

# Real-World Characteristics, Treatment Patterns, Health Care Resource Use, and Costs of Patients with Diffuse Large B-Cell Lymphoma in the U.S.

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Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** Diffuse B-cell lymphoma • Health care resource utilization • Patient characteristics • Costs • Treatment patterns

## ABSTRACT

**Background.** Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin lymphoma in the U.S., but current real-world data are limited. This study was conducted to describe real-world characteristics, treatment patterns, health care resource utilization (HRU), and health care costs of patients with treated DLBCL in the U.S.

**Materials and Methods.** A retrospective study was conducted using the Optum Clinformatics Data Mart database (January 2013 to March 2018). Patients with an International Classification of Diseases, Tenth Revision, Clinical Modification diagnosis for DLBCL after October 2015 and no prior International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis for unspecified DLBCL or primary mediastinal large B-cell lymphoma were classified as *incident*; those with such codes were classified as *prevalent*. An adapted algorithm identified lines of therapy (e.g., first line [1L]). All-cause HRU and costs were calculated per-patient-per-year (PPPY) among patients with a  $\geq 1L$ .

**Results.** Among 1,877 incident and 651 prevalent patients with  $\geq 1L$ , median age was 72 years and 46% were female. Among incident patients, 22.6% had at least two lines (2L), whereas 38.4% of prevalent patients had  $\geq 2L$ . The most frequent 1L therapy was rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Incident patients had 1.3 inpatient and 42.0 outpatient (OP) visits PPPY, whereas prevalent patients had 0.8 and 31.3 visits PPPY, respectively. Total costs were \$137,156 and \$81,669 PPPY for incident and prevalent patients, respectively. OP costs were the main driver of total costs at \$88,202 PPPY, which were higher within the first year.

**Conclusion.** This study showed that a large portion of patients require additional therapy after 1L treatment to manage DLBCL and highlighted the substantial economic burden of patients with DLBCL, particularly within the first year following diagnosis. *The Oncologist* 2021;26:e817–e826

**Implications for Practice:** Patients diagnosed with diffuse large B-cell lymphoma (DLBCL) carry a substantial clinical and economic burden. A large portion of these patients require additional therapy beyond first-line treatment. There is significant unmet need among patients with DLBCL who require additional therapy beyond first-line treatment. Patients who do not respond to first-line therapy and are not eligible for transplants have very high health care resource utilization and costs, especially in the first 12 months following initiation of treatment.

## BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) in the U.S., representing 24% of all new NHL cases per year [1] with an estimated incidence of 27,650 new cases in 2016 [2, 3].

DLBCL has a slight male predominance and typically affects older adults, with a peak incidence in people aged 65–74 years (median age = 66 years); the 5-year relative survival rate of DLBCL is 63.2%, which declines further with age [4].

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Although new rates of DLBCL have decreased steadily each year over the past 10 years and trends show an increase in the proportion of surviving patients [4], DLBCL remains an aggressive disease that requires immediate treatment [1].

According to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines), the current standard first-line (1L) treatment for DLBCL is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) [5]. Although the addition of rituximab to standard CHOP results in improved survival [6] making R-CHOP effective in 50%–70% of patients with DLBCL, 30%–50% are refractory to treatment or eventually relapse [7–10]. Following relapse or refractoriness, outcomes are particularly poor and costs remain high [1, 11, 12]. The recommended second-line (2L) treatment options include other rituximab-based chemoimmunotherapy regimens followed by a stem cell transplant (SCT), and targeted therapies such as ibrutinib. Chimeric antigen receptor T-cell (CAR-T) therapies were recently approved for third line and beyond [5].

Despite the availability of a range of treatment options, DLBCL remains associated with substantial morbidity and mortality [4]. Current data on treatment patterns and health care utilization of patients in clinical practice are limited [13–16]. Although it was previously classified together with biologically similar lymphomas, DLBCL has undergone several stratifications with each revision of the World Health Organization classification of lymphoid neoplasms [17–19]. In October 2015, DLBCL was distinguished from primary mediastinal B-cell lymphoma (PMBCL), primary central nervous system lymphoma, and reticulosarcoma with the introduction of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) DLBCL-specific administrative codes in the U.S., which allows for a more accurate examination of these questions. Therefore, this study was conducted to describe the real-world demographic, clinical characteristics, and current treatment patterns among patients diagnosed with DLBCL and treated in the U.S., as well as to assess their health care resource utilization (HRU) and associated costs. The patient characteristics and outcomes were also described specifically for patients with relapsed and refractory DLBCL (rrDLBCL).

## MATERIALS AND METHODS

### Data Source

Optum Clinformatics covers 13 million annual lives of UnitedHealth Group members in all census regions in the U.S. The Optum's Clinformatics Data Mart maintains longitudinal records of patient demographics, insurance coverage (i.e., commercial, Medicare, and Medicaid), dates of eligibility and death, claims for inpatient [IP], outpatient [OP], and emergency room [ER] visits, and costs of services for more than 36 months. Therefore, deidentified health care insurance claims from this database were used to conduct the current study, with data spanning from January 2013 to March 2018.

