < 0.0001$). Patients older than 80 years comprised 40% of the untreated cohort compared with 23% in the treated cohort. Treated patients were more likely to present with advanced stage (65%) than those who were not treated (48%).

Approximately half of all CLL patients were diagnosed with advanced disease (n = 4213). There was a slightly higher mean age at diagnosis (79 years) in this subset compared to all CLL patients. Of patients who were diagnosed with advanced disease 1805 (43%) received treatment while 2408 (57%) did not. Similar to the overall treated population, patients with advanced disease who received treatment were also more likely to be younger (77 vs 80 years; $p < 0.0001$) and male (57% vs 49%; $p < 0.0001$). (**Table 1**)

3.2. Comorbidity Burden

Treated patients were generally healthier than those who were not treated as indicted by the lower NCI comorbidity scores and number of CIRS organ systems affected ($p < 0.0001$; **Table 1**). As age increased, the incidence and severity of comorbidities as assessed by both the NCI and CIRS-SYS comorbidity scores increased (**Figure 1**). Among patients in the highest comorbidity categories (CIRS-SYS ≥ 4 and NCI Score ≥ 3), 39% to 43% respectively were > 80 years old.

More than half of the patients had comorbidities involving the Blood Pressure System, followed by 44% of patients with comorbidities related to the Vascular System and/or the Heart System (**Table 2**). In general, treated patients had fewer affected organ systems compared to untreated patients. Patients with advanced disease had higher rates of affected organ systems compared to the general CLL population. The most common spe-

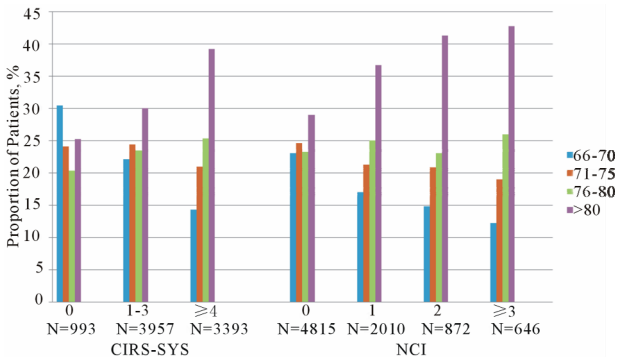

Figure 1. Comorbidity burden by age at diagnosis.

Table 1. Demographic and clinical characteristics at baseline.

Characteristics	Total (N = 8343)	All CLL			Advanced Stage		
		Treated (N = 3366)	Not Treated (N = 4977)		Treated (N = 1805)	Not Treated (N = 2408)	
Age at Diagnosis	%	%	%	*P*-value	%	%	*P*-value
66 - 70	19.9	23.4	17.5	<0.0001	19.0	12.5	<0.0001
71 - 75	23.0	27.0	20.2		23.6	16.6	
76 - 80	23.9	26.6	22.1		29.0	22.1	
>80	33.2	22.9	40.1		28.4	48.9	
Sex							
Male	54.2	58.3	51.4	<0.0001	56.8	49.3	<0.0001
Female	45.8	41.7	48.6		43.2	50.7	
Race/ethnicity							
White	92.4	91.8	92.8	0.1090	90.5	91.0	0.6177
Non-white	7.6	8.2	7.2		9.5	9.0	
Stage*							
Non-advanced	49.5	46.4	51.6	<0.0001			
Advanced	50.5	53.6	48.4				
CIRS-SYS							
0	11.9	12.7	11.4	<0.0001	10.0	6.4	<0.0001
1 - 3	47.4	50.7	45.2		44.7	38.2	
≥4	40.7	36.6	43.4		45.3	55.4	
NCI Comorbidity Score							
0	57.7	61.4	55.2	<0.0001	54.4	45.5	<0.0001
1	24.1	23.3	24.6		25.0	26.5	
2	10.5	9.1	11.4		11.2	13.9	
≥3	7.7	6.2	8.8		9.4	14.1	

Abbreviations: CIRS-SYS, number of organ systems involved in the Cumulative Illness Rating Scale; NCI, National Cancer Institute; Note: *Advanced stage disease was approximated by the presence of anemia and/or thrombocytopenia in the claims data.

cific comorbidities were hypertension (53%), hyperlipidemia (38%), coronary artery disease (24%), diabetes (21%), and osteoarthritis (21%), and these rates were higher for advanced stage patients compared to the general CLL population, and in the untreated subgroups (**Supplementary Table 1**). In the unadjusted overall survival analysis, as CIRS-SYS and NCI comorbidity scores increased, unadjusted overall survival decreased (log rank $p < 0.0001$; **Figure 2**).

In patients diagnosed with advanced disease, treated patients had lower NCI and CIRS-SYS comorbidity scores (**Table 1**) and a lower proportion of each type of CIRS organ system involved (**Table 2**) compared with untreated patients.

