Original Article

Timeliness and Quality of Diagnostic Care for Medicare Recipients With Chronic Lymphocytic Leukemia

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BACKGROUND: Little is known about the patterns of care relating to the diagnosis of chronic lymphocytic leukemia (CLL), including the use of modern diagnostic techniques such as flow cytometry. **METHODS:** The authors used the SEER-Medicare database to identify subjects diagnosed with CLL from 1992 to 2002 and defined diagnostic delay as present when the number of days between the first claim for a CLL-associated sign or symptom and SEER diagnosis date met or exceeded the median for the sample. The authors then used logistic regression to estimate the likelihood of delay and Cox regression to examine survival. **RESULTS:** For the 5086 patients analyzed, the median time between sign or symptom and CLL diagnosis was 63 days (interquartile range [IQR] = 0-251). Predictors of delay included age ≥75 (OR 1.45 [1.27-1.65]), female gender (OR 1.22 [1.07-1.39]), urban residence (OR 1.46 [1.19 to 1.79]), ≥1 comorbidities (OR 2.83 [2.45-3.28]) and care in a teaching hospital (OR 1.20 [1.05-1.38]). Delayed diagnosis was not associated with survival (HR 1.11 [0.99-1.25]), but receipt of flow cytometry within thirty days before or after diagnosis was (HR 0.84 [0.76-0.91]). **CONCLUSIONS:** Sociodemographic characteristics affect diagnostic delay for CLL, although delay does not seem to impact mortality. In contrast, receipt of flow cytometry near the time of diagnosis is associated with improved survival. ***Cancer* 2011;117:1470–7.** © *2010 American Cancer Society.*

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Delays in referral and diagnosis may negatively affect outcomes associated with many childhood malignancies and adult solid tumors.[1-4] In contrast, little research has examined the relationship between diagnostic delay and outcomes for adult hematologic malignancies,[5] despite improved techniques for pathologic diagnosis, staging, prognostication, and therapy. Such innovations may offer significant benefits for those who are referred, diagnosed, and treated in a timely manner—such has been demonstrated for younger patients with acute myelogenous leukemia[6]—even for patients with indolent malignancies such as chronic lymphocytic leukemia (CLL). Indeed, timeliness of care was identified as 1 of 6 aims of healthcare quality improvement in the Institute of Medicine's *Crossing the Quality Chasm* report.[7] Given that CLL is the most common type of leukemia,[8] even small differences in outcomes driven by diagnostic delays have the potential for significant societal impact.

CLL is a disease of older adults. It has a median age of diagnosis in the United States of 72 years, with 89% of patients initially diagnosed at or above the age of 65 years.[9] Perhaps because of its indolence and predilection for the elderly, many cases of CLL are identified incidentally or diagnosed presumptively in physician's offices without pathologic

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confirmation. Moreover, even when a pathologist is involved, it is difficult to distinguish CLL from a morphologically similar disease such as mantle cell lymphoma.[8] Because of its utility for definitive diagnosis,[10-11] confirmatory flow cytometry has been increasingly recommended as a baseline test—and a measure of quality of care—for patients with CLL. For example, the National Comprehensive Cancer Network has long recommended baseline immunophenotyping on bone marrow or peripheral blood with flow cytometry for all patients with CLL.[12] In addition, in 2008, the National Quality Forum working with the American Society of Hematology and the American Medical Association's Physician Consortium for Performance Improvement endorsed baseline flow cytometry for all patients with CLL as a quality of care standard.[13]

It is not currently known what clinical and sociodemographic factors predict delays in CLL diagnosis and, given its mostly indolent nature, whether delays have any effect on survival. In this context, we sought to estimate the time between CLL-associated signs or symptoms and diagnosis and to assess several covariates of delay. We also aimed to understand the correlates of receipt of baseline flow cytometry and to evaluate the effect that delays in diagnosis and receipt of flow cytometry might have on survival after a CLL diagnosis.

MATERIALS AND METHODS

Our overall analytic approach has been previously published.[14] Below, we briefly review data sources, sample selection, measures, and data analysis.

