Research Article

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Economic burden and treatment patterns for patients with diffuse large B-cell lymphoma and follicular lymphoma in the USA

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Aim: Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are common types of non-Hodgkin's lymphoma, and real-world evidence continues to be lacking for healthcare costs and utilization among DLBCL and FL patients. Our study aims to describe medical and pharmacy costs and health resource utilization and to characterize longitudinal treatment patterns among these patients. **Methods:** A retrospective observational study was performed among adult patients with DLBCL or FL using the US MarketScan (Truven) administrative claims data from 1 January 2007 to 31 December 2015. Diagnoses of DLBCL and FL were based upon ICD-9 codes. Identifications of treatment lines involved 30 lymphoma-specific anticancer systemic agents. Direct healthcare costs and utilizations were computed in the 1-year postdiagnosis period. Generalized linear models with a gamma link were used to compare healthcare costs between therapies with and without rituximab. **Results:** A total of 2767 DLBCL and 5989 FL patients received frontline therapy. The majority received treatment within 3 months after initial diagnosis (DLBCL 79.9% and FL 62.4%) and were treated with rituximab or bendamustine either alone or in combination (DLBCL 67.4% and FL 84.7%). The total healthcare costs were US $15,555 and $10,192 per patient per month within 1 year following their initial diagnosis for DLBCL and FL, respectively. The medical costs were nearly twice as much as the drug costs for DLBCL patients. Both DLBCL and FL patients receiving rituximab had higher pharmacy costs but lower medical costs ($p < 0.001$). During the first year following initial diagnosis, the resource utilization (per patient per month) of DLBCL patients included 0.21 inpatient admissions, 0.26 radiation therapy, 2.63 outpatient or office visits, 0.18 emergency room visits, 0.06 intensive care unit admissions and 0.10 stem cell transplantation. FL patients occupied less health resources than DLBCL patients. **Conclusion:** The healthcare costs and health resources utilized were considerable in non-Hodgkin's lymphoma, especially DLBCL patients.

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Keywords: diffuse large B-cell lymphoma • follicular lymphoma • healthcare costs • resource utilization • treatment

Non-Hodgkin's lymphoma (NHL) is a cancer that typically starts in lymphocytes in the lymph nodes and other lymphoid tissues, such as the spleen and bone marrow, which serve as part of the immune system. NHL is one of the most common cancers in the USA, with approximately 72,240 Americans diagnosed with NHL in 2017 [1]. For unknown reasons, NHL incidence rates have almost doubled since the 1970s [1]. Furthermore, substantial healthcare costs and utilization have become a significant burden for both the healthcare system and the patient's family [2,3].

Approximately 85% of NHL cases are diagnosed with B-cell lymphomas in the USA, and diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL, representing approximately one out of every three lymphoma diagnoses [4]. DLBCL can affect any age group but occurs most frequently among older individuals.

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DLBCL usually begins as a quickly growing mass in a lymph node deep within the body, such as in the chest or abdomen, or in a lymph node in the neck or armpit, but it can also start in other areas, such as the intestines, bone, or even brain or spinal cord [4]. The five-drug chemoimmunotherapy combination R-CHOP remains the standard frontline treatment of DLBCL and has not changed in more than 15 years since the anti-CD20 monoclonal antibody rituximab was added to the CHOP backbone as standard-of-care for DLBCL in 2002 [5]. However, at least a third of patients are not cured by R-CHOP, and relapsed or refractory DLBCL is fatal in approximately 90% of patients [6]. Recently, genomics and personalized medicine have been discussed to improve treatment options for DLBCL [7].

Another common type of NHL is follicular lymphoma (FL) accounting for approximately 15–30% of all NHLs in developed countries [3,8,9]. The term follicular indicates that the cells tend to grow in a nodular pattern within the lymph nodes. The average age for patients with FL is 60 years and usually occurs throughout many lymph node sites in the body and bone marrow [4]. FL is known as 'indolent' or 'low-grade' but is difficult to cure. Death occurs at a median of 12.5 years after diagnosis [10], generally as a consequence of resistant disease, transformation to diffuse large B-cell pathology, or side effects from therapy. FL patients younger than 40 have a median overall survival of 24 years [10]. It has been suggested that these lymphomas might not require treatment prior to a clinical need to do so because of a lack of associated survival advantage [8]. FL may be untreated or treated by radiation only in the early stages. Advanced disease can be treated with a variety of options, often including chemotherapy plus immunotherapy, with rituximab frequently used in combination or alone as an immunotherapeutic agent [11].