3.3. Predictors of Treatment

In the Cox multivariate regression analysis of time to treatment within the first year after diagnosis (**Table 3**), the treatment rate was significantly lower among patients >80 years old (HR = 0.51; 95% CI = 0.46 - 0.56) and among females (HR = 0.86; 95% CI = 0.80 - 0.92). The treatment rate significantly decreased with higher CIRS-SYS. In a sensitivity analysis, the models were virtually unchanged when replacing CIRS-SYS with NCI comorbidity score. Compared to patients diagnosed at an earlier stage disease, advanced stage patients had a significantly higher treatment rate (HR = 1.47; 95% CI = 1.37 - 1.58). Findings from the logistic regression analysis of treatment within the first year after diagnosis were generally consistent with those from the Cox regression analysis.

4. Discussion

This observational study revealed that about 60% of all CLL patients are not receiving treatment for their disease.

Table 2. Cumulative illness rating scale organ system type by treatment status.

Organ System	Total (N = 8343)	All CLL			Advanced Stage		
		Treated (N = 3366)	Not Treated (N = 4977)		Treated (N = 1805)	Not Treated (N = 2408)	
	%	%	%	*P*-value	%	%	*P*-value
Blood Pressure	53.1	51.0	54.5	0.0017	68.6	74.4	<0.0001
Vascular	44.4	43.4	45.1	0.1360	67.0	67.1	0.9523
Heart	43.9	40.8	45.9	<0.0001	63.8	71.3	<0.0001
Endocrine/Metabolic	31.1	28.8	32.7	0.0002	46.5	50.7	0.0061
Genitourinary	29.6	29.8	29.6	0.8350	49.0	54.2	0.0009
Musculoskeletal	29.1	27.0	30.6	0.0004	43.5	52.2	<0.0001
Respiratory	21.0	19.9	21.7	0.0482	39.1	41.6	0.1081
Neurological	16.9	13.0	19.6	<0.0001	24.0	36.1	<0.0001
Upper GI	12.4	12.3	12.4	0.8197	27.5	28.4	0.5143
Lower GI	10.7	10.1	11.1	0.1727	26.6	28.4	0.2178
Psychiatric	9.5	5.2	12.4	<0.0001	11.2	26.9	<0.0001
Ear/Nose/Throat	6.6	7.3	6.1	0.0365	12.4	10.3	0.0316
Renal	5.7	4.3	6.7	<0.0001	13.2	18.8	<0.0001
Liver	2.3	2.3	2.2	0.7258	10.1	8.8	0.1727
No CIRS Comorbidity	11.9	12.7	11.4	0.0691	2.0	0.7	0.0001

Abbreviations: CLL, chronic lymphocytic leukemia; GI, gastrointestinal.

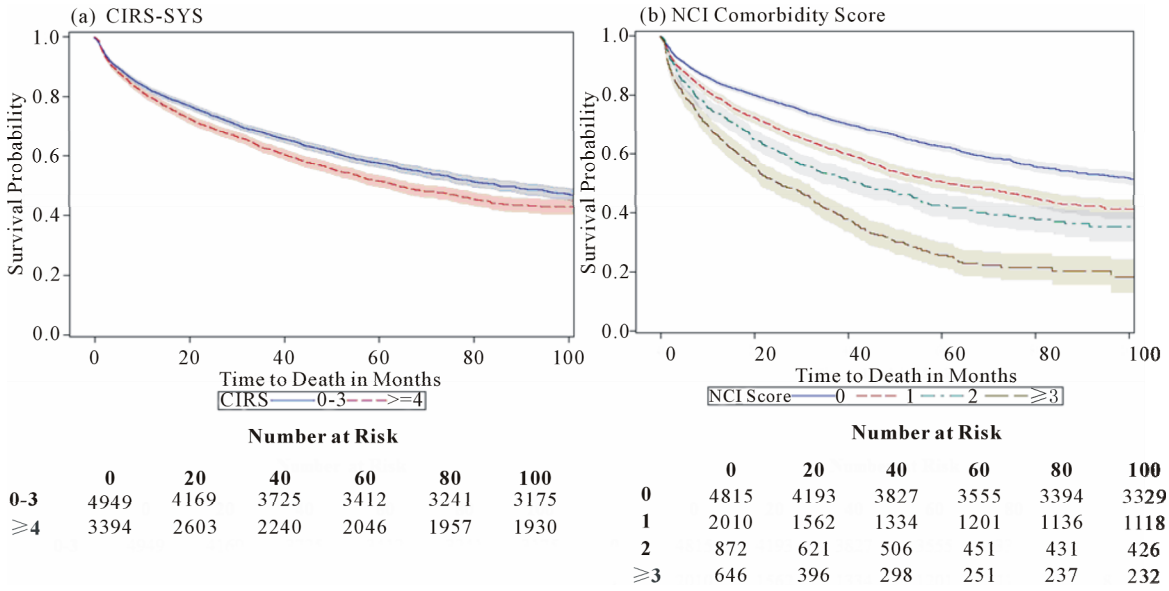

Figure 2. Unadjusted overall survival by comorbidity burden.