Sources of Data

The Surveillance, Epidemiology, and End Results (SEER)–Medicare dataset was used to identify patients diagnosed with CLL. The SEER-Medicare dataset combines cancer registry information with complete claims data for adults age 65 years and older who are enrolled in traditional Medicare Parts A and B.[15] The analysis sample contained patients diagnosed with CLL between February 1, 1992 and December 31, 2002. The 16 registries in this dataset cover a representative sample of 26% of the population of the United States and are oversampled to capture racial and ethnic minorities.[32,33] Participating tumor registries are estimated to capture approximately 97% of incident cases reported by hospitals.[16] The Dana-Farber Cancer Institute Institutional Review Board granted exempt review status to our study protocol. The protocol was also reviewed by the institutional review board at the Centers for Disease Control, and a signed data-use agreement was executed with the SEER-Medicare coordinating center.

Patient Sample

By using the SEER registry data, we identified patients with CLL diagnoses that were confirmed by pathologic or laboratory findings. Patients with multiple cancers were eligible only when CLL was the first cancer diagnosed. Because the availability of complete claims was required to measure healthcare utilization with accuracy, we applied several additional selection criteria: the SEER diagnosis date of CLL (henceforth defined as diagnosis date) had to be on, or after, the patient's date of Medicare enrollment; patients had to survive 6 or more months after diagnosis; and patients had to be continuously enrolled in both Part A and Part B Medicare for the year preceding CLL diagnosis through at least 6 months after diagnosis. We identified 5831 patients in the participating registries who were diagnosed with CLL between 1992 and 2002 and who met eligibility criteria. Of these, we excluded 745 patients based on the following: diagnosis at autopsy, eligible for Medicare because of end-stage renal disease or disability, and participation in health maintenance organizations during the study period. The final analytic sample consisted of 5086 patients.

Study Variables

Patient Characteristics

We used the Patient Entitlement and Diagnosis Summary File (PEDSF) to measure patient characteristics, including age, sex, race/ethnicity, geographic region of residence (Northeast, Midwest, South, and West), and residence in an urban versus rural area (as defined by residence in a metropolitan statistical area). Medicare inpatient (MEDPAR), outpatient (OUTSAF), and physician (NCH) files were used to construct a modified Charlson comorbidity score for all patients by reviewing claims for the year before the SEER diagnosis date.[17] Comorbidity was identified by using methods reported in previously published studies.[15,18]

Signs, Symptoms, and Diagnostic Procedures

After literature review and consultation with clinical experts, we matched possible signs and symptoms of CLL to diagnoses and procedures from the claims data by using International Classification of Diseases, 9th edition (ICD-9) and Current Procedural Terminology (CPT) codes. (The frequencies of these diagnoses and procedures

are reported in the Results section of this article; a list of the specific codes used is available from the authors upon request.) We created dichotomous measures to identify the presence or absence of claims for these signs and symptoms for 1 year preceding the SEER diagnosis date.

CLL diagnosis and delay

We measured the number of days between the first claim for a CLL sign or symptom and the SEER CLL diagnosis date. By using a similar approach to our prior research on delays,[14] we defined diagnostic delay as occurring in patients whose time between sign or symptom claim and diagnosis date exceeded the median number of days for the sample. SEER provides only month and year for diagnosis. However, researchers have identified that SEER diagnosis month and year are concordant with clinical diagnosis dates found in claims within a window of ±30 days.[19] Accordingly, we set diagnosis dates to the 15th day of the SEER-recorded month and year for all subjects. In our analyses described below, we then reran our analytic models with adjusted calculations of the time between diagnosis dates and dates of signs, symptoms, or diagnostic procedures, using ±30 days as a conservative estimate.

Processes of care

ICD-9 diagnosis, CPT procedure, and Health Care Procedure Coding System (HCPCS) codes identified in MEDPAR, OutSAF, and NCH files were used to measure the receipt of systemic chemotherapy within the first 6 months of diagnosis (a list of these codes is available from the author). Patient claims for inpatient services in MEDPAR files were reviewed to identify whether patients were treated in teaching hospitals (as defined by the Medicare Provider of Service survey) in the year preceding diagnosis. We also identified patients who had a claim for flow cytometry performed within 30 days before or after their CLL diagnosis date.

Data Analysis

We used SAS 9.1.3 (SAS Institute, Cary, NC) for all analyses. Coefficients obtained from logistic regression models were expressed as odds ratios with 95% confidence intervals. Coefficients from Cox regression models were reported as hazard ratios with corresponding 95% confidence intervals.

Examination of Delays

For the 4081 patients who had a claim for a sign or symptom related to CLL occurring before diagnosis, we used logistic regression models to estimate the effect of patient characteristics on the likelihood of delay as defined above. Patient demographics, comorbidities, healthcare utilization in the prior year, and initial source of diagnosis were included in the model.