Given the rapid evolution in diagnostic subtyping as well as treatment regimens, it is important to examine the economic burden, treatment patterns and outcomes among these patients based on real-world evidence utilizing secondary databases to assist in informing those involved in the decision-making process. Our study aimed to describe total healthcare costs and resource utilization in patients with DLBCL and FL and to characterize real-world longitudinal treatment patterns among them, including the type, duration and sequence of therapy.

Patients & methods

Study design & data source

A retrospective observational study was performed among adult patients with DLBCL or FL using the US MarketScan (Truven) administrative claims data from 1 January 2007 to 31 December 2015. This database has commercial and Medicare Advantage enrollees, comprising of inpatient admissions, inpatient services, outpatient services, outpatient drug claims, detail enrollment and laboratory test results. Data are available for over 170 million patients who have been sampled since 1995. The MarketScan and other claims databases are some of the best tools available to some research questions when clinical trials are not feasible. Since this study utilized a retrospective unidentified database, we have identified no risks of relapse or survival rates for these patients.

Identification of treatment lines

The diagnoses of DLBCL and FL were based upon the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes (200.7× for DLBCL, 202.0× for FL). Identification of treatment lines involved 30 lymphoma-specific anticancer systemic agents: bendamustine, brentuximab vedotin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytarabine, cytosine, doxorubicin, epirubicin, etoposide, filgrastim, fludarabine, gemcitabine, ibritumomab tiuxetan, idelalisib, lenalidomide, mesna, methotrexate, methylprednisolone, mitoxantrone, oxaliplatin, procarbazine, rituximab, tositumomab, vincristine, ibrutinib, ifosfamide, dexamethasone and prednisone. These agents were extracted by the corresponding codes derived from the Healthcare Common Procedure Coding System and/or National Drug Code (NDC). All agents received within 30 days following the day of the first infusion or fill date constituted frontline therapy. The date of the first infusion or fill associated with frontline therapy was the index frontline therapy date. Prednisone alone was not considered as a treatment line, whereas dexamethasone alone was considered if it was received continuously for 42 days or more.

The second and subsequent lines of therapy were identified if a patient switched to a different agent/regimen (e.g., from rituximab-based to bendamustine-based), if an agent was added to the regimen (except dexamethasone and prednisone), or if the same or similar regimen had a treatment gap of greater than 120 days. Two regimens were considered to be similar if they included the same agents, except for dexamethasone and prednisone.

Inclusion & exclusion criteria

Patients included in this analysis met the following criteria: had at least one inpatient claim or two outpatient claims with diagnosis of DLBCL/FL at least 60 days apart (but less than 1 year apart) during the study period; were continuously enrolled with medical and pharmacy benefits for at least 12 months prior to the index diagnosis date through at least 30-days postindex diagnosis date; and were age 18 years or older at the index diagnosis. Patients who had claims for DLBCL/FL, another primary cancer, or metastatic disease during the 12-month period prior to the index date were excluded. The follow-up period was from the index diagnosis of DLBCL/FL through disenrollment, death, or end of available data, whichever occurred earlier.

Statistical analysis

Descriptive results were reported using frequency and percentage for categorical variables, and mean, standard deviation, median and quartile for continuous variables. Treatment patterns were categorized by drug class (rituximab/bendamustine either alone or in combination, vs others), autologous stem cell transplant therapy ([SCT], with and without chemotherapy/immunotherapy) and specific regimens as well as durations, which were reported for each therapy line.