### Study Design

A retrospective cohort design was used to describe patients with DLBCL who are treated. Study participants were

identified and selected using ICD-10-CM diagnoses codes for DLBCL. However, because DLBCL-specific codes that administratively distinguish it from other morphologically similar lymphomas are only available since October 2015, the observation period for patients with newly diagnosed DLBCL since 2015 was limited. Therefore, patients with a previous International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code associated with unspecified DLBCL before October 2015 were handled differently, and patients were divided into two cohorts: *incident* patients in reference to those with DLBCL and no ICD-9-CM diagnosis prior to October 2015, and *prevalent* patients in reference to those with a previous ICD-9-CM diagnosis code (i.e., prior to October 2015) associated with unspecified DLBCL. These groups were mutually exclusive.

The *index date* was defined as the earliest date of (a) the first ICD-10-CM code for DLBCL or ICD-10-CM code for other nonfollicular lymphoma or unspecified non-Hodgkin lymphoma for incident patients or (b) the date of the first ICD-9-CM diagnosis associated with unspecified DLBCL prior to October 1, 2015, for prevalent patients. The 12-month period prior to the index date was defined as the *baseline period* for all patients. The *observation period* (i.e., follow-up period) ranged inclusively from the index date up to the earliest date among end of data availability or end of continuous health plan enrollment.

### Study Population

Patients were included in the study if they were at least 18 years of age at the index date and had at least 12 months of continuous enrollment prior to the index date (i.e., the baseline period). Patients were also required to have at least one IP stay or two OP encounters with a billing code of DLBCL after October 1, 2015 (ICD-10-CM code: C83.3x); incident patients had a first ICD-10-CM diagnosis for DLBCL after October 1, 2015, and no ICD-9-CM diagnosis for unspecified DLBCL prior to that date, and prevalent patients had an ICD-10-CM diagnosis code for DLBCL and an unspecified ICD-9 diagnosis code for DLBCL before October 1, 2015. Furthermore, only patients with at least 1L anticancer therapy observed with identifiable agents were included in the analysis.

Patients were excluded from the study if they had any ICD-10-CM diagnosis for PMBCL or prior diagnosis of Hodgkin lymphoma, multiple myeloma, or other selected lymphomas (i.e., mature T/natural killer-cell lymphomas and neoplasms of uncertain behavior of plasma cells) during the 12-month baseline period. Prior diagnosis of follicular lymphoma was allowed in order to capture patients with transformed follicular lymphoma.

Incident and prevalent patients with DLBCL were further stratified by the following lines of therapy: (a) patients with 1L therapy observed, (b) patients with 2L therapy, (c) patients with third-line (3L) therapy observed, and (d) patients with fourth-line (4L) therapy observed. Moreover, patients with a 2L were categorized as rrDLBCL and classified as *relapsed* if they initiated 2L treatment  $\geq 90$  days after the last dose of the 1L therapy, and as *refractory* if

they initiated 2L treatment <90 days after the last dose of 1L therapy.

### Algorithm to Identify Lines of Therapy

A claims-based algorithm adapted from previously published papers [20–23] was used to identify lines of therapy in patients with DLBCL (supplemental online Fig. 1). All records of anticancer systemic agents were identified using Generic Product Identifier, Healthcare Common Procedure Coding System, Current Procedural Terminology, and National Drug Code codes. The 1L of therapy was defined by all unique agents observed within the first 21 days following initiation of the first anticancer therapy, a period that corresponds to the longest recommended duration of an R-CHOP or rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH-R) cycle (based on NCCN Guidelines) [5]. A new line of therapy was distinguished by the initiation of a new agent not included in the 1L of therapy. Each new line of therapy was defined by the unique agents used within the first 21-day period following the initiation of the new line of therapy (supplemental online Fig. 1, Scenario 4). Discontinuation of a line of therapy was defined as a 90-day discontinuation of all agents. Reinitiation of the same agents after a 90-day gap was considered a new line of therapy (supplemental online Fig. 1, Scenario 2). The discontinuation of a single agent or more than one agent from a combination therapy was not considered a new line of therapy (supplemental online Fig. 1, Scenario 5). Radiation therapy was not considered as a new line of therapy [21–23]. Moreover, if a patient received radiation therapy within 90 days of the end of a specific line of therapy (e.g., 1L), radiation therapy was considered part of this line (except if a new line of therapy was started before 90 days; in this case, radiation therapy was considered part of the 1L only for the period spanning from the end of the 1L therapy to the start of the 2L therapy).

### Outcome Measures

Demographic and clinical characteristics of incident and prevalent patients were collected at the index date or during the 12-month baseline period, and included age, gender, year of index date, region, insurance plan type, Charlson comorbidity index (CCI) score, and comorbidities (non-psychiatric and psychiatric).

Treatment patterns of anticancer systemic agents were evaluated during the observation period for each line of therapy (i.e., 1L, 2L, 3L, 4L) to assess the proportion of patients where a specific line of therapy was observed (for 2L, 3L, 4L), the duration of therapy (DOT) for each line of treatment, defined as the number of days from the date of initiation of a new anticancer treatment up to the discontinuation of all agents in the line of therapy, a switch to another line, or the addition of a new agent to the current line, the time from index date to 1L initiation, defined as the number of days from the first ICD-9 (for prevalent patients) or ICD-10 (for incident patients) diagnosis to 1L treatment, patients with a next line of therapy, defined as the number of patients in each line of therapy receiving the subsequent line of therapy, and any anticancer therapy

initiated after the first DLBCL diagnosis, including monotherapy and combination therapies based on, but not limited to, the NCCN Guidelines [5].