Use and Predictors of Flow Cytometry

The Cochran-Armitage test for trend was used to examine the proportion of patients who received flow cytometry in each year of the study period. A multivariate logistic regression model estimated the likelihood of undergoing flow cytometry analysis within 30 days of CLL diagnosis. Independent variables included the patient characteristics described above.

Examination of Survival

Cox regression was used to estimate the impact of diagnosis delays and receipt of flow cytometry within 30 days of CLL diagnosis on overall survival.[20] Covariate selection was accomplished by including those variables significantly associated with delay in our prior models plus sociodemographic factors.

Sensitivity Analyses

There is no accepted standard to define diagnostic delay. We, thus, examined diagnostic delay by using a variety of additional measurement approaches, including treating it as a continuous measure, considering diagnoses that exceeded the mean (as opposed to the median value as above), and analyzing tertiles and quartiles of median time to diagnosis. In addition, we re-estimated a Cox model with empirically derived independent variables. This was accomplished by including delay in all models and adding each independent variable in turn to examine for significant effects. Variables were retained at $P < .05$, and first-order interaction terms were examined and retained with similar criteria.

RESULTS

The study inclusion criteria identified 5086 patients for the analysis of receipt of flow cytometry and of survival (full sample). Because not all patients had a claim for a sign or symptom before diagnosis, 4081 (80%) were included in the analysis of delays (delay sample). Table 1 shows the characteristics of study patients by sample. The median age for both samples was 75 years; approximately 30% of patients in both had at least 1 comorbidity as measured by the modified Charlson Comorbidity Index. Chi-square and Student *t* tests revealed no significant

Table 1. Characteristics of Study Patients by Analytic Sample

Characteristics	Full Sample n=5086	Delay Sample n=4081
	No. (%) [IQR]	No. (%) [IQR]
Age, y, median [IQR]	75 [70-85]	75 [71-81]
Race		
White	4702 (92.4)	3758 (92.1)
Black	234 (4.6)	195 (4.8)
Other	150 (3.0)	128 (3.1)
Sex		
Men	2751 (54.1)	2128 (52.1)
Women	2335 (45.9)	1953 (47.9)
Urban resident	4400 (86.5)	3534 (86.6)
Modified Charlson score		
0 or no claims	3722 (73.2)	2865 (70.2)
1	952 (18.7)	827 (20.3)
2	245 (4.8)	231 (5.7)
3 or more	167 (3.3)	158 (3.8)
Region of residence		
Northeast	858 (16.9)	701 (17.2)
South	507 (10.0)	436 (10.7)
Midwest	1522 (29.9)	1262 (30.9)
West	2199 (43.2)	1682 (41.2)
Care in teaching hospital[a]	2852 (56.1)	2346 (57.5)

IQR indicates Interquartile range.
[a] Within the year prior to diagnosis.

Table 2. Presenting Signs, Symptoms, and Diagnostic Tests Before SEER Diagnosis Date[a]

Presentation and Tests	No.	%
Signs and Symptoms		
Infection	1640	32.2
Lymphocytosis	1461	28.7
Anemia	1214	23.9
Fatigue	843	16.6
Lymphadenopathy	359	7.1
Thrombocytopenia	245	4.8
Fever	204	4.0
Splenomegaly	194	3.8
Weight loss	152	3.0
Abdominal fullness	71	1.4
Rhinitis	71	1.4
Monoclonal gammopathy	39	0.8
Hepatomegaly	38	0.7
Night sweats	29	0.6
Hypogammaglobulinemia	24	0.5
Bleeding	<11	<0.3
Failure to thrive	<11	<0.3
Diagnostic procedures		
Complete blood count	2868	56.4
Flow cytometry	1026	20.2
Bone marrow biopsy	803	15.8
Lymph node biopsy	107	2.1

[a] Full Sample (n=5086).

differences in patient characteristics between the full and the delay samples (results not shown).

Table 2 shows the presenting signs, symptoms, and diagnostic tests reported in the full sample for the year preceding the diagnosis date. The most common Medicare claim was for infection (32.2%), followed by lymphocytosis (28.7%), anemia (23.9%), and fatigue (16.6%). Just over half had a complete blood count performed during the year before diagnosis.