Direct healthcare costs were computed in the 1-year postdiagnosis period utilizing the variable 'total pay' in the claims data, which represents the combined health plan reimbursement (payouts from the insurance/payers) and patient paid amounts (out of pocket from patients). Average total costs were reported on a per patient per month basis in 2015 US dollars, which were adjusted by the annual medical care component of the consumer price index. Total costs were calculated and presented in categories of pharmacy costs, and medical costs which consisted of inpatient costs, outpatient facility costs, office visit costs, emergency room (ER) costs and other outpatient costs. During the same time period, healthcare resource utilization was also reported, including inpatient admissions, facility outpatient or office visits, ER visits and intensive care unit (ICU) admissions.

Generalized linear models with a gamma link were used to compare healthcare costs between therapies with and without rituximab. All relevant statistical tests were two-tailed with a 0.05 cut-off value for statistical significance.

Results

Patient characteristics

Based upon the inclusion and exclusion criteria, from a total of 50,173 patients, 4651 DLBCL and 10,429 FL patients were identified. Of these, 2794 DLBCL patients and 6021 FL patients received one of the proposed treatments (SCT, chemo, or immunotherapy) and met the other inclusion and exclusion criteria (Figure 1). The average age was 61 (standard deviation [SD] 14.3) years for DLBCL patients and 60 (SD 13.1) years for FL patients. The proportion with inpatient claims were 54.9 and 34.3%, for DLBCL and FL respectively (Table 1). Demographics were otherwise similar between DLBCL and FL patients. The top three co-morbidities were cancer, diabetes without complications and chronic pulmonary disease for both DLBCL and FL patients (Table 2). Among those receiving therapy, the majority received frontline treatment within 3 months after initial diagnosis (79.9% for DLBCL, 62.4% for FL). Of DLBCL patients, 977 received second-line treatment, and 330 received three or more lines of treatments. Of FL patients, 2406 received second-line treatment, and 406 received three or more lines of treatment.

Treatment patterns

Among 2767 DLBCL patients who received frontline treatment, their physician specialties included oncology (36.3%), radiotherapy (27.9%), internal medicine (26.8%), hematology (31.1%) and multispecialty (8.2%). During frontline treatment, 4.5% received both SCT and chemo/immunotherapy, and 67.4% were treated by rituximab or bendamustine either alone or in combination (Figure 2). More patients received SCT in the second-line (10.3%) and third-line (14.5%) of treatment (Figure 3). The percentage of patients who received G-CSF agents as supportive care were 65.8, 48.1 and 40.9% during frontline, second-line and third-line therapies respectively.

For FL patients, their physician specialties were similar to those described for DLBCL patients. During frontline treatment, 1.9% received both SCT and chemo/immunotherapy, and 84.7% were treated by rituximab or bendamustine either alone or in combination (Figures 2 & 3). The percentage of patients who received G-CSF agents as supportive care were 35.6, 32.2 and 26.8% during frontline, second-line and third-line of treatment respectively.

