



Real-World Treatment Patterns, Adverse Events, Resource Use, and Costs Among Commercially Insured, Younger Patients with Chronic Lymphocytic Leukemia in the USA: A Retrospective Cohort Study

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ABSTRACT

Introduction: Amidst a changing treatment landscape, real-world evidence on the burden of chronic lymphocytic leukemia (CLL) is limited. The purpose of this study was to describe treatment patterns, adverse events (AEs), and economic burden among treated patients with CLL.

Methods: A retrospective cohort study was conducted with IQVIA PharMetrics® Plus. Patients at least 18 years old with CLL treatment between November 1, 2013 and May 31, 2018 were identified; index date was first observed CLL treatment. Patients had at least one CLL diagnosis pre-index and a second diagnosis anytime during the study period, at least 1-year pre- and at least 30-day post-index continuous enrollment and no pre-index CLL treatment.

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Analyses focused on patients receiving one of the four most common regimens observed. Outcomes included treatment patterns, frequency of incident AEs, and healthcare resource use and costs. Multivariable logistic regression and generalized linear modelling were used to evaluate risk of hospitalization and all-cause costs per patient per month (PPPM).

Results: A total of 1706 patients were included in the study (median [interquartile range] age 58 [55–62] years, 66% male, median Charlson Comorbidity Index 2 [2–3], median follow-up 16 [8–28] months). Common regimens, irrespective of treatment line, were bendamustine–rituximab (B-R, 27%), ibrutinib monotherapy (I, 27%), rituximab monotherapy (R, 19%), and fludarabine combined with cyclophosphamide and rituximab (FCR, 16%); 59% had at least one incident AE (B-R, 62%; I, 60%; R, 25%; FCR, 79%). Mean total all-cause healthcare cost over follow-up was $\$13,858 \pm 14,626$ PPPM. Increased number of AEs was associated with increased odds of hospitalization (odds ratio = 2.9; 95% confidence interval [CI] 2.5–3.4) and increased mean cost PPPM (cost ratio = 1.2; 95% CI 1.1–1.2).

Conclusion: This study highlights the treatment toxicity and associated economic burden among patients with CLL in the USA. As novel therapies are increasingly used, further research examining outcomes will inform the risks, benefits, and value of novel agents to prescribers and patients.

Keywords: Adverse events; Chronic lymphocytic leukemia; Costs; Healthcare resource use; Real world; Treatment patterns

Key Summary Points

Why carry out this study?

There are approximately 21,000 new cases of chronic lymphocytic leukemia (CLL) in the USA each year.

While there is no cure for CLL, the CLL treatment landscape has evolved over the last decade with the development of promising targeted drugs. These novel therapies are increasing available and used, but evidence of treatment toxicity, associated healthcare resource use, and costs among patients with CLL receiving these treatments is limited. Further real-world evidence on the burden of novel and conventional therapies for CLL is crucial to patients and healthcare providers as they decide on an appropriate treatment plan.

The purpose of this retrospective observational study was to describe real-world treatment patterns in a large cohort of commercially insured, younger patients with CLL in the USA. The study also described treatment-related toxicity, healthcare resource use (HRU), and costs.

What was learned from the study?

This study highlighted the current, commonly used CLL treatments among younger patients with CLL in the USA, as well as the associated clinical and economic burden.

In this study, the most common regimens observed among treated patients with CLL were bendamustine–rituximab (27%), ibrutinib monotherapy (27%), rituximab monotherapy (19%), and fludarabine combined with cyclophosphamide and rituximab (16%); more than half of treated patients (59%) had evidence of at least one incident adverse event (AE).

The economic burden among patients with CLL was substantial and driven by treatment costs. Patients with AE(s) had additional clinical and economic burden from treatment-related toxicities.

HRU and costs consistently increased as the number of AEs increased, suggesting a potential association between greater treatment toxicity and higher HRU; results persisted in adjusted analyses.

INTRODUCTION

Chronic lymphocytic leukemia (CLL), a disorder of malignant B cells, is characterized by a heterogeneous clinical course and has recently been reclassified as a type of lymphoma. An estimated 21,000 new cases of CLL are diagnosed in the USA each year [1]. CLL is primarily diagnosed in older individuals, with an average age of 68 years at diagnosis [2]. The prognosis has improved in recent years, with the 5-year overall survival increasing from 60% in 2000–2004 to 84% based on data from 2008–2014, due to newer therapeutic approaches such as chemoimmunotherapy combinations [3–5].

The CLL treatment landscape has evolved significantly over the last few decades, first with the introduction of immunomodulating agents and CD20 (e.g., rituximab, obinutuzumab, and ofatumumab) and CD52 (e.g., alemtuzumab) monoclonal antibodies, which led to expanded therapeutic options with chemoimmunotherapy regimens, and more recently, with the development of small molecule inhibitors targeting several critical signaling pathways such as ibrutinib, a selective Bruton tyrosine kinase (BTK) inhibitor, and venetoclax, a selective B cell lymphoma/leukemia 2 (BCL2) inhibitor [6, 7]. Ibrutinib was first approved by the USA Food and Drug Administration (FDA) in 2014 for the treatment of patients with CLL who have received at least one prior treatment; approval was expanded that same year to those who have chromosomal 17p deletion or del(17p) [8]. Two years later, approval was expanded to the first-line setting, regardless of

chromosome 17p deletion status [8]. Venetoclax was first approved by the FDA in 2016 for the treatment of CLL with del(17p); approval was expanded in 2018 to patients with CLL and at least one prior therapy, regardless of chromosome 17p deletion status, for use in combination with rituximab [9].

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN guidelines[®]) for CLL from 2014 to 2018 (time period relevant for the present study) [6, 7] provide treatment options based on patient's age, comorbidities, and performance status, as well as the presence or absence of del(17p) (or *TP53* mutations, as first mentioned in the 2017 version). If del(17p) or *TP53* mutation is present, a clinical trial is recommended for all patients, and the preferred treatment among agents with a label in CLL is ibrutinib for both untreated patients and relapsed/refractory patients. If both del(17p) and *TP53* mutation are absent, obinutuzumab with chlorambucil is recommended as a preferred first-line treatment for older or frail patients and fludarabine-based chemoimmunotherapy (e.g., fludarabine combined with cyclophosphamide and rituximab [FCR]) for younger, healthier patients. For relapsed/refractory patients without del(17p)/*TP53*, ibrutinib with or without rituximab is the preferred treatment; other options include idelalisib, venetoclax, or chemoimmunotherapy.

Given that more intensive therapies and novel agents are used to treat CLL today, treatment-related toxicity profiles should be considered when developing a treatment plan. The decision to undergo intensive treatment should balance the trade-offs between efficacy and tolerability. Recently approved BTK inhibitors have unique adverse event (AE) profiles, with a real-world study of patients with CLL who discontinued ibrutinib or idelalisib reporting that toxicity was the most common reason for discontinuation (reported in more than half of patients) [10]. Of particular concern is the risk of cardiac events, such as atrial fibrillation (AF), observed in 10% of patients with CLL newly treated with ibrutinib in a real-world study [11], 5% of patients with previously treated relapsed or refractory CLL in the RESONATE trial [12], and 17% of older patients with untreated CLL in the

Alliance trial [13]. The rates reported here are for AF of any grade for all three studies. Most clinical trials investigating ibrutinib regimens have excluded patients with CLL under 65 years old (i.e., excluded in RESONATE-2 [14] and Alliance [13]); therefore, the data on ibrutinib-treated patients with CLL younger than 65 years of age is limited (e.g., included in one study, ECOG-E1912 [15]). Further research is needed to assess treatment toxicity, as well as associated health-care resource use (HRU) and costs in the real-world setting, particularly among patients younger than 65 years of age who have not been included in most clinical trials to date.

Research on the association of treatment toxicity, HRU, and costs among patients treated for CLL is limited. To that end, real-world evidence on the burden of novel and conventional therapies for CLL is important to help guide treatment planning. The primary focus of this retrospective observational study was to describe treatment patterns in a real-world setting. This study also described treatment-related toxicity, HRU, and costs in a large cohort of treated patients with CLL.