In the delay sample (n = 4081), the mean time between first sign or symptom and CLL diagnosis was 121.5 days, with a median of 63 days (interquartile range [IQR], 0 to 251 days). Results were adjusted for year of diagnosis and were from a multivariate logistic regression model that was used to estimate the likelihood of delay between sign or symptom and diagnosis (Table 3). The presence of 1 or more comorbidities was strongly predictive of diagnostic delay (odds ratio [OR], 2.83; 95% confidence interval [CI], 2.45-3.28). Patients aged 75 years or older were 45% more likely to experience delay (95% CI, 1.27-1.65). Females (OR, 1.22; 95% CI, 1.07-1.39) and urban residents (OR, 1.46; 95% CI, 1.19-1.79) were also more likely to experience delay. Patients who had received care in a teaching hospital before CLL diagnosis were 20% more likely to experience diagnostic delay (95% CI, 1.05-1.38).

Approximately half (2282) of the study patients had a claim for flow cytometry at any time during the study period; 1965 (38.6%) patients had their initial flow cytometry performed within 30 days before or after the SEER diagnosis date. The use of flow cytometry increased significantly over the study period (Fig. 1). (A Cochran-Armitage test for trend was significant at $P < .01$. It should be noted that Medicare initiated a national coverage decision for flow cytometry in 2000.) The results from the logistic regression predicting flow cytometry at any time during the study period are shown in Table 4 and were also adjusted for year of diagnosis. Significant predictors of flow cytometry were age younger than 75 years (OR, 1.46; 95% CI, 1.30-1.66), urban residence (OR, 1.27; 95% CI, 1.05-1.53), and residence in the Northeast (OR, 2.01; 95% CI, 1.69-2.39) or South (OR, 1.51; 95% CI, 1.22-1.89) when compared with the West (the Western classification includes the state of Hawaii). Of note, because of low numbers of cases from some

Table 3. Factors Predicting Likelihood of Diagnostic Delay[a]

	Odds Ratio	95% CI
Age, y		
≥75	1.45	1.27-1.65
<75	-	-
Race		
Nonwhite	1.11	0.87-1.42
White	-	-
Sex		
Women	1.22	1.07-1.39
Men	-	-
Urban resident		
Urban resident	1.46	1.19-1.79
Rural resident	-	-
Modified Charlson score		
1 or more comorbidities	2.83	2.45-3.28
Zero or no claims	-	-
Region of residence		
Northeast	0.95	0.78-1.14
South	0.96	0.76-1.20
Midwest	1.11	0.94-1.31
West	-	-
Care in teaching hospital[b]	1.20	1.05-1.38

CI indicates confidence interval.
Model additionally adjusted for year of diagnosis (output suppressed), c-statistic 0.67, Likelihood Ratio χ^2: 403.5, 20 degrees of freedom (df), $P < .0001$.
[a] n=4081.
[b] Within the year prior to diagnosis.

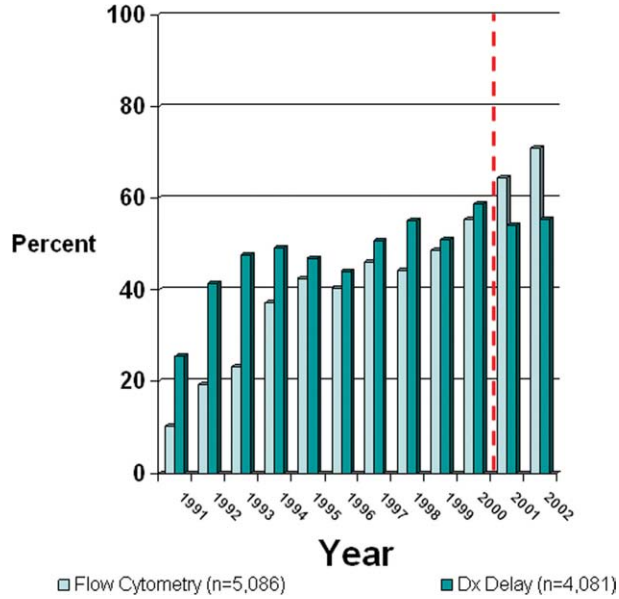

Figure 1. The use of flow cytometry has increased over the study period. Delays in diagnosis were least frequent in 1991 and were most frequent in 2000. In 2000, the Center for Medicare and Medicaid Services issued a national coverage decision to reimburse for diagnostic flow cytometry. Cochran-Armitage tests for trend were significant for both flow cytometry and diagnostic delay at $P < .0001$.

registries, we report these results by geographic region of the United States; however, our parameter estimates did not change when SEER registries were included as covariates. Finally, an increased number of signs or symptoms before diagnosis was associated with an increased likelihood of having flow cytometry performed (OR, 1.15; 95% CI, 1.08-1.22). Patients with comorbidities were less likely to receive flow cytometry (OR, 0.88; 95% CI, 0.76-1.02), but the difference was not statistically significant.