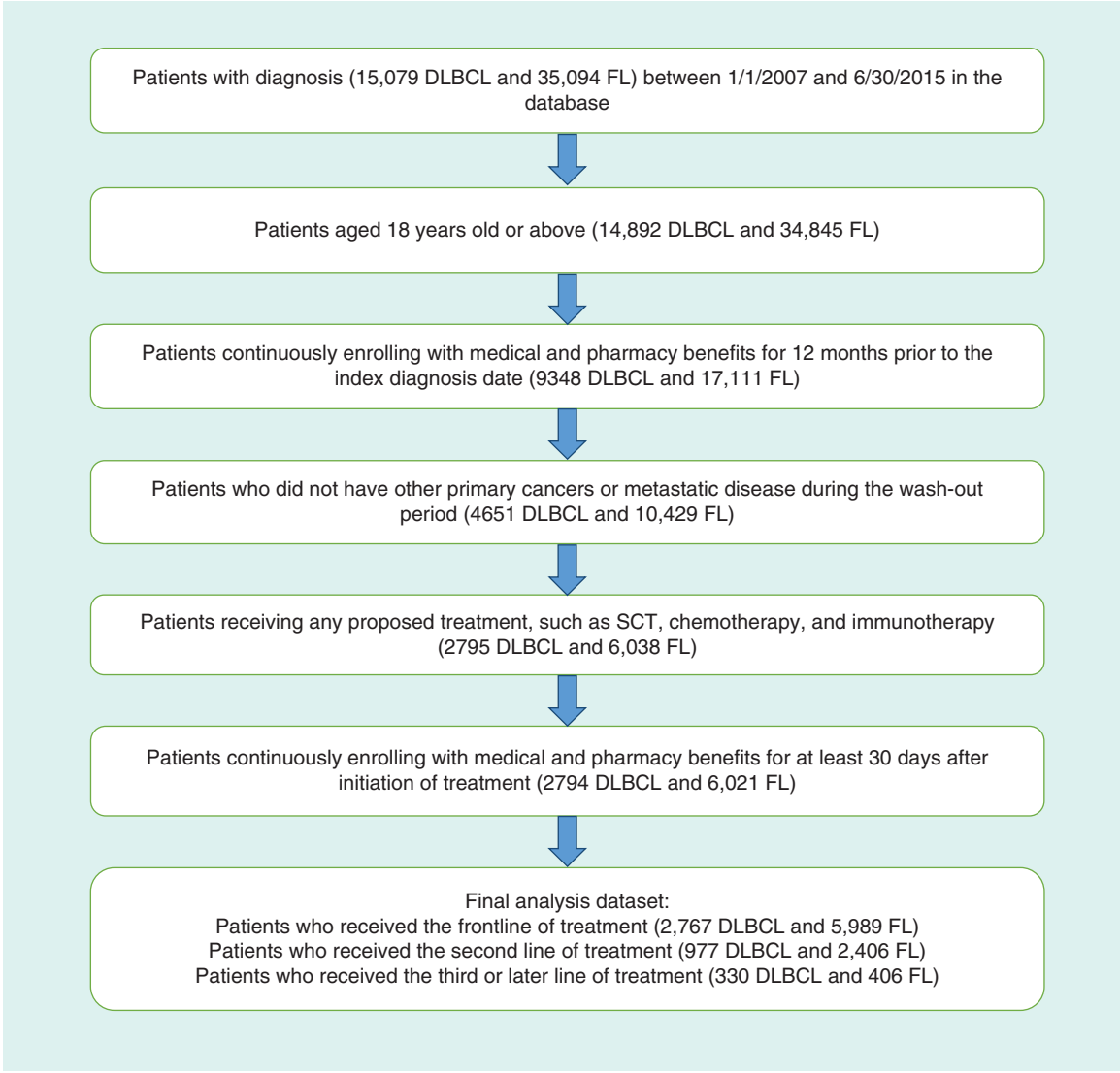

Figure 1. Population selection.
DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; SCT: Stem cell transplantation.

Healthcare costs

The averages of all healthcare costs were $15,555 and $10,192 per patient per month (PPPM) within 1 year after initial diagnosis for DLBCL and FL, respectively (Table 3). Two-thirds of total costs were medical costs ($10,398 per patient per month) for DLBCL patients, and 56% of total costs were medical costs ($5731 per patient per month) for FL patients.

As depicted in Table 4, compared with those who did not received rituximab, DLBCL patients receiving rituximab had higher pharmacy costs ($5473 vs $2118; $p < 0.001$) and lower medical costs ($6417 vs $8782; $p < 0.001$) within 1 year after initial diagnosis. Similarly, FL patients receiving rituximab also had higher pharmacy costs ($6387 vs $2406, $p < 0.001$) and lower medical costs ($4740 vs $7138; $p < 0.001$).

Health resource utilization

During the first year after initial DLBCL diagnosis, the average healthcare resource utilization PPPM included 0.21 inpatient admissions, 0.26 radiation therapy, 2.63 outpatient or office visits, 0.18 ER visits, 0.06 ICU admissions and 0.10 stem cell transplantation. During the study period, the percentages of DLBCL patients receiving at least once inpatient admission, radiation therapy, ICU, or SCT were 78.1, 29.5, 34.5 and 9.6%, respectively. Overall,

Table 1. Demographics.