METHODS

This retrospective cohort study utilized patient data from IQVIA PharMetrics[®] Plus database from November 1, 2012 through June 30, 2018. This database is comprised of fully adjudicated medical and pharmacy claims for more than 150 million unique commercially insured enrollees across the USA, with data from 90% of US hospitals and 80% of all US doctors. Owing to the broad reach of these data, records in the database are representative of the commercially insured US national population for patients under 65 years of age. All data are Health Insurance Portability and Accountability Act (HIPAA) compliant to protect patient privacy and, therefore, institutional review board approval was not required for this study.

Adult patients (at least 18 years old) who had at least one claim for a CLL treatment (defined on the basis of the NCCN guidelines [16] and expert opinion reported in Supplemental Table 1) between November 1, 2013 and May

31, 2018 were identified. The first date of treatment was defined as the index date. Patients were required to have at least one diagnosis of CLL (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 204.1x or ICD-10-CM code C91.1x, C83.0x) before index and at least one diagnosis anytime during the study period, at least 12 months of continuous enrollment prior to the index date (variable baseline period), and at least 30 days of continuous enrollment after the index date (variable follow-up period) to be included in the study. Patients with evidence of CLL-related treatment(s) any time before the index date (using all available look-back) were excluded. All inclusion and exclusion criteria are specified in Fig. 1.

After all treated patients with CLL were selected into the study, we categorized patients into treatment regimens. In an effort to focus the analysis on understanding treatment-related toxicity and associated HRU and costs for commonly used treatment regimens, we described only the four most common regimens observed. Patients who received one or more of these regimens at any point during follow-up (representing more than 75% of all treated patients with CLL in the study) were identified and included in the analysis.

The start of a treatment episode was defined as the first date of a CLL-related systemic treatment. The combination of all agents used in the first 35 days of the beginning of a treatment episode comprised a treatment regimen; product-specific drug and infusion administration codes (National Drug Codes [NDC] and Healthcare Common Procedure Coding System codes [HCPCS]) were used to identify treatments. Each treatment episode continued until a switch to a new regimen, modification of the starting regimen (addition and removal of rituximab was allowed, as this was expected in real-world clinical practice), discontinuation of the regimen, end of study follow-up, or end of continuous enrollment, whichever occurred first. When switching or modification of treatment occurred, the end date of the treatment episode was defined as 1 day before the start date of the next treatment episode. Discontinuation was defined as a gap of at least 60 days in treatment to be

consistent with prior studies [17–20]. When discontinuation occurred, the end date was defined as 90 days after the last prescription was filled (for oral medications) or 30 days after the last infusion was administered (for non-oral medications). These definitions were implemented after review of the fill and administration data and validated with expert opinion. When systemic and oral treatments were used concomitantly, the end of the treatment episode was defined on the basis of the oral medication supply. Furthermore, patients receiving rituximab maintenance therapy were excluded since these patients may be in remission after using a prior rituximab-containing chemotherapy and are therefore not comparable to the other treatment groups. Rituximab maintenance therapy was defined as monotherapy with rituximab (with or without corticosteroids) starting at most 210 days (7 months) after the end of a rituximab-containing combination therapy and lasting fewer than 68 days, or when the count of unique infusion days of rituximab divided by length of monotherapy with rituximab in days was at most 0.017 [21–24]. First, second, and third observed treatment episodes were identified and categorized as first-, second-, and third-line therapies.

Baseline demographic and clinical characteristics were measured during the 12-month pre-index period. Clinical characteristics included Charlson Comorbidity Index (CCI; based on 15 conditions using Dartmouth-Manitoba version, without malignancy or metastatic solid tumor [25]), AF risk status (based on risk factors present in the baseline period, calculated using Chyou et al.'s method [26]), daily pill burden (defined as the total quantity of pills [all-cause prescription medications] during the 30 days pre-index, divided by 30 days, among patients with at least one oral prescription for CLL-related treatments), and comorbidities (identified by at least one claim of pre-defined ICD-9-CM, ICD-10-CM, and/or HCPCS codes for each condition in the 12-month pre-index period). In addition, evidence of genetic testing, including testing of karyotype and fluorescence in situ hybridization (FISH) on the index date or within 90 days before the index date, was measured using current procedural terminology

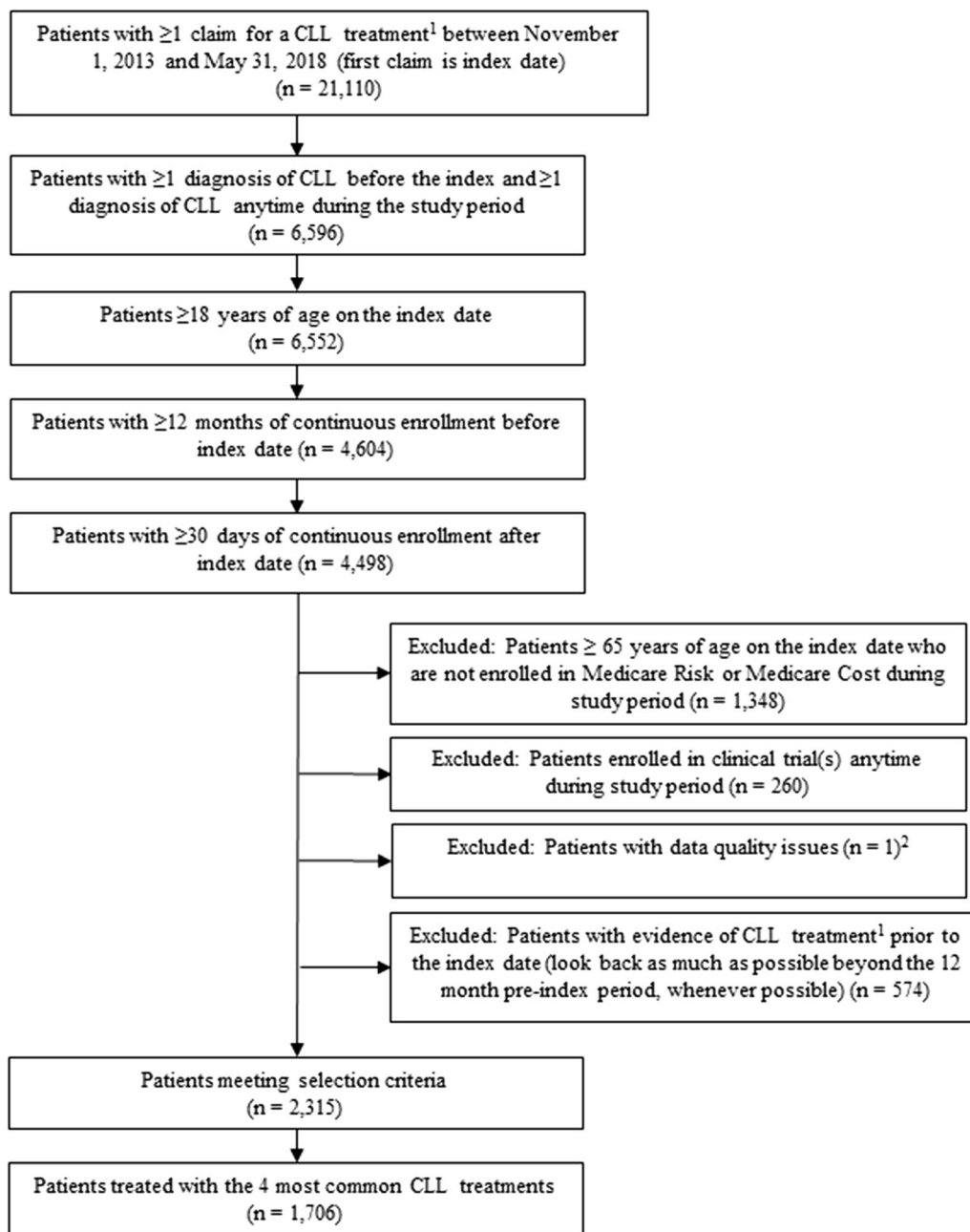


Fig. 1 Patient attrition flowchart

(CPT) codes; test results were not available in the data. All baseline measures were reported for all patients.