All-cause HRU (i.e., IP [including hospitalizations and skilled nursing and long-term care facilities], OP, ER, and other [including home services and hospice] visits) was evaluated for both incident and prevalent patients treated with any regimen and those treated in 1L with R-CHOP during the observation period. All-cause health care costs (i.e., IP, OP, ER, other, and pharmacy costs) were evaluated for both incident and prevalent patients treated with any regimen and those treated in 1L with R-CHOP during the observation period. Both analyses were repeated using data only up to 12 months from the date of 1L treatment initiation in order to balance the follow-up period between incident and prevalent patients. HRU and health care costs (in 2018 U.S. dollars) were reported per-patient-per-year (PPPY).

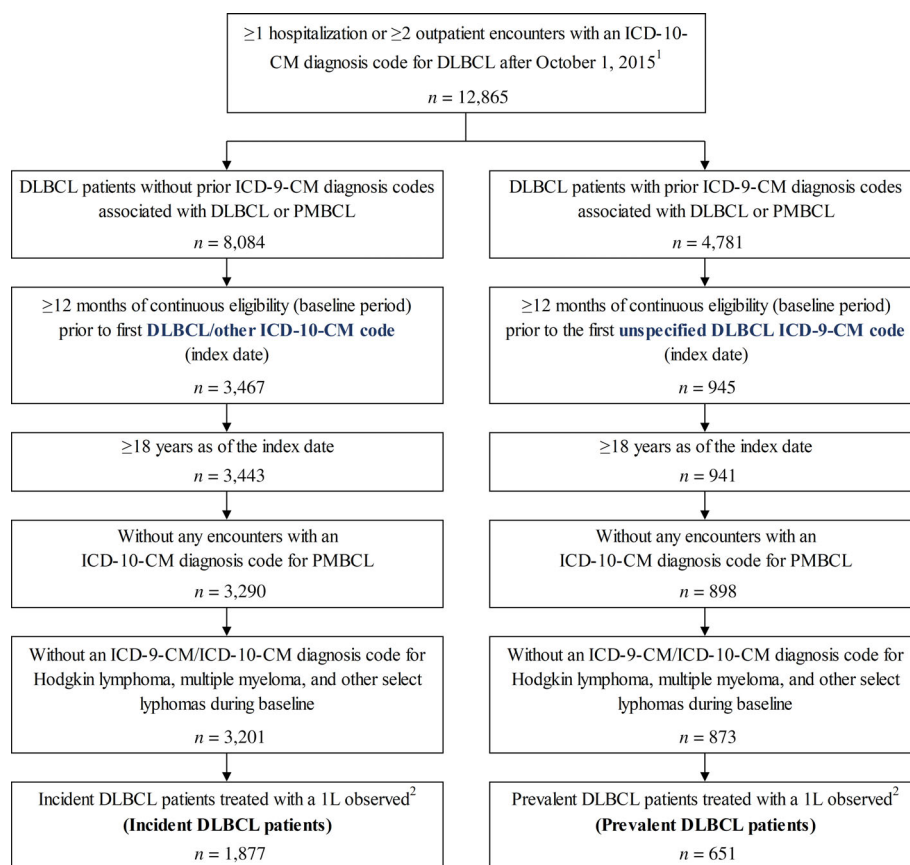
### Statistical Analysis

All analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC). Patient characteristics and treatment patterns were summarized using descriptive statistics and included means ( $\pm$  SDs) and medians for continuous variables and frequencies and proportions for categorical variables. Rates of HRU PPPY were calculated as number of events (i.e., IP stays, ER visits, OP visits) divided by patient-years of observation. Health care costs PPPY were calculated as the total cost divided by the total number of days of enrollment, multiplied by 365 days where costs were weighted by each patient's length of follow-up to avoid overestimating costs by annualizing data for patients observed for less than 1 year. Because a large proportion of patients identified in the database are insured through Medicare, a sensitivity analysis was also conducted to describe treatment patterns, HRU, and costs among patients treated with 1L and insured through Medicare only. Because this study is purely descriptive, no statistical comparisons were conducted between patient groups.

## RESULTS

### Baseline Characteristics

A total of 2,528 patients with DLBCL and a 1L treatment observed were identified, including 1,877 incident and 651 prevalent patients (Fig. 1). Among incident patients, the median age was 74 years and 45.8% were female; among prevalent patients, the median age was 72 years and 45.5% were female. Incident and prevalent patients had mean CCI scores of 2.7 and 2.3, respectively. During baseline, the most common Elixhauser comorbidities among incident and prevalent patients were hypertension (70.5% and 65.6%, respectively) and diabetes (31.5% and 29.0%, respectively), whereas the most prevalent psychiatric comorbidity was sleep-wake disorders (13.8% and 13.4%, respectively; Table 1). Baseline demographics and clinical characteristics were similar among patients treated with 1L and insured through Medicare (supplemental online Table 1).



**Figure 1.** Patient disposition.

<sup>1</sup>DLBCL can only be administratively differentiated from other morphologically similar lymphomas using ICD-10-CM codes, which have been available since October 1, 2015, in the U.S.