This high non-treatment rate may be partly explained by the "watch and wait" strategy for asymptomatic disease. Historically, patients with low- or intermediate-risk early stage disease are managed with active surveillance (watch and wait) while treatment is indicated for patients with advanced disease [2,27]. However, understanding the intent of treatment or no treatment is a challenge with claims-based investigations. In our study, we used "advanced stage disease" as an indicator of higher risk status and thus likely eligibility for treatment, making the high non-treatment rate (57%) in this subgroup noteworthy. The high proportion of advanced stage patients who went untreated may be explained by the medical fitness of patients. This is evidenced by the slightly older at diag-

Table 3. Multivariate analysis of treatment within the first year after diagnosis.

Characteristics	N	Cox Model of Time to Treatment		Logistic Regression of Treatment	
		HR	95% CI	OR	95% CI
Age at Diagnosis					
66 - 70 (ref)	1661				
71 - 75	1917	1.00	0.91 - 1.10	1.06	0.90 - 1.25
76 - 80	1996	0.91	0.83 - 1.01	0.97	0.83 - 1.15
>80	2769	0.51	0.46 - 0.56	0.62	0.53 - 0.73
Sex					
Male (ref)	4521				
Female	3822	0.86	0.80 - 0.92	0.76	0.68 - 0.86
Race/ethnicity					
Non-White (ref)	632				
White	7711	0.96	0.85 - 1.09	1.02	0.83 - 1.27
Stage*					
Non-advanced (ref)	4130				
Advanced	4213	1.47	1.37 - 1.58	2.29	2.04 - 2.58
CIRS-SYS					
0 (ref)	993				
1 - 3	3957	0.97	0.87 - 1.08	0.64	0.55 - 0.77
≥4	3393	0.79	0.70 - 0.88	0.56	0.47 - 0.67
Geographic region					
MidWest (ref)	1077				
Northeast	533	1.07	0.90 - 1.27	0.94	0.72 - 1.25
South	3760	1.08	0.97 - 1.21	0.95	0.80 - 1.13
West	2973	1.06	0.95 - 1.19	0.91	0.78 - 1.10
Median Income Quartiles					
1-Low (ref)	2166				
2	2059	1.06	0.96 - 1.17	1.09	0.93 - 1.29
3	2061	1.12	1.02 - 1.24	1.15	0.99 - 1.36
4-High	2057	1.12	1.01 - 1.23	1.12	0.96 - 1.33

Abbreviations: CIRS-SYS, number of organ systems involved in the Cumulative Illness Rating Scale; Note: *Advanced stage disease was approximated by the presence of anemia and/or thrombocytopenia in the claims data.

nosis and/or higher comorbidity burden in advanced stage patients compared to all CLL patients. Although our multivariate regression models confirmed that advanced stage patients had a 47% higher likelihood of receiving treatment compared to patients with non-advanced disease; both older age and higher comorbidity were significant independent predictors of decreased likelihood of receiving treatment and appear to carry more weight, rather than disease stage, in clinicians' decisions to treat.

Major comorbidities were evident in 42% of the patients based on the NCI comorbidity index while 41% had multiple comorbidities involving at least 4 organ systems according to the CIRS. The frequency of comorbidities in our analysis is comparable to the rate of 46% reported by Thurmes and colleagues in an analysis of 1195 patients newly diagnosed with CLL at the Mayo Clinic from 1995 to 2006 [10]. The median age at diagnosis in that study was 68 years compared to 77 in the current study. In the current analysis, a simple count of affected organ systems based on the CIRS revealed at least one coexisting medical condition (regardless of severity) for 88% of patients. This was also consistent with the 89% of patients with at least one coexisting medical condition reported by Thurmes and colleagues [10].

The CIRS has been utilized as a tool for some clinical

investigators in order to identify patients with coexisting medical conditions that might influence the efficacy and safety of treatment [28].

Importantly, among patients in the highest comorbidity categories (CIRS-SYS ≥ 4 and NCI Score ≥ 3), 39% to 43% respectively were >80 years old. We found that higher comorbidity was associated with decreased unadjusted overall survival. However, this finding may be confounded by the fact that the presence of comorbidities may have resulted in the decision to withhold treatment due to tolerability concerns; and this lack of treatment may have contributed to the lower overall survival.

Patient preferences, physicians' tendencies to treat patients according to chronologic age and lack of evidence-based guidelines for treating elderly patients are cited as factors that lead to under-treatment [29]. There is a great need in CLL to evaluate efficacy and safety of treatment in trials that include more elderly patients so that treatment strategies for elderly patients can be better supported by clinical trial results.