Outcomes were collected during the variable follow-up period (minimum 30 days). Our primary focus was treatment patterns including number and frequency of patients treated with the four most common treatment regimens by

line of therapy. The frequency of incident AEs of interest during treated follow-up, time from treatment initiation to incident AF and hemorrhage/bleeding over the first treatment episode by regimen, and all-cause and CLL-related monthly HRU and costs per patient were also described. Patients were considered to have an incident AE (identified by ICD-9-CM, ICD-10-

CM, and HCPCS codes) if they had at least one claim associated with an AE during a treatment episode with no evidence of that AE prior to the treatment initiation date. AEs of interest were selected on the basis of those that commonly occur among patients with CLL and those previously observed in clinical trials, package inserts, and expert clinical opinion [8, 13, 14]. For non-chronic symptoms and acute conditions that patients with CLL may experience before and after treatment initiation, such as infection and anemia, we additionally explored and reported the number and proportion of patients who had evidence of these conditions after treatment initiation, regardless of history of the same AE prior to treatment initiation. AF and hemorrhage/bleeding were of interest in this study given their associations with BTK inhibitors in controlled trials [10, 27] and the expected increase in use of ibrutinib over time [28–30]. CLL-related HRU and costs were defined as the subset of all medical claims with a diagnosis code for CLL in any position, or (pharmacy and medical) claims for CLL-related treatments. HRU and costs during follow-up were reported separately for patients by the number of unique AEs (0, 1–2, 3–5, and at least 6) and were categorized into hospitalizations, emergency department (ED) visits, outpatient visits, pharmacy, and other outpatient services (laboratory, ancillary [supplemental or auxiliary services to support the diagnosis and treatment of conditions such as diagnostic services, occupational therapy, and physical therapy], etc.). Healthcare costs were measured during the variable follow-up period using allowed amounts (negotiated rates between the plan and providers), reported as cost per patient per month (PPPM), and inflated to 2018 values using the Consumer Price Index.

All study measures were reported using frequencies and percentages for categorical variables and measures of central tendency (mean, median) and variability (standard deviation [SD], interquartile range [IQR]) for continuous variables. Kaplan–Meier survival analysis was used to compare the rate of occurrence of incident AF or hemorrhage/bleeding during the first treatment episode by regimen, and survival functions were compared using log-rank tests.

Patients were censored at the end of the treatment episode, end of continuous enrollment, or end of study period, whichever occurred earliest. Hazard ratios (HRs) for the risks of AF and hemorrhage/bleeding were calculated using Cox proportional hazards models. A generalized linear model with a log link and a gamma family distribution of the dependent variable was used to evaluate all-cause healthcare cost PPPM, and multivariable logistic regression models were used to evaluate the predictors of hospitalization, and of AF and hemorrhage/bleeding in the first-line setting. Model covariates were baseline demographic and clinical characteristics: All of the models included age at index (continuous), geographical region, insurance plan type, CCI score (continuous), baseline AF risk status, baseline comorbidities and acute conditions (evidence of AF, hemorrhage/bleeding, infection, hypertension, arthralgia/myalgia, neutropenia, and anemia for the monthly cost and hospitalization models; evidence of infection, hypertension, anemia, fatigue/asthenia, and thrombocytopenia for the AF and hemorrhage/bleeding models), and treatment regimen; in the monthly cost and hospitalization models, number of incident AEs was additionally included. *P* values less than 0.05 were considered statistically significant. Analyses were conducted using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Study Population Characteristics

Of the 2315 patients with CLL meeting the inclusion and exclusion criteria, 2182 patients had a drug-specific code and were able to be classified into a treatment regimen. The most common observed treatment regimens across all lines of therapy were B-R, ibrutinib monotherapy, rituximab monotherapy, and FCR. Of the 2182 patients, 1706 (78.2%) received at least one of these four CLL treatment regimens during follow-up and were included in the study (Fig. 1).

The mean \pm SD age was 58.2 ± 7.4 years; 66.3% of patients were male (Table 1). The

Table 1 Demographic and baseline clinical characteristics

Measures	All patients ^a (<i>n</i> = 1706)	
	<i>N</i>	%
Age at index, years		
Mean ± SD	58.2 ± 7.4	
Median (IQR)	59 (55, 62)	
18–44	68	4.0
45–54	355	20.8
55–64	1185	69.5
65–79	64	3.8
80 and older	34	2.0
Gender		
Male	1131	66.3
Female	575	33.7
Geographic region		
South	558	32.7
Midwest	490	28.7
Northeast	416	24.4
West	223	13.1
Unknown	19	1.1
Payer type		
Commercial	1002	58.7
Self-insured	532	31.2
Medicare advantage	104	6.1
Medicaid	53	3.1
Other	15	0.9
Health plan type		
PPO	1338	78.4
HMO	231	13.5
POS	89	5.2
Other	31	1.8
Unknown	17	1.0
CCI score		
Mean ± SD	3.0 ± 1.6	

Table 1 continued

Measures	All patients ^a (<i>n</i> = 1706)	
	<i>N</i>	%
Median (IQR)	2	(2, 3)
Comorbid conditions ^b		
Hypertension	719	42.1
Fatigue/asthenia	468	27.4
Thrombocytopenia	368	21.6
Hemorrhage/bleeding	203	11.9
Myalgia	77	4.5
Atrial fibrillation	58	3.4
Arthralgia	3	0.2
Other acute conditions of interest		
Infection	875	51.3
Anemia	544	31.9
Pneumonia	173	10.1
Neutropenia	107	6.3
Atrial fibrillation risk status		
Low risk	1338	78.4
High risk	368	21.6
Daily pill burden, pills		
Mean ± SD	3.6 ± 4.1	
Median (IQR)	2.4 (0.8, 5.0)	
Monthly all-cause cost per patient during the 12 months baseline period, USD\$		
Mean ± SD	\$2709 ± 4458	
Median (IQR)	\$1570 (\$792, \$3020)	
Evidence of genetic testing on the index date or within 90 days before the index date ^c (not mutually exclusive)		
Prognostic panel for CLL (without karyotype)	891	52.2%
Chromosome analysis for CLL/LPD (karyotype)	479	28.1%

Table 1 continued

Measures	All patients ^a (<i>n</i> = 1706)	
	<i>N</i>	%
Molecular pathology procedure (for approximately 50 genes including <i>TP53</i>)	47	2.8%
Molecular pathology procedure (unlisted codes)	71	4.2%
Molecular cytogenetics (FISH test)	538	31.5%

CCI Charlson Comorbidity Index, *CLL* chronic lymphocytic leukemia, *FISH* fluorescence in situ hybridization, *HMO* health maintenance organization, *IQR* interquartile range, *LPD* lymphoproliferative disorder, *POS* point of service, *PPO* preferred provider organization, *SD* standard deviation

^a The 1706 patients include all patients who received at least one of the four most commonly observed CLL treatment regimens at some point during follow-up, regardless of line of therapy (i.e., patient could be indexed on another CLL treatment)

^b Conditions reported in at least 10% of all patients and/or included as the AEs of interest in adjusted models are reported in this table

^c The following current procedure codes (CPT) were used to identify each genetic testing category: prognostic panel, 82232, 81263, 88184, 88185, 88271, 88275; chromosome analysis for CLL/LPD, 88237, 88264; molecular pathology procedure (50 genes including *TP53*), 81405; molecular pathology procedure (unlisted codes), 81479; molecular cytogenetics (FISH test), 88271, 88275, 88291

geographic distribution of patients was diverse with the most common region being the south (32.7%), followed by the midwest (28.7%) and the northeast (24.4%). Most patients were commercially insured (58.7%) or self-insured (31.2%). During the baseline period, the mean CCI score was 3.0 ± 1.6 (median 2.0 [2.0–3.0]); mean CCI score excluding cancer was 0.9 ± 1.3 (median 0.0 [0.0–1.0]); 21.6% of patients were classified as high risk of AF, and the mean number of pills taken daily was 3.6 ± 4.1 (median 2.4 [0.8–5.0]). The three most common comorbid conditions were hypertension (42.1%), fatigue or asthenia (27.4%), and

thrombocytopenia (21.6%). Infection and anemia during the baseline period were also common, at 51.3% and 31.9%, respectively. During the 12 months before CLL treatment initiation, patients incurred a mean all-cause healthcare costs of $\$2709 \pm 4458$ PPPM. During the 90-day period before index (inclusive of the index date), 28.1% and 31.5% of patients had evidence of a karyotype test for CLL and a FISH test, respectively (Table 1).