<sup>2</sup>Including codes referring to nonidentifiable agents (e.g., ICD-9-CM: V58.11, ICD-10-CM: Z51.11, Current Procedural Terminology: 96401, Healthcare Common Procedure Coding System: J8999), 2,450 incident patients and 798 prevalent patients had a 1L observed. Because this study focuses on agents included in each line of therapies, patients with nonidentifiable agents only were not selected. Abbreviations: 1L, first line; DLBCL, diffuse large B-cell lymphoma; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; PMBCL, primary mediastinal large B-cell lymphoma.

## Treatment Patterns

Analysis of observed treatment patterns with identifiable agents showed that the mean  $\pm$  SD DOT in 1L for incident patients was  $81.1 \pm 65.9$  days and  $110.1 \pm 125.3$  days for prevalent patients (Table 2). Mean  $\pm$  SD time from index date to the 1L initiation was  $47.1 \pm 62.1$  days for incident patients and  $73.9 \pm 158.8$  days for prevalent patients. The most frequently observed 1L therapies of both incident and prevalent patients were R-CHOP (65.3% and 66.8%, respectively), rituximab monotherapy (7.2% and 7.1%, respectively), and bendamustine plus rituximab (4.7% and 5.2%, respectively; Fig. 2). 22.6% of incident patients and 38.4% of prevalent patients treated received  $\geq 2$ L (mean  $\pm$  SD DOT =  $74.2 \pm 91.9$  and  $123.2 \pm 206.9$  days, respectively). The most commonly observed 2L treatment among incident and prevalent patients was R-CHOP (31% and 20%, respectively). 21.9% of incident patients and 39.2% of prevalent patients treated received  $\geq 3$ L, with progressively shorter DOT for subsequent lines of therapy ( $60.3 \pm 83.8$  and  $93.5 \pm 146.5$  days, respectively). The most commonly observed 3L treatment among incident and prevalent patients was rituximab monotherapy (15% and 20%, respectively). 28.0% of

incident and 40.8% of prevalent patients treated received  $\geq 4$ L (DOT =  $47.5 \pm 76.7$  and  $56.6 \pm 62.4$  days, respectively). The most commonly observed 4L treatment among incident and prevalent patients was rituximab monotherapy (19% and 20%, respectively). SCT was given to 3.8% and 6.0% in the 2L, 3.2% and 3.1% in the 3L, and 3.8% and 5.0% in the 4L. Treatment patterns were similar among patients insured through Medicare (supplemental online Table 2).

## Health Care Resources Utilization and Cost

For incident and prevalent patients, the mean evaluation period was 330.4 and 900.6 days, respectively. Incident patients treated with any regimen had an average of 1.3 IP stays, 1.3 ER visits, and 42.0 OP visits PPPY, whereas prevalent patients had an average of 0.8 stays, 0.9 visits, and 31.3 visits PPPY, respectively. For incident and prevalent patients treated with R-CHOP regimens in 1L, the mean evaluation period was 344.0 and 933.1 days, respectively. Incident patients treated with R-CHOP regimens had average of 1.0 IP stays, 1.3 ER visits, and 41.2 OP visits PPPY, whereas prevalent patients had an average of 0.6 stays, 0.8 visits, and

**Table 1.** Baseline demographic and clinical characteristics for patients with DLBCL

Characteristics	Patients with incident DLBCL (n = 1,877)	Patients with prevalent DLBCL (n = 651)
Observation period, days, mean $\pm$ SD [median]	377.5 $\pm$ 233.8 [331]	974.5 $\pm$ 367.7 [1,020]
Demographics <sup>a</sup>		
Age, years, mean $\pm$ SD [median]	71.9 $\pm$ 11.2 [74]	70.3 $\pm$ 11.6 [72]
By category, n (%)		
<35	19 (1.0)	11 (1.7)
35–49	71 (3.8)	24 (3.7)
50–64	262 (14.0)	117 (18.0)
65–79	1,059 (56.4)	359 (55.1)
$\geq 80$	466 (24.8)	140 (21.5)
Gender, female, n (%)	859 (45.8)	296 (45.5)
Year of index date, <sup>a</sup> n (%)		
2014	0 (0.0)	285 (43.8)
2015	153 (8.2)	366 (56.2)
2016	739 (39.4)	0 (0.0)
2017	885 (47.1)	0 (0.0)
2018	100 (5.3)	0 (0.0)
Region, <sup>a</sup> n (%)		
South	707 (37.7)	209 (32.1)
West	430 (22.9)	165 (25.3)
Midwest	509 (27.1)	184 (28.3)
Northeast	223 (11.9)	91 (14.0)
Insurance plan type, <sup>a</sup> n (%)		
Commercial insurance	363 (19.3)	177 (27.2)
Medicare	1,514 (80.7)	474 (72.8)
CCI, <sup>b</sup> mean $\pm$ SD [median]	2.7 $\pm$ 2.6 [2]	2.3 $\pm$ 2.4 [2]
Comorbidities (nonpsychiatric), <sup>b,c</sup> n (%)		
Hypertension	1,324 (70.5)	427 (65.6)
Diabetes	591 (31.5)	189 (29.0)
Cardiac arrhythmias	448 (23.9)	125 (19.2)
Chronic pulmonary disease	438 (23.3)	146 (22.4)
Hypothyroidism	419 (22.3)	123 (18.9)
Comorbidities (psychiatric), <sup>b,d</sup> n (%)		
Sleep-wake disorders	259 (13.8)	87 (13.4)
Depressive disorders	234 (12.5)	70 (10.8)
Anxiety disorders	238 (12.7)	43 (6.6)
Other conditions that may require a focus of clinical attention	213 (11.3)	74 (11.4)
Substance-related and addictive disorders	189 (10.1)	60 (9.2)
All-cause HRU, <sup>b</sup> mean $\pm$ SD [median]		
IP stays <sup>e</sup>	0.28 $\pm$ 0.72 [0]	0.22 $\pm$ 0.50 [0]
ER visits	0.9 $\pm$ 2.2 [0]	0.8 $\pm$ 1.8 [0]
OP visits	17.6 $\pm$ 20.3 [14]	16.0 $\pm$ 14.5 [13]
Other visits <sup>f</sup>	4.1 $\pm$ 9.5 [0]	3.9 $\pm$ 8.7 [0]
All-cause health care costs, <sup>b</sup> U.S.\$ 2018, mean $\pm$ SD		
Total costs (medical + pharmacy)	\$23,092 $\pm$ 39,299	\$19,618 $\pm$ 30,851
Total medical costs	\$19,518 $\pm$ 34,702	\$17,475 $\pm$ 29,176