The median survival time for the full sample was 10.4 years. Patients who survived beyond the end of the observation period were censored at 5056 days (13.8 years, the end of the study period). The results of the multivariate Cox regression model are shown in Table 5; hazard ratios (HR) and 95% confidence intervals are reported. This model estimated the effect of patient characteristics, as well as processes of care, on overall survival. Patients diagnosed at the age of 75 years or older, males, and patients with comorbidities had significantly shorter survival times. Whereas the receipt of systemic chemotherapy within 6 months of diagnosis (HR, 1.58; 95% CI, 1.42-1.77) and history of care in teaching hospitals (HR, 1.23; 95% CI, 1.14-1.34) were also associated with shorter survival times, patients who had flow cytometry performed had significantly increased survival times (HR, 0.84; 95% CI, 0.76-0.91). We did not observe a significant effect of delay between sign or symptom and diagnosis on overall survival (HR, 1.11; 95% CI, 0.99-1.25]). In the sensitivity analyses described above, the relations reported were similar when delay was treated as a continuous measure, as a tertile, or as a quartile, as well as when time from sign or symptom to diagnosis exceeded the mean (as opposed to the median) for the sample. When we compared parameter estimates, hazard ratios, and statistical significance for the dependent variables in a re-estimated Cox model with empirically derived independent variables, these also did not change appreciably. Although diagnostic delay remained not significant, an interaction term between delay and comorbidity was marginally significant (OR, 1.21; 95% CI, 1.01-1.44; $P = .034$).

DISCUSSION

We found that older patients, female patients, and sicker patients were more likely to experience delay in

Table 4. Factors Predicting Likelihood of Flow Cytometry[a]

Factors	Odds Ratio	95% CI
Age, y		
<75	1.46	1.30-1.66
≥75	-	-
Race		
Nonwhite	0.94	0.75-1.18
White	-	-
Sex		
Male	0.99	0.88-1.12
Female	-	-
Urban resident		
Urban resident	1.27	1.05-1.53
Rural resident	-	-
Charlson score		
1 or more comorbidities	0.88	0.76-1.02
Zero or no claims	-	-
Region of residence		
Northeast	2.01	1.69-2.39
South	1.51	1.22-1.89
Midwest	1.11	0.95-1.29
West	-	-
Care in teaching hospital[b]	1.12	0.98-1.27
No. of signs or symptoms[c]	1.15	1.08-1.22

CI indicates confidence interval.
Model additionally adjusted for year of diagnosis (output suppressed), c-statistic 0.73,
Likelihood Ratio χ^2: 872.73, 21 df, $P < .0001$.
[a] (n=5086)
[b] Within the year prior to diagnosis.
[c] Before diagnosis.

Table 5. Effect of Selected Covariates on Overall Survival

	Hazard Ratio	95% CI
Patient Characteristics		
Age, y		
≥75	1.92	1.77-2.08
<75	-	-
Race		
Nonwhite	1.12	0.96-1.30
White	-	-
Sex		
Men	1.25	1.16-1.35
Women	-	-
Urban resident		
Urban resident	0.98	0.88-1.10
Rural resident	-	-
Region of Residence	0.99	0.96-1.03
Charlson score		
1 or more comorbidities	1.49	1.37-1.63
Zero or no claims	-	-
No. of signs or symptoms before diagnosis	1.01	0.95-1.07
Processes of care		
Systemic chemotherapy administered	1.58	1.42-1.77
Care in teaching hospital[a]	1.23	1.14-1.34
Flow cytometry performed[b]	0.84	0.76-0.91
Diagnostic delay present	1.11	0.99-1.25

CI indicates confidence interval.
Model additionally adjusted for year of diagnosis.
[a] In the year before diagnosis.
[b] ±30 days of SEER diagnosis date.

diagnosis for CLL, a finding similar to our prior study of Medicare recipients with multiple myeloma.[14] As the presenting signs and symptoms in CLL are often seen first by primary care providers—and given mounting interest in "medical homes" to provide initial evaluation and coordination for a majority of patient problems[21]—it is increasingly likely that primary care providers will be responsible for the initial diagnosis of patients with CLL. The literature on childhood malignancies and adult solid tumors has linked such delays to both the frequency of patients seen by primary care providers in clinical practice[22-25] and knowledge gaps regarding screening and diagnosis.[24,26] As with those malignancies, educational and policy initiatives to support clinicians' evaluations of hematologic abnormalities seen in primary care may be required to ensure appropriate diagnosis and referral of patients with CLL.