Treatment Patterns

The overall mean length of follow-up after initiation of one of the four most common treatments was 19.3 ± 13.8 months (BR, 19.9 ± 14.3 months; ibrutinib, 17.2 ± 12.9 months; rituximab monotherapy, 18.6 ± 13.6 months; FCR, 20.4 ± 14.2 months). As previously noted, of the 2182 patients meeting the selection criteria, 78.2% (*n* = 1706) had at least one of the four most common CLL treatment regimens across all observed lines of therapy: B-R (*n* = 590), ibrutinib monotherapy (*n* = 578), rituximab monotherapy (*n* = 490), and FCR (*n* = 343). The treatments received by the remaining patients with CLL (21.8%) varied and included predominantly chemotherapy-based treatments (e.g., chlorambucil).

In the first-line setting (*n* = 2182), B-R was the most common regimen (24.0%), followed by ibrutinib monotherapy (19.7%), FCR (14.6%), and rituximab monotherapy (14.1%) (Fig. 2). There were 678 patients (31.1% of the 2182 patients) who had subsequent lines of therapy observed during the follow-up. In the second- and third-line settings (*n* = 678 and *n* = 232, respectively), ibrutinib was most common (21.4% and 26.3%), followed by rituximab monotherapy (16.2% and 11.6%); fewer patients received B-R (9.4% and 4.7%) and FCR (3.4% and 1.3%) (Fig. 2).

Treatment Toxicity

Overall, 58.7% of the patients receiving the four most common regimens regardless of observed line of therapy had at least one AE of interest

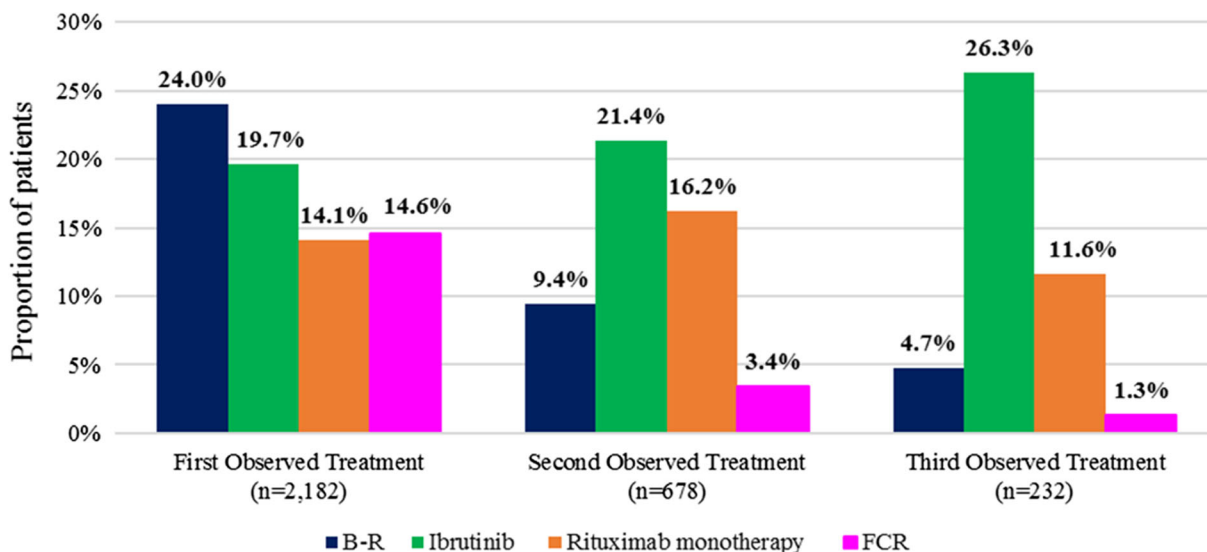


Fig. 2 Proportion of patients treated with B-R, ibrutinib, rituximab monotherapy, or FCR (the four most common treatments) out of all patients classified into a treatment regimen by line of therapy

during a treatment episode. The mean number of AEs per patient was 1.0 ± 1.2 (median 1.0; IQR 0.0–2.0). The most common incident AE, regardless of treatment regimen or line of therapy, was neutropenia (31.8%), followed by infection (10.6%), anemia (8.7%), and thrombocytopenia (8.2%). More patients had evidence of infection and anemia (34.8% and 28.3%, respectively) when not considering evidence of these conditions before treatment initiation. The frequency of AEs varied by regimen, with the highest rate among FCR-treated patients (76.7% had at least one AE during a FCR regimen), followed by B-R (58.6%), ibrutinib (56.1%), and rituximab monotherapy (24.4%) (data not shown). AF and bleeding were most frequently observed in patients receiving ibrutinib (AF, 7.4% vs. 0.7–1.2% in other three regimens; bleeding, 9.2% vs. 1.4–3.2%). Table 2 reports the number of AEs and the proportion of patients who experienced each of the AEs of interest during the first observed therapy (not adjusted for age or CCI), by treatment regimen.

In the first-line setting ($n = 1579$), the rates of incident AF and bleeding were compared. Patients receiving ibrutinib ($n = 429$) had significantly higher hazard of experiencing AF than patients treated with B-R (HR 4.3; 95% confidence interval [CI] 1.4, 12.7) and FCR (HR

5.5; 95% CI 1.3, 23.8), respectively (Fig. 3). The risk of AF in patients treated with ibrutinib compared to those with rituximab monotherapy was similar (HR 1.8; 95% CI 0.6, 5.5) (Fig. 3). Patients receiving ibrutinib had a higher risk of bleeding than those with B-R (HR 2.3; 95% CI 1.0, 5.3) (Fig. 4). The risk of bleeding in patients treated with ibrutinib was similar to those with rituximab monotherapy (HR 0.7; 95% CI 0.3, 1.5) and FCR (HR 1.2; 95% CI 0.6, 2.4).

A logistic regression model, controlling for baseline demographic and clinical characteristics and regimen, confirmed the increased odds of AF among patients treated with ibrutinib compared to the other three regimens. When compared to B-R and FCR, the findings from unadjusted analyses persisted in adjusted analyses. The risk of AF for ibrutinib patients during the first-line setting was 10.4 times higher than B-R (odds ratio [OR] B-R vs. ibrutinib = 0.1; 95% CI 0.03–0.28) and 11.2 times higher than FCR (OR = 0.1; 95% CI 0.02–0.38) (Supplemental Table 2). In adjusted analysis comparing patients receiving ibrutinib and rituximab monotherapy, the difference in the risk of AF became significant (5.7 times higher for ibrutinib patients; OR = 0.2; 95% CI 0.06–0.52). As in the unadjusted analyses, the risk of bleeding for

Table 2 Incident adverse events during the first observed therapy by treatment regimen