(continued)



**Table 1.** (continued)

Characteristics	Patients with incident DLBCL ( <i>n</i> = 1,877)	Patients with prevalent DLBCL ( <i>n</i> = 651)
IP costs <sup>e</sup>	\$4,748 ± 16,653	\$5,029 ± 22,025
ER costs	\$2,412 ± 5,992	\$2,121 ± 5,703
OP costs	\$10,786 ± 27,242	\$8,642 ± 12,300
Other costs <sup>f</sup>	\$1,573 ± 5,686	\$1,683 ± 5,935
Pharmacy costs	\$3,574 ± 13,055	\$2,143 ± 4,754

<sup>a</sup>Evaluated at the index date.<sup>b</sup>Evaluated during the 12 months prior to the index date.<sup>c</sup>Most prevalent among the Elixhauser comorbidities.<sup>d</sup>Most prevalent among comorbidities from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition.<sup>e</sup>Includes hospitalizations and skilled nursing and long-term care facilities.<sup>f</sup>Includes visits such as home services and hospice.

Abbreviations: CCI, Charlson comorbidity index; DLBCL, diffuse large B-cell lymphoma; ER, emergency room; HRU, health care resource utilization; IP, inpatient; OP, outpatient.

**Table 2.** Observed treatment patterns with identifiable drugs for patients with diffuse large B-cell lymphoma

Treatment patterns	Patients with at least			
	1L therapy	2L therapy	3L therapy	4L therapy
Incident patients ( <i>n</i> = 1,877)				
Number of patients, <i>n</i> (%)	1,877 (100.0)	424 (22.6)	93 (5.0)	26 (1.4)
Observation period, days, mean ± SD [median]	377.5 ± 233.8 [331]	442.1 ± 214.8 [405]	542.6 ± 193.8 [537]	619.3 ± 190.1 [648]
DOT, days, mean ± SD	81.1 ± 65.9	74.2 ± 91.9	60.3 ± 83.8	47.5 ± 76.7
Time from index date to 1L initiation, days, mean ± SD [median]	47.1 ± 62.1 [32]	NA	NA	NA
Patients with a next line of therapy, <i>n</i> (%)	424 (22.6)	93 (21.9)	26 (28.0)	3 (11.5)
Prevalent patients ( <i>n</i> = 651)				
Number of patients, <i>n</i> (%)	651 (100.0)	250 (38.4)	98 (15.1)	40 (6.1)
Observation period, days, mean ± SD [median]	974.5 ± 367.7 [1,020]	981.7 ± 346.1 [1,013]	1,003.7 ± 340.2 [1,011]	1,074.8 ± 273.2 [1,050]
DOT, days, mean ± SD	110.1 ± 125.3	123.2 ± 206.9	93.5 ± 146.5	56.6 ± 62.4
Time from index date to 1L initiation, days, mean ± SD [median]	73.9 ± 158.8 [31]	NA	NA	NA
Patients with a next line of therapy, <i>n</i> (%)	250 (38.4)	98 (39.2)	40 (40.8)	23 (57.5)

Abbreviations: 1L, first line; 2L, second line; 3L, third line; 4L, fourth line; DOT, duration of therapy; NA, not applicable.