Although we did find that certain clinical and sociodemographic characteristics were associated with delay, delay did not impact survival. This is not surprising because most patients have early stage disease at diagnosis and do not require therapy for some time. Indeed, 2 randomized trials found that chemotherapy for early stage CLL slowed disease progression but did not confer a survival benefit.[27] Also expected was our finding that older age and increased comorbidity were associated with poorer survival. Our data suggest that for a subset of older patients with significant health problems, the more effective therapeutic options for CLL may be initially withheld by treating clinicians, not well& tolerated when given, or both.

We observed a significant tendency for men to be diagnosed quicker than women. Such a gender gap in CLL diagnostic delay is consistent with that seen in other conditions such as cardiovascular disease.[28-29] Important gender differences in incidence, stage, and biology of CLL have also been previously reported.[30] Our data support a complicated picture of diagnostic care for older women generally and speak to the need for observational cohort studies to understand whether such differences are due to

patient- or provider-related factors. Finally, urban residents were more likely to experience delays, which might seem unexpected because urban areas tend to have more high-quality teaching hospitals. Teaching status, however, is only modestly associated with delay. Such findings may be explained in part by increasing evidence that those who live in rural areas tend to have more consistent sources of care (as opposed to urban residents),[31] which may be critical for diagnoses of indolent diseases such as CLL.

Our finding that those patients who had flow cytometry performed early in their diagnosis experienced an overall survival benefit is provocative. There are several possible explanations for this observation. First, the physicians caring for those patients who received flow cytometry might have been better informed in the diagnosis and management of CLL and better able to manage or refer these patients. Second, flow cytometry might not have been performed for patients deemed poor candidates for therapy and who were less likely to survive at baseline. Third, the use of flow cytometry might have excluded patients who had morphologically similar diseases with a worse prognosis (eg, those with mantle cell lymphoma), and those patients with CLL confirmed by flow cytometry might have received more appropriate (ie, less toxic) therapy than those whose disease was not definitively identified. Despite explanation, our data support the routine use of flow cytometry for diagnosis of CLL as suggested in current national clinical guidelines. Our findings also provide external validity to proposals to assess flow cytometry performance in CLL as a quality of care performance measure.

Our study has limitations. First, we did not have data on patient experiences and actual clinical encounters; chart reviews or interviews with patients and providers would have enriched our findings. Second, we were not able to capture CLL diagnoses that were not reported to cancer registries, a well known issue with population-based studies of CLL.[32] Although cancer registries routinely receive case reports from hospitals and pathologists, when a diagnosis is based on a complete blood count in a private physician's office, it is less likely to be directly reported to a cancer registry.[10,32] Third, the availability of only the month (vs the actual date) of SEER-reported CLL diagnosis is clearly a limitation of our data source; however, we did perform sensitivity analyses keeping the original definition of delay but moving individual patient diagnosis dates up or back by 30 days and did not find appreciable differences in our results. Fourth, our study was restricted to traditional Medicare enrollees who resided in SEER registry areas and did not participate in managed care plans. Despite including the diagnostic experience of a large number of older adult patients with CLL, these factors limit the representativeness of the sample and the generalizability of our findings. Data augmentation from other registries, such as the CDC's National Program of Cancer Registries, would have expanded our population coverage.

In summary, although we did not see evidence of a relation between diagnostic delay and survival for patients with CLL, we did observe significant associations between delay and patient characteristics such as age, sex, area of residence, and clinical complexity. In addition, certain patient characteristics made receipt of baseline flow cytometry more likely, and the use of flow cytometry was associated with improved survival. Our data suggest that diagnostic flow cytometry is an appropriate measure of the quality of diagnostic care for patients with CLL. Especially given our finding that its use is increasing, an important next step would be to assess its cost effectiveness.

CONFLICT OF INTEREST DISCLOSURES

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