Incident adverse event	First observed therapy							
	B-R (<i>N</i> = 524)		Ibrutinib (<i>N</i> = 429)		Rituximab monotherapy (<i>N</i> = 308)		FCR (<i>N</i> = 318)	
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%
Number of AEs ^a								
Mean ± SD	0.9 ± 1.0		1.1 ± 1.3		0.4 ± 0.7		1.4 ± 1.2	
Median (IQR)	1 (0, 1)		1 (0, 2)		0 (0, 0)		1 (1, 2)	
No AE	199	38.0	174	40.6	232	75.3	67	21.1
At least one AE	325	62.0	255	59.4	76	24.7	251	78.9
Specific AE of interest								
Anemia	40	7.6	40	9.3	12	3.9	42	13.2
Arthralgia/myalgia	12	2.3	12	2.8	7	2.3	12	3.8
Atrial fibrillation	4	0.8	30	7.0	4	1.3	2	0.6
Cerebrovascular	6	1.1	17	4.0	0	0.0	4	1.3
Diarrhea	23	4.4	42	9.8	8	2.6	11	3.5
Hemorrhage/bleeding	8	1.5	40	9.3	10	3.2	11	3.5
Hepatotoxicity	1	0.2	4	0.9	1	0.3	5	1.6
Hypertension	18	3.4	57	13.3	4	1.3	10	3.1
Infection	43	8.2	72	16.8	13	4.2	28	8.8
Leukopenia	25	4.8	6	1.4	7	2.3	14	4.4
Myocardial infarction	7	1.3	13	3.0	2	0.6	1	0.3
Neutropenia	233	44.5	24	5.6	23	7.5	221	69.5
Renal failure	19	3.6	31	7.2	5	1.6	17	5.3
Secondary malignancy ^b	27	5.2	45	10.5	8	2.6	15	4.7
Thrombocytopenia	29	5.5	39	9.1	6	1.9	44	13.8

AE adverse event, *B-R* bendamustine–rituximab, *FCR* fludarabine/cyclophosphamide/rituximab, *IQR* interquartile range, *SD* standard deviation

^a For individual treatments, the AE must occur during the course of a given treatment (regardless of whether the treatment was the first/second/third). All AEs reported are incident AEs: only AEs observed during treatment episode(s) but not observed prior to the start of treatment episode including baseline period are reported in this table

^b Required at least two claims with diagnoses of the same cancer at least 7 days apart for the patient to be considered to have that secondary malignancy. ICD diagnosis codes for “Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue” (ICD-9-CM, 202; ICD-10-CM, C96) were excluded from secondary malignancy

patients receiving ibrutinib was higher than those receiving B-R in adjusted analyses (6.5 times higher for ibrutinib; OR = 0.2; 95% CI

0.07–0.33). The risk of bleeding for patients receiving ibrutinib compared to rituximab monotherapy and FCR became significantly

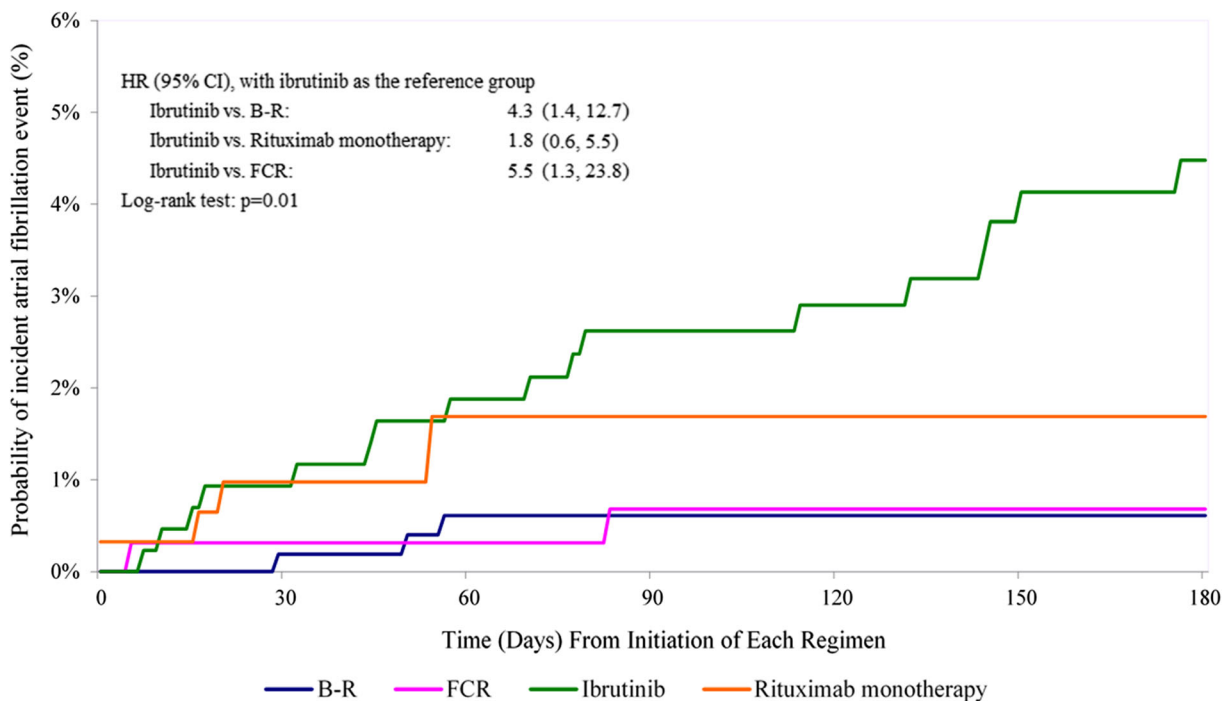


Fig. 3 Kaplan-Meier Analysis for Time from Treatment Initiation to Incidence of Atrial Fibrillation by Regimen, over the First Treatment Episode

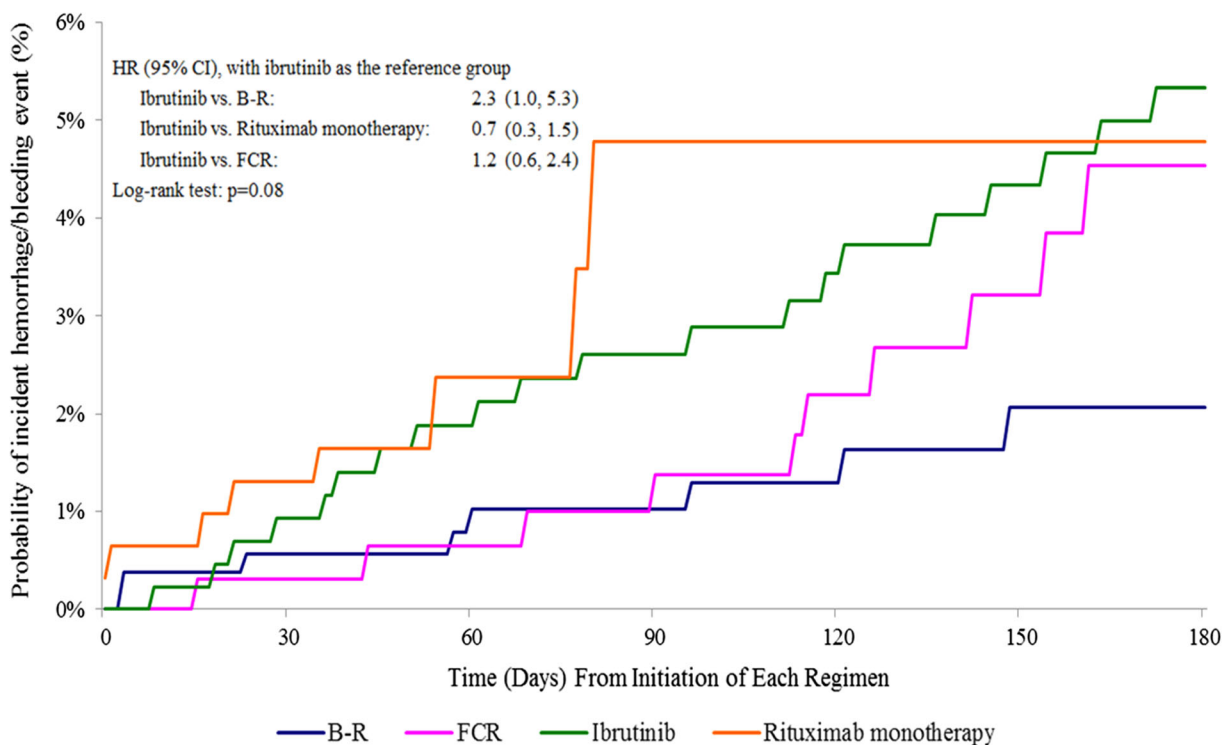


Fig. 4 Kaplan-Meier Analysis for Time from Treatment Initiation to Incidence of Hemorrhage/Bleeding by Regimen, over the First Treatment Episode

higher in adjusted analyses (3.2 times higher than rituximab monotherapy [OR = 0.3; 95% CI 0.15–0.65]; 2.6 times higher than FCR [OR = 0.4; 95% CI 0.19–0.78]) (Supplemental Table 3).