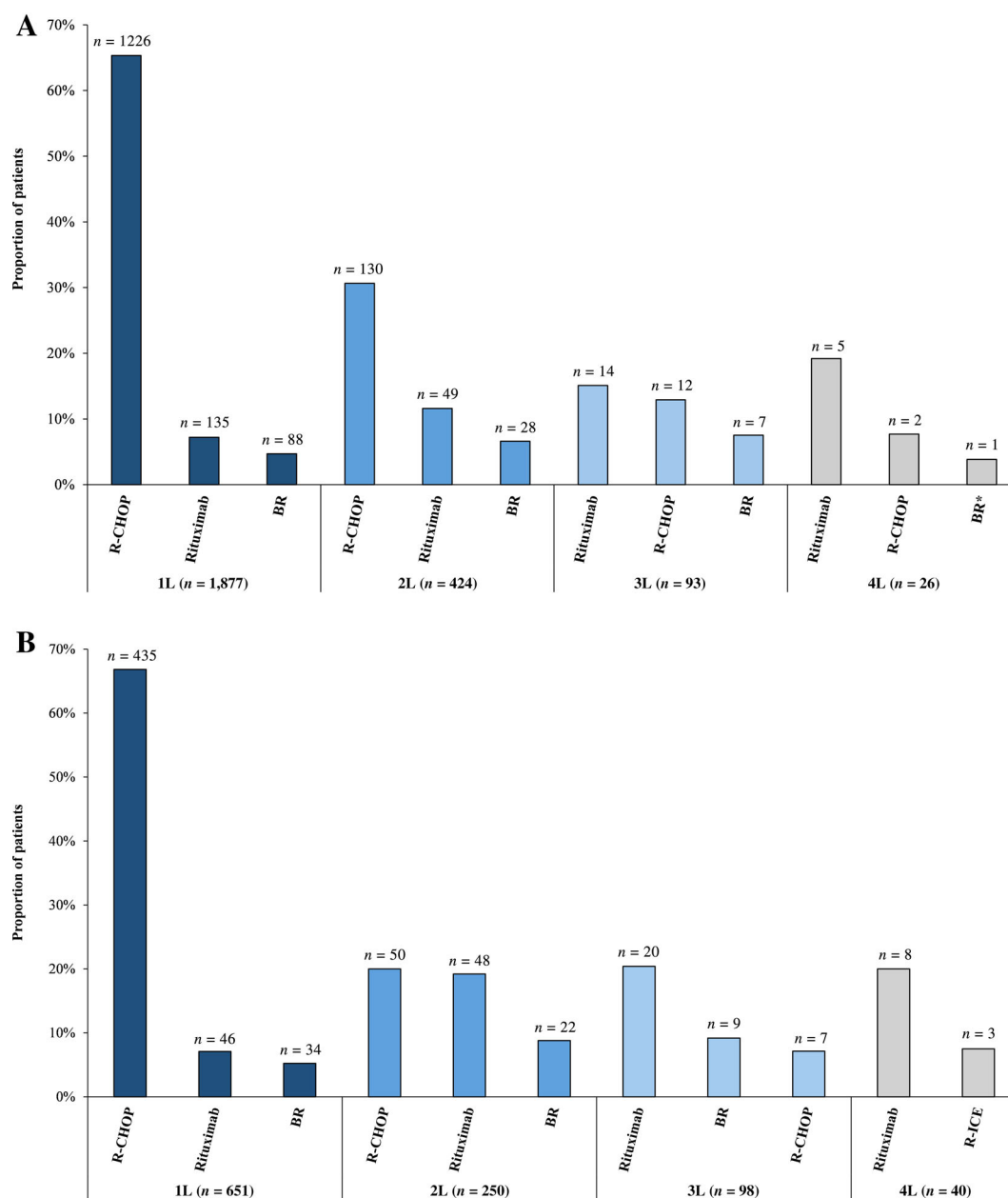
30.2 visits PPPY, respectively (Table 3). When restricting the evaluation period up to 12 months from the date of 1L treatment initiation, HRU PPPY for all treated incident patients was slightly higher, with 1.6 IP stays, 1.5 ER visits, and 48.7 OP visits during a mean evaluation period of 247.0 days. A similar trend was found for all treated prevalent patients, with 1.3 IP stays, 1.1 ER visits, and 45.1 OP visits during a mean evaluation period of 344.4 days.

For the overall evaluation period, the corresponding mean ± SD total health care costs (medical and pharmacy) were \$137,156 ± 123,753 and \$127,202 ± 98,282 for all treated incident patients and those treated with R-CHOP, respectively. Corresponding OP costs (including costs of administered therapies) were \$88,202 ± 89,417 and \$87,616 ± 77,362, respectively, and were the main drivers of total health care costs. Although similar trends were observed for prevalent patients, the mean total health care costs were lower for all treated prevalent patients (\$81,669 ± 114,414) relative to all treated incident patients (Fig. 3); however, follow-up

periods were longer for prevalent patients (~2.5 years) compared with incident patients (~11 months). A sensitivity analysis restricting patients' evaluation periods up to 12 months (mean follow-up periods of 8 months for incident and 11 months for prevalent patients) yielded more similar results (mean ± SD total health care costs for all treated patients: \$169,776 ± 113,618 for incident and \$140,786 ± 86,428 for prevalent), and highlighted increased costs incurred within the first year following a DLBCL diagnosis. The findings were consistent among patients insured through Medicare (supplemental online Table 3).

### Relapsed/ Refractory Stratification (2L)

Among incident patients treated with 2L therapy, 139 (32.8%) were defined as relapsed and 68 as refractory (16.0%) cases, whereas among prevalent patients, 153 (61.2%) were defined as relapse and 21 (8.4%) as refractory cases. The median age for incident patients was 74 and 72 years for relapse and refractory, respectively, and 72 years



**Figure 2. (A):** Most frequently observed treatments during the observation period for patients with incident diffuse large B-cell lymphoma (DLBCL). \*, In addition to BR, R-CEOP (rituximab plus cyclophosphamide, etoposide, vincristine, and prednisone) was also used in 4L by one person. **(B):** Most frequently observed treatments during the observation period for patients with prevalent DLBCL.