Study Strengths and Limitations

This study has several strengths, including the large sample size from the SEER-Medicare database, a population-based registry that includes a wide geographic representation of patients with a diagnosis of CLL in the United States. The database includes information about inpatient and outpatient claims, covered services, all claims regardless of residence or service area, and longitudinal data with claims for services from the time a person is eligible for Medicare until the date of death. However, use of the SEER-Medicare data for this type of analysis has some limitations, particularly for determining accurate utilization rates of oral chemotherapy. Medicare claims data more accurately identify agents that are intravenously administered since oral agents are covered under Medicare Part D [30] and it is estimated that only 53% of Medicare beneficiaries with cancer were enrolled in Medicare Part D in 2009 [31]. Incomplete enrollment in Medicare Part D may be a factor that contributed to our finding of low treatment rates due to the lack of treatment information for patients who only received oral agents or who may have received these oral treatments prior to their coverage from Medicare Part D.

The SEER registry does not collect staging information for leukemia. We included claims for anemia and/or thrombocytopenia as a surrogate for advanced stage and this may not adequately assess stage for all patients in our study. Also, the use of anemia as a marker of disease severity may be subject to bias as there may be multiple causes of anemia in elderly patients, such as renal impairment. The incidence of renal impairment increases significantly in this age group. However, <6% of our entire cohort had renal impairment making it unlikely to introduce significant bias into the analysis.

The SEER-Medicare database also does not provide data on performance status or lifestyle factors. These factors could affect the treatment rates we observed or clinicians' decision to treat these patients. This analysis also does not provide information about patients enrolled in HMOs since claims data for these patients are not collected by Medicare. It is conceivable that treatment patterns, and prognosis may differ between HMO and Medicare enrollees. Another area that warrants further research is a comparison of the treatment patterns and outcomes of patients enrolled in HMOs compared with those in fee-for-service plans. Research is also required to evaluate patterns and outcomes of care for patients with varying performance status since this information is not included in the SEER-Medicare database and we were unable to examine possible interactions between performance status and probability of receiving treatment.

Furthermore, our assumption that patients with multiple CIRS conditions have a higher comorbidity burden may be subject to interpretation error since we had no information about the severity of comorbidities. The database did not provide information about the length of time since the patient was diagnosed with a specific comorbid condition or the impact of comorbidity on performance status and activities of daily living. However, given the nature of the claims-based data source, we assumed that the conditions were of sufficient severity (moderate to severe) to warrant consultation with a physician or receipt of treatment for the condition that resulted in a claim.

5. Conclusion

In summary, this real-world analysis of Medicare eligible CLL patients showed that regardless of disease stage, elderly patients with a high comorbidity burden are less likely to receive treatment for their disease. The current findings suggest an opportunity to improve treatment approaches of elderly patients with coexisting medical conditions in order to achieve more favorable clinical outcomes in an increasingly aging population.

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Supplementary Table 1. Cumulative illness rating scale conditions by treatment status.

Top CIRS Conditions (Organ System)	Total (N = 8343)	All CLL		Advanced Stage	
		Treated (N = 3366)	Not Treated (N = 4977)	Treated (N = 1805)	Not Treated (N = 2408)
	(%)	(%)	(%)	(%)	(%)
Hypertension (Blood Pressure)	53.1	51.0	54.5	55.3	60.8
Hyperlipidemia(Vascular)	37.5	38.9	36.6	43.1	40.3
Coronary Artery Disease (Heart)	23.8	23.3	24.2	28.0	30.7
Diabetes (Endocrine)	21.1	20.2	21.8	23.8	25.5
Osteoarthritis (Musculosketal)	20.9	19.5	21.8	22.8	25.8
Atrial Fibrillation (Heart)	19.8	17.9	21.0	21.4	26.5
Chronic Obstructive Pulmonary Disease (Respiratory)	15.6	14.5	16.4	17.3	20.3
BPH (Genitourinary)	14.1	16.0	12.8	17.3	14.1
Congestive Heart Failure (Heart)	13.6	9.9	16.1	13.9	22.3
Hypothyroid (Endocrine)	12.6	11.3	13.5	14.3	16.2
Urosepsis (Genitourinary)	12.2	10.0	13.6	12.1	18.0
Cerebral Vascular Accident (Neurological)	11.8	9.9	13.1	12.5	17.4
Osteoporosis (Musculoskeletal)	10.9	9.3	12.0	10.7	14.5
Valvular Disease (Heart)	10.3	9.6	10.8	12.5	14.7
Acute Urinary Retention (Genitourinary)	10.2	9.9	10.4	11.5	12.7

Abbreviations: CIRS, Cumulative Illness Rating Scale.