HRU

Among patients treated with the four most common regimens during follow-up, 30.7% had at least one hospitalization, with a mean length of stay of 6.4 ± 5.1 days, during the variable follow-up period (Table 3). The proportion of patients requiring hospitalization increased as the number of unique incident AEs during a specific treatment regimen increased (i.e., from 8.2% among 428 patients with no AEs to 89.1% among 64 patients with at least six AEs) (Table 3; Fig. 5). Furthermore, 41.4% of all patients had at least one ED visit, and the proportion of patients with at least one ED visit also increased as the number AEs increased, from 19.4% among patients with no AEs to 82.8% among patients with at least six AEs (Table 3; Fig. 5). Almost all patients had at least one office visit (99.6%) and other outpatient services such as laboratory or ancillary services (99.8%). Mean all cause-pharmacy use was 6.8 ± 5.6 prescriptions/injection administrations PPPM. Similar to hospitalizations and ED visits, increased number of office visits, pharmacy, and other outpatient services was observed as the number of AEs increased (Table 3). Trends for CLL-related HRU were generally similar to all-cause findings described and are shown in Table 3.

A multivariable logistic regression model, controlling for demographic and clinical characteristics and regimen, confirmed the increased odds of hospitalization as the number of incident AEs increased during the first observed treatment episode (OR = 2.9; 95% CI 2.5–3.4; Table 4). The risk of inpatient admission was 1.6 and 2.0 times higher for patients receiving ibrutinib compared to patients receiving B-R (OR = 0.6; 95% CI 0.4–0.9) and FCR (OR = 0.5; 95% CI 0.3–0.8), respectively. The risk of inpatient admission was similar for patients receiving ibrutinib and patients

receiving rituximab monotherapy (OR = 0.7; 95% CI 0.4–1.1).

Healthcare Costs

The mean total all-cause healthcare cost over the entire follow-up period (mean 19.3 months) was $\$13,858 \pm 14,626$ PPPM. Total CLL-related costs (mean $\$11,791 \pm 13,291$ PPPM) accounted for 85.1% of the total costs (Table 3). The largest contributor to total all-cause and total CLL-related costs was medication costs (mean $\$9938 \pm 9235$ for all-cause, and $\$8982 \pm 8918$ for CLL-related). Other outpatient services cost and inpatient cost were the second largest contributors for all-cause and CLL-related costs, respectively (Table 3). Total all-cause cost PPPM generally increased as the number of AEs increased, from $\$13,287$ for patients with no AEs to $\$20,807$ for patients with at least six AEs, with the exception of higher total all-cause costs among patients with 1–2 AEs (mean $\$13,809$ PPPM) compared to patients with 2–3 AEs (mean $\$13,453$ PPPM). The trend for total CLL-specific costs was similar to total all-cause cost. Mean all-cause and CLL-related costs PPPM for all resource categories except for pharmacy and office visits increased as the number of AEs increased (Table 3).

A generalized linear model, controlling for demographic and clinical characteristics and regimen, showed a trend toward higher total all-cause cost PPPM as the number of incident AEs increased (cost ratio [CR] = 1.2, 95% CI 1.1–1.2; Supplemental Table 4). The total all-cause cost PPPM was 1.2 times higher for patients receiving ibrutinib as the first observed therapy compared to both patients receiving rituximab monotherapy (CR = 0.9; 95% CI 0.8–0.97) or FCR (CR = 0.8; 95% CI 0.8–0.94; Supplemental Table 4) as the first observed therapy.

DISCUSSION

This study describes the four most common CLL treatments and associated toxicities, HRU, and costs in a recent commercially insured population of treated patients with CLL. Patients in

Table 3 All-cause and CLL-related monthly healthcare utilization and costs per patient by number of unique incident AEs experienced

	All-cause utilization and costs				CLL-related utilization and costs ^c				
	All patients ^a		No AE		All patients ^a		No AE		
	(N = 1706)	(N = 428)	(N = 1706)	(N = 428)	(N = 1706)	(N = 428)	(N = 1706)	(N = 428)	
	N	%	N	%	N	%	N	%	
Total cost									
Mean ± SD	\$13,858 ± 14,626	\$13,287 ± 11,447	\$13,809 ± 14,465	\$13,453 ± 14,894	\$20,807 ± 27,295	\$11,791 ± 13,291	\$11,827 ± 11,095	\$11,773 ± 12,570	\$10,863 ± 13,674
Hospitalization									
Patients with ≥ 1 admission	524	30.7	35	8.2	196	23.9	448	26.3	213
Mean ± SD number of visits	0.1 ± 0.2	0.0 ± 0.1	0.0 ± 0.2	0.1 ± 0.2	0.2 ± 0.3	0.0 ± 0.1	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2
LOS per admission among patients with ≥ 1 admission (Mean ± SD in days)	6.4 ± 5.1	5.8 ± 6.8	6.3 ± 5.6	6.6 ± 4.6	6.8 ± 4.0	6.7 ± 6.0	7.6 ± 14.8	6.4 ± 5.1	6.7 ± 4.5
Mean ± SD cost	\$1784 ± 9168	\$282 ± 1653	\$1405 ± 7695	\$3043 ± 11,900	\$8893 ± 22,878	\$1438 ± 8493	\$204 ± 1389	\$1003 ± 6299	\$2523 ± 11,512
ED visit									
Patients with ≥ 1 visit	707	41.4	83	19.4	316	38.6	289	16.9	35
Mean ± SD number of visits	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1
Mean ± SD cost	\$69 ± 209	\$37 ± 133	\$70 ± 235	\$91 ± 213	\$149 ± 203	\$23 ± 104	\$14 ± 78	\$24 ± 126	\$26 ± 78
Office visit									
Patients with ≥ 1 visit	1700	99.6	426	99.5	815	99.5	1615	94.7	401
Mean ± SD number of visits	1.9 ± 1.4	1.7 ± 1.2	1.8 ± 1.5	2.1 ± 1.4	2.5 ± 1.5	0.9 ± 0.8	1.0 ± 0.8	0.9 ± 0.8	1.0 ± 0.8
Mean ± SD cost	\$236 ± 195	\$206 ± 165	\$233 ± 215	\$261 ± 172	\$313 ± 210	\$121 ± 120	\$121 ± 111	\$118 ± 130	\$123 ± 109
Treatment (oral or injection)^d									
Patients with ≥ 1 prescription/injection administration	1706	100.0	428	100.0	819	100.0	1706	100.0	428
Mean ± SD number of claims	6.8 ± 5.6	6.1 ± 5.3	7.1 ± 6.1	6.8 ± 4.7	7.7 ± 4.8	3.3 ± 4.2	3.2 ± 4.3	3.7 ± 4.7	2.8 ± 3.1
Mean ± SD cost	\$9938 ± 9235	\$11,341 ± 10,120	\$10,309 ± 9928	\$7893 ± 6170	\$8426 ± 7259	\$8982 ± 8918	\$10,415 ± 10,002	\$9376 ± 9509	\$6916 ± 5761
Other services^b									
Patients with ≥ 1 claim	1702	99.8	424	99.1	819	100.0	1690	99.1	416
Mean ± SD number of claims	11.8 ± 9.6	10.3 ± 9.2	11.6 ± 9.6	13.2 ± 9.8	16.2 ± 10.0	8.0 ± 7.9	7.6 ± 7.7	8.0 ± 8.1	8.2 ± 7.7
Mean ± SD cost	\$1832 ± 2800	\$1421 ± 2412	\$1792 ± 2659	\$2165 ± 3301	\$3025 ± 3076	\$1228 ± 2212	\$1074 ± 2009	\$1252 ± 2175	\$1275 ± 2493