Abbreviations: 1L, first line; 2L, second line; 3L, third line; 4L, fourth line; BR, bendamustine plus rituximab; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-ICE, rituximab plus ifosfamide, carboplatin, and etoposide phosphate.

for both relapse and refractory prevalent patients (baseline characteristics of rrDLBCL cohorts are presented in supplemental online Table 4). Among incident patients, there was higher use of rituximab monotherapy in relapsed (30.9%) than refractory (8.8%) patients, who favored other monotherapy regimens (22.1% vs. 12.9%) concurrently with radiation therapy (17.6% vs. 9.4%). Among relapsed prevalent patients, 30.1% received rituximab monotherapy, whereas none was administered to refractory patients. HRU of patients with rrDLBCL is reported in supplemental online Table 5. The associated health care costs were \$164,631 and \$159,729 PPPY for

incident relapse and refractory patients, respectively, and \$112,653 and \$95,465 PPPY for prevalent relapse and refractory patients, respectively (supplemental online Fig. 2). Overall, the total health care costs were driven by OP costs, which included anticancer therapy, drug administration, and laboratory tests.

## DISCUSSION

This study evaluated real-world patient demographics, clinical characteristics, treatment patterns, HRU, and associated

**Table 3.** HRU during follow-up among patients with diffuse large B-cell lymphoma treated at 1L with any regimen and with R-CHOP

HRU	Patients at 1L treated with	
	Any regimen	R-CHOP
<b>Incident patients</b> ( <i>n</i> = 1,877)		
Number of patients, <i>n</i>	1,877	1,226
Evaluation period, days, mean $\pm$ SD [median]	330.4 $\pm$ 231.6 [277]	344.0 $\pm$ 236.0 [297]
All-cause HRU, PPPY, mean $\pm$ SD [median]		
IP stays <sup>a</sup>	1.3 $\pm$ 2.2 [0]	1.0 $\pm$ 1.7 [0]
ER visits	1.3 $\pm$ 2.6 [0]	1.3 $\pm$ 2.7 [0]
OP visits	42.0 $\pm$ 29.1 [38]	41.2 $\pm$ 27.1 [38]
Other visits <sup>b</sup>	9.8 $\pm$ 19.7 [1]	8.7 $\pm$ 18.5 [1]
<b>Prevalent patients</b> ( <i>n</i> = 651)		
Number of patients, <i>n</i>	651	435
Evaluation period, days, mean $\pm$ SD [median]	900.6 $\pm$ 388.1 [964]	933.1 $\pm$ 393.2 [999]
All-cause HRU, PPPY, mean $\pm$ SD [median]		
IP stays <sup>a</sup>	0.8 $\pm$ 2.3 [0]	0.6 $\pm$ 1.8 [0]
ER visits	0.9 $\pm$ 2.4 [0]	0.8 $\pm$ 2.3 [0]
OP visits	31.3 $\pm$ 33.9 [29]	30.2 $\pm$ 33.8 [27]
Other visits <sup>b</sup>	7.1 $\pm$ 21.0 [1]	6.4 $\pm$ 18.9 [1]

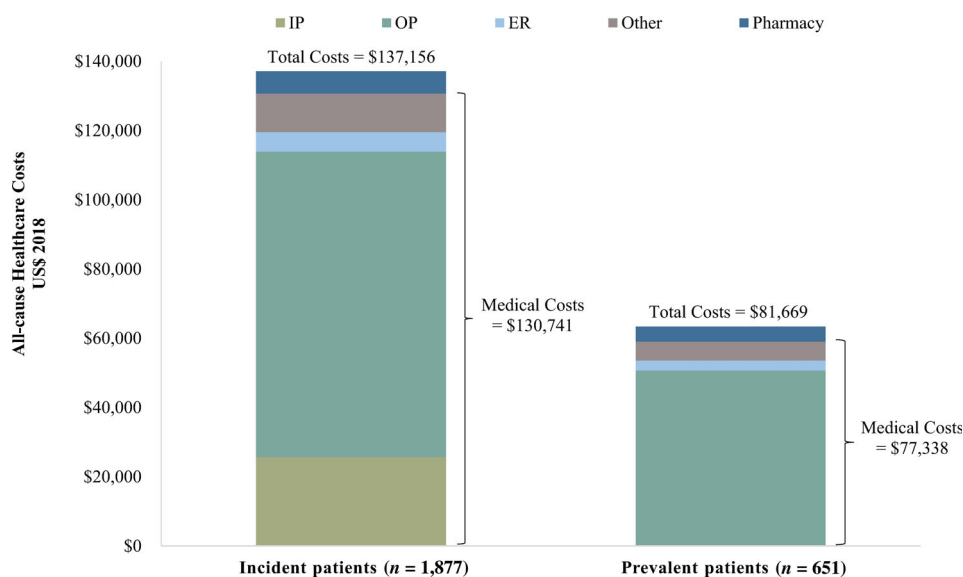
<sup>a</sup>Includes hospitalizations and skilled nursing and long-term care facilities.

<sup>b</sup>Includes visits such as home services and hospice.

Abbreviations: 1L, first line; ER, emergency room; HRU, health care resource utilization; IP, inpatient; OP, outpatient; PPPY, per-patient-per-year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

costs for patients with DLBCL using health insurance claims in the U.S. Most incident and prevalent patients were treated with at least one line of therapy, and a substantial portion of these patients required additional lines of therapy. Among patients treated with at least one line of therapy, total PPPY health care costs were \$137,156 in incident patients and \$81,669 in prevalent patients; more than 60% of these costs were driven by OP visits. In a sensitivity analysis performed over the first 12 months following initiation of 1L, total PPPY health care costs increased to \$169,776 and \$140,786 for incident and prevalent patients, respectively, highlighting the increased health care costs incurred within the first year following a DLBCL diagnosis. Moreover, rrDLBCL presents an additional economic burden.