Characteristics	Label	DLBCL (n = 2794)		FL (n = 6021)	
		n	%	n	%
Age group (years):	– 18–44	322	11.5	633	10.5
	– 45–64	1428	51.1	3330	55.3
	– 65–69	264	9.4	585	9.7
	– 70–74	258	9.2	528	8.8
	– 75–79	221	7.9	452	7.5
	– 80+	301	10.8	493	8.2
Sex:	– Males	1585	56.7	3067	50.9
	– Females	1209	43.3	2954	49.1
Patient type:	– Inpatients	1533	54.9	2064	34.3
	– Outpatients	1261	45.1	3957	65.7
Region:	– Northeast	456	16.5	1016	17.1
	– North Central	788	28.5	1740	29.3
	– South	1084	39.2	2277	38.4
	– West	436	15.8	901	15.2
Data type:	– Fee for service	1470	52.6	3283	54.5
	– Encounter	174	6.2	398	6.6
	– Medicare	1052	37.7	2136	35.5
	– Medicare encounter	98	3.5	204	3.4
Insurance plan:	– Comprehensive	612	21.9	1152	19.1
	– HMO	248	8.9	558	9.3
	– POS	144	5.2	337	5.6
	– PPO	1434	51.3	3219	53.5
	– Others	356	12.7	755	12.5

DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; HMO: Health maintenance organization; POS: Point-of-service; PPO: Preferred provider organization.

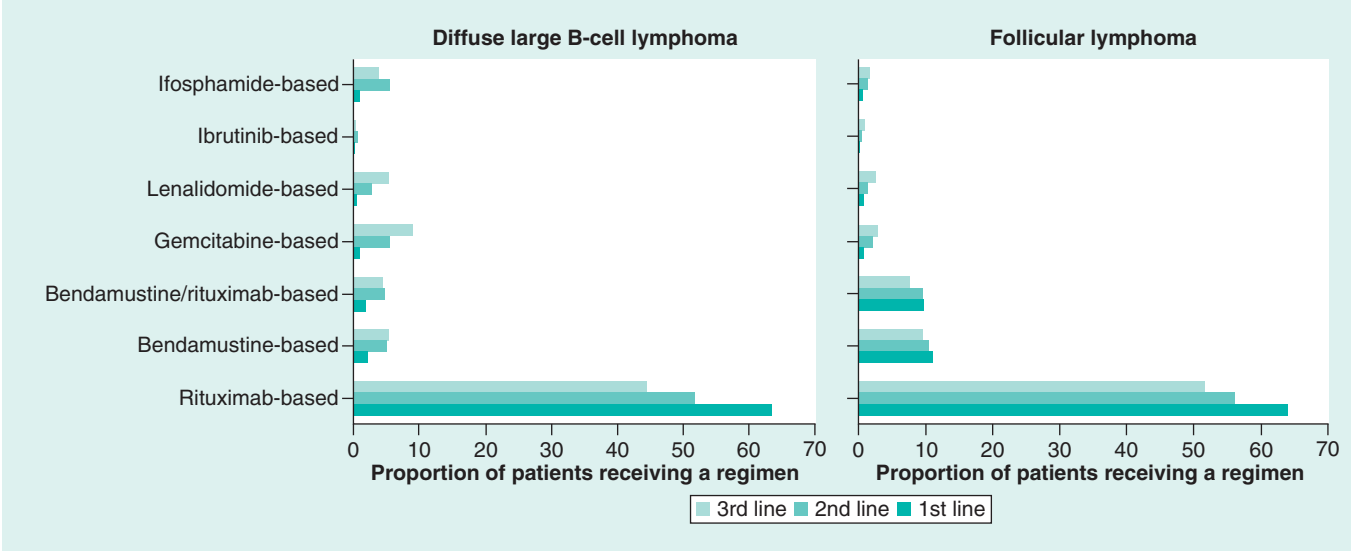

Figure 2. Regimens for diffuse large B-cell lymphoma