AE adverse event, CLL chronic lymphocytic leukemia, ED emergency department, FCR fludarabine/cyclophosphamide/rituximab, LOS length of stay, SD standard deviation, USD United States dollar
^a The 1706 patients include all patients who received at least one of the four most commonly observed CLL treatment regimens at some point during follow-up, regardless of line of therapy (i.e., patient could be indexed on another CLL treatment)
^b Other services include laboratory and pathology, radiology, surgery, ancillary, and all other outpatient services
^c CLL-related utilization and costs were defined as medical and inpatient claims with a diagnosis code for CLL at any position or pharmacy and medical claims for CLL-related treatments
^d Treatment included both oral prescription medications and injection administrations. As all patients were required to have at least one CLL treatment on the index date, all patients have at least one treatment in this table

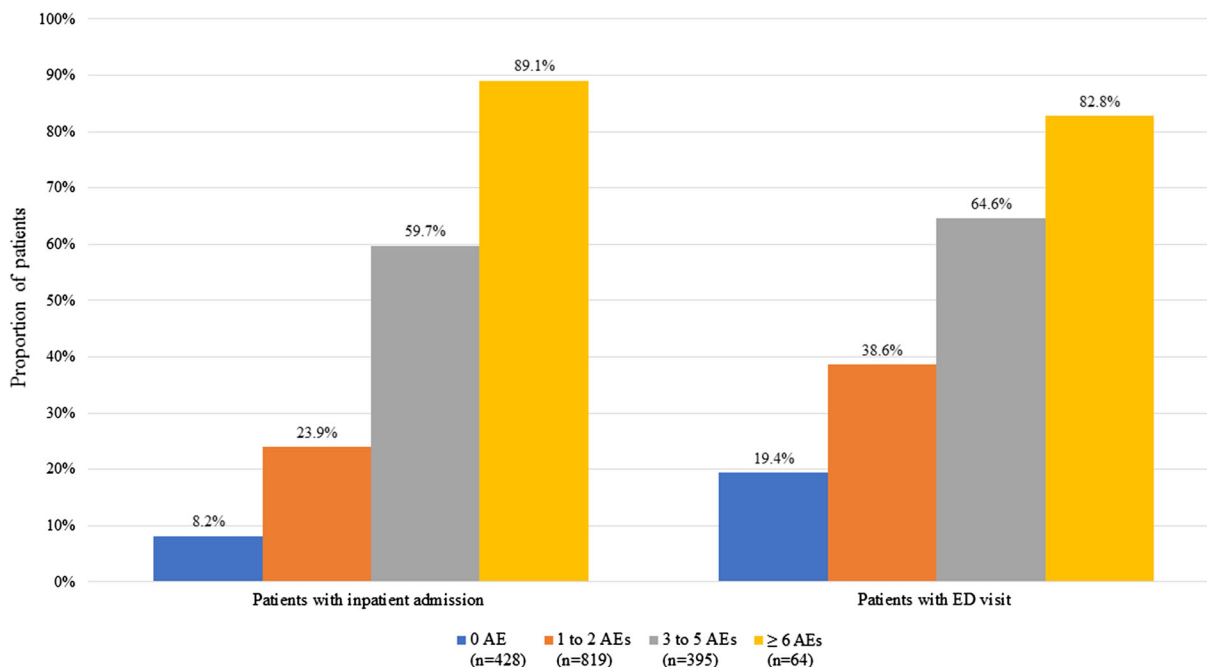


Fig. 5 Proportion of Patients with All-Cause Inpatient Admission and ED Visit by Number of Incident Adverse Events

our study were about 10 years younger than the general CLL population in the USA (median age 59 years in our study vs. 68 years in the general CLL population [3]), a reflection of the largely commercially insured population in the study database. The burden of comorbidities prior to initiating CLL treatment in our study was moderate (median CCI score 2) and consistent with a multicenter patient registry study of newly treated patients with CLL [31]. The proportion of patients at high risk of AF (22%) was lower than that in a claims-based observational study of newly diagnosed patients with CLL, with a higher median age of 66 (47%) [21]; this difference may be explained by the younger population in our study. About one-third of patients had evidence of prognostic biomarker testing on the index date or within 90 days before the index date (i.e., FISH) which appears to be in line with the multicenter CLL registry study reporting a FISH testing rate of 31% among treated patients with CLL [31] primarily treated in the community setting, but lower than a large electronic health records (EHR)-based study of treated patients with CLL (60% had evidence of FISH testing) [32].

Our study included patients treated for CLL in recent years and provides data on the rates of the four most common CLL treatment regimens and associated toxicities of these regimens. The four most common treatments observed in the first-line setting were B-R (24%), ibrutinib monotherapy (20%), FCR (15%), and rituximab monotherapy (14%). This is consistent with a recent EHR-based analysis that evaluated front-line therapies from 2008 to 2017 (B-R, 23%; ibrutinib monotherapy, 18%; FCR, 7%; and rituximab monotherapy, 12%), and the higher rate of FCR in our study is likely reflective of our younger population [32]. It is important to note that our study leveraged administrative claims data only to determine treatment regimens. The relatively frequent use of rituximab monotherapy in the first-line setting (more than 10%) was observed in our study and also reported in the EHR-based study [32]. While rituximab monotherapy was not one of the front-line treatments recommended by the NCCN guidelines [6], it is important to note that frequent use is observed in studies leveraging real-world data [32]. We also observed that B-R was the most common regimen in the first-line setting

Table 4 Multivariable logistic regression model assessing risk of inpatient admission among patients receiving the most common treatments for the first observed therapy

Outcome: inpatient admission (Yes/No)	Patients receiving the most common treatments for the first observed therapy (<i>N</i> = 1579)					
	Parameter estimate	Standard error	Chi-square	<i>P</i> value	Odds ratio	95% CI
Treatment regimen (ref = ibrutinib)						
B-R	− 0.49	0.20	6.14	0.01	0.61	0.41 0.90
Rituximab monotherapy	− 0.37	0.26	2.13	0.14	0.69	0.42 1.14
FCR	− 0.67	0.23	8.84	< 0.01	0.51	0.33 0.80
Number of incident adverse events						
Continuous	1.07	0.08	203.72	< 0.0001	2.92	2.52 3.39
Age at index						
Continuous	− 0.02	0.01	3.90	0.05	0.98	0.96 1.00
Region (ref = south)						
Northeast	0.34	0.22	2.46	0.12	1.41	0.92 2.16
Midwest	0.14	0.21	0.45	0.50	1.15	0.77 1.72
West	0.01	0.28	< 0.01	0.97	1.01	0.59 1.73
Unknown	0.01	0.72	< 0.01	0.98	1.01	0.25 4.20
Plan type (ref = PPO)						
HMO	0.09	0.23	0.13	0.71	1.09	0.69 1.72
POS	− 0.72	0.42	2.90	0.09	0.49	0.21 1.12
Other and unknown	− 0.64	0.58	1.24	0.26	0.53	0.17 1.63
CCI score						
Continuous	0.14	0.06	4.81	0.03	1.15	1.02 1.30
AF risk status at baseline (ref = low risk)						
High risk	− 0.02	0.25	< 0.01	0.95	0.98	0.61 1.59
Baseline comorbidities (ref = No)						
Atrial fibrillation	0.48	0.39	1.48	0.22	1.61	0.75 3.48
Hemorrhage/bleeding	0.22	0.23	0.97	0.33	1.25	0.80 1.96
Neutropenia	0.55	0.29	3.62	0.06	1.74	0.98 3.07
Hypertension	0.43	0.19	5.41	0.02	1.54	1.07 2.22
Arthralgia myalgia	0.78	0.31	6.10	0.01	2.17	1.17 4.02
Other acute conditions of interest (ref = No)						
Infection	0.59	0.17	12.79	< 0.01	1.81	1.31 2.50