The NCCN Guidelines currently recommend R-CHOP for 1L treatment in newly diagnosed DLBCL and, similar to previous reports [14], the current data show that R-CHOP was administered to 65.3% of incident and 66.8% of prevalent patients who were treated. Among all patients who received at least a 1L of therapy, 22.6% of incident and 38.4% of prevalent patients required additional therapy after 1L. Although consolidation therapy with high-dose chemotherapy and SCT has long been regarded as the most successful approach for patients requiring 2L therapy, a surprisingly small proportion of patients are eligible to receive SCT, likely because of age or specific comorbidities [24, 25]. Furthermore, subsequent lines of treatment are noticeably more heterogeneous because there is no standard of care for patients who are not eligible for SCT, and whose outcomes are consequently poor [26, 27]. In line with a recent study examining treatment patterns in DLBCL [14], our data show that rituximab-based combination therapies (R-CHOP and bendamustine plus rituximab) were the most used in 2L treatment, with rituximab monotherapy as the most common single agent administered. In 3L and 4L treatments, the proportion of patients treated with combination

**Figure 3.** Health care costs per patient per year during the observation period for patients with diffuse large B-cell lymphoma treated with at least one line of therapy.

Abbreviations: ER, emergency room; IP, inpatient; OP, outpatient.



therapy decreases in favor for rituximab monotherapy. Among patients with rrDLBCL, relapsed patients more commonly received rituximab as part of their treatment regimen than refractory patients (30.9% vs. 8.8% of incident patients, and 30.1% vs. 0.0% of prevalent patients), which is consistent with previous findings [16].

HRU and the associated costs up to 12 months post 1L were similar between prevalent and incident patients, and were consistently driven by high OP costs, including treatment costs. Rituximab was a component in most treatments received by patients with DLBCL, which has been associated with cost differences depending on the setting in which it was administered [28]. Moreover, a recent study by Morrison and colleagues reported the substantial economic burden of patients diagnosed with DLBCL, and specifically within the first year following diagnosis [29]. In patients with rrDLBCL, the incurred HRU and accompanying costs were substantial, with a trend toward higher IP stays for refractory patients which suggests a worse prognosis. However, the total health care costs were similar, offset by higher anticancer therapy costs among relapsed patients. Because the treatment landscape for rrDLBCL has changed in recent years with the approval of novel options such as CAR-T therapies, it is expected that treatment costs in this population will change over time.

The present study is subject to a number of limitations. First, coding inaccuracies or omissions in procedures and diagnoses could have occurred because of the nature of claims databases. Second, the analysis period of this study included data immediately following the discontinuation of ICD-9-CM in October 2015, and the use of ICD-10-CM codes for DLBCL may change over time. Third, because a claims-based algorithm was used to identify lines of therapy, the classification of anticancer agents within each line of therapy may not have always faithfully reflected the actual treatment regimens of the patients. For example, the algorithm may have reclassified patients in 1L of treatment with R-CHOP who had additional drugs added to their primary line of treatment at a later date as 2L patients, therefore overestimating the use of R-CHOP in 2L. Fourth, costs in this study were estimated using the amount paid, which can be dependent on contractual agreements; however, Optum standardized these costs using standard pricing algorithms to account for differences in pricing across health plans and provider contracts [30]. Finally, the proportion of patients treated might be underestimated because the medications used during hospitalization (such as chemotherapy) are not fully captured in the database. Although revenue or diagnosis codes may indicate the administration of chemotherapy for some patients (if data are available), these codes are nonspecific and thus do not identify the chemotherapy drug used.

## CONCLUSION

This real-world assessment of patient characteristics, treatment patterns, HRU, and costs highlights the substantial clinical and economic burden of patients diagnosed with

DLBCL and treated with an identifiable 1L therapy. Furthermore, this study shows that a large portion of patients require additional therapy after 1L treatment to manage DLBCL, highlighting the significant unmet need in this population, as well as the very low use of “standard” salvage therapy such as SCT. There is no standard of care beyond 1L therapy for patients who are not eligible for transplants. Moreover, HRU and health care costs of these patients were high, especially in the first 12 months following initiation of treatment. New affordable and safe treatment options are necessary for those who cannot tolerate combination therapies as outcomes are poor, and with the advent of novel treatment options for DLBCL, further research is warranted to evaluate their use in real-world setting and their benefit to the patient population as a whole, beyond that of patients enrolled on clinical trials.

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## DISCLOSURES

**Xiaoqin Yang:** Merck & Co., Inc. (E); **François Laliberté:** Merck & Co., Inc. (RF), Analysis Group (E); **Guillaume Germain:** Merck & Co., Inc. (RF), Analysis Group (E); **Monika Raut:** Merck & Co., Inc. (E); **Mei Sheng Duh:** Merck & Co., Inc. (RF), Analysis Group (OI); **Shuvayu S. Sen:** Merck & Co., Inc. (E); **Dominique Lejeune:** Merck & Co., Inc. (RF), Analysis Group (E); **Kaushal Desai:** Merck & Co., Inc. (E); **Philippe Armand:** Merck & Co., Inc. (RF).

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