Table 4 continued

Outcome: inpatient admission (Yes/No)	Patients receiving the most common treatments for the first observed therapy (<i>N</i> = 1579)					
	Parameter estimate	Standard error	Chi- square	<i>P</i> value	Odds ratio	95% CI
Anemia	0.65	0.17	15.23	< 0.0001	1.92	1.38 2.65

AF atrial fibrillation, *B-R* bendamustine–rituximab, *CCI* Charlson Comorbidity Index, *CI* confidence interval, *FCR* fludarabine/cyclophosphamide/rituximab, *HMO* health maintenance organization, *POS* point of service, *PPO* preferred provider organization

and that ibrutinib monotherapy was the most common in the second- and third-line settings, consistent with previous real-world research [21].

This study highlights the clinical and economic burden among treated patients with CLL. The majority of patients in the study population had evidence of at least one incident AE during their treatment (59%). In this claims-based study, it is possible that AEs are underreported since they are captured by diagnostic coding only and those AEs that did not lead to a healthcare visit may have been missing. Among the four most common CLL treatment regimens, the frequency of incident AEs was highest among patients treated with FCR (77%), followed by B-R (59%), ibrutinib (56%), and rituximab monotherapy (24%). The most commonly observed incident AE in our study was neutropenia (32%, irrespective of treatment regimen or line of therapy), followed by infection (11%), anemia (9%), and thrombocytopenia (8%); these findings are generally consistent with previous real-world studies and clinical trials [21, 33]. As for the incident AEs observed for ibrutinib, regardless of observed line of therapy, we found that infection (15%) was the most common AE; the occurrence of AF (7%), bleeding (9%), and arthralgias (4%) among ibrutinib-treated patients appeared higher than those treated with B-R, FCR, or rituximab monotherapy, similar to a prior claims analysis of older patients with CLL [21]. The majority (75%) of ibrutinib-treated patients received

ibrutinib in the first-line setting, and in the adjusted analyses focusing on the first-line setting, we confirmed the higher risks of AF and bleeding for ibrutinib-treated patients in this setting. These findings are comparable to previous real-world and clinical studies [14, 21, 34], and small discrepancies such as proportion of patients with AEs not requiring treatment or office visits (i.e., anemia, diarrhea, etc.) are expected as our study leverages claims data of younger patients with CLL, which may underreport these AEs.

In our study, 31% of patients were hospitalized during the follow-up period. Although our follow-up was longer (median 16 months) than prior studies and was not focused on treated follow-up for HRU, this is comparable to previous retrospective claims studies of patients with CLL (majority newly treated with B-R, rituximab monotherapy, ibrutinib, or FCR in one study and B-R, rituximab monotherapy, or FCR in another study), which reported a hospitalization rate of 24–25% during the first line of therapy [18, 35]. Our study also found that nearly all patients (99.6%) had an office visit and less than half (41%) had an ED visit, similar to previous real-world studies (96% for office visit; 31–33% for ED visit during the first line of therapy) [18, 35].

Overall, we found that the proportion of patients utilizing each healthcare resource category increased as the number of incident AEs increased. For example, the hospitalization rate among patients experiencing 1–2 AEs (24%) was

less than half of those of patients experiencing 3–5 AEs (60%). Adjusted analyses further confirmed the trend towards higher risk of hospitalization as the number of incident AEs increased. This suggests that, if similar or better efficacy can be achieved when mitigating adverse events, decreasing toxicity may reduce HRU burden among patients with CLL. No prior study reported these results for patients with CLL; however, our results are aligned with a claims-based study of patients with mantle cell lymphoma reporting that increased AEs resulted in increased HRU, including hospitalization and ED visits [36].

Our study also quantified the current healthcare burden among treated patients with CLL. The total healthcare cost from start of CLL treatment through end of follow-up (mean [SD] \$13,858 [\$14,550] PPPM) was five times higher than it was in the 12 months before treatment initiation (mean [SD] \$2709 PPPM [\$4458]). The cost after starting treatment was comparable to the mean total costs reported in previous real-world studies (\$7943 [\$15,757]–\$17,442 [\$15,715] PPPM) [21, 35], highlighting that the healthcare burden among patients with CLL continues to be substantial. Given the limitations of this claims-based approach in capturing AEs and associated HRU, our estimated healthcare costs may be underestimated from true costs incurred. Furthermore, there may be residual confounding of these unadjusted results, such as disease progression, which may impact timing and receipt of treatment. Moreover, pharmacy costs for oral and infused agents accounted for 72% of total cost, with all-cause inpatient and other outpatient services such as laboratory or ancillary services being the next largest contributors to cost. The large portion of total cost attributed to pharmacy cost is reflective of increased treatment costs and high HRU after treatment initiation reported in the literature [18, 37, 38]. Not only are the costs of a newer agent (ibrutinib, in our study) higher, but HRU and costs associated with treatment-related AEs are substantial; this has been documented for other cancers previously [39], but not in any prior studies among patients with

CLL. The unadjusted costs rose as the number of AEs increased, and this finding was internally validated in the adjusted cost model, and consistent with a previous claims-based study which also reported the increase in unadjusted monthly costs per patient when the number of AEs increased [21].

This study is subject to limitations common to retrospective database analyses, including possible billing and coding errors, and that the data were not collected for research purposes. Our study leveraged administrative claims data which lacks comprehensive clinical information (e.g., AEs not requiring medical attention, prognostic factors such as lactate dehydrogenase and white blood cell count). To that end, our findings on AEs and associated HRU and costs are likely underestimated. We were also unable to assess tumor burden and other factors which could have influenced treatment choice. Clinical information to assess severity, grade, and additional details for the observed AEs were not available. In order to explore the burden of AEs associated with treatments, we measured and compared HRU and costs among patients experiencing 0, 1–2, 3–5, and at least 6 incident AEs identified using diagnosis codes. A causal relationship between AEs, HRU, and cost cannot be established without additional clinical information and confirmation that the HRU and costs were directly related to the AEs. Patients with more lines of therapy and longer follow-up have a greater opportunity to incur AEs and costs, and this study did not adjust for follow-up time. The minimum follow-up required was at least 30 days, to be inclusive. The implications of this are that some patients were not in the database for very long to incur AEs and high costs and second- and third-line therapy. Therefore, longer follow-up in a larger sample of patients would likely provide a more comprehensive picture into differences among treatment regimens over time. Despite these limitations, the volume and comprehensiveness of IQVIA PharMetrics® Plus provides the ability to observe treatments, events, HRU, and costs in all settings of care longitudinally.

CONCLUSION

This study highlights the clinical and economic burden associated with current and commonly used CLL treatments. In this study of younger patients treated in the real-world setting, the most common regimens observed among patients with CLL were B-R, ibrutinib monotherapy, rituximab monotherapy, and FCR. More than half of newly treated patients had evidence of at least one incident AE. HRU and costs consistently increased as the number of AEs increased, suggesting a potential association between greater treatment toxicity and higher HRU. Adjusted models confirmed the trend of the healthcare costs and odds of hospitalization increasing as the burden of treatment toxicity increased. As more novel therapies become incorporated into clinical practice, further research examining clinical and economic outcomes, in particular treatment toxicities and associated HRU and costs in a real-world setting, may help prescribers and patients evaluate the risks, benefits, and value of novel agents.

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Compliance with Ethics Guidelines. This study was based on secondary, de-identified data which comply with the Health Insurance Portability and Accountability Act (HIPAA). Institutional review board approval was not required for this study.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request. The data will not be deposited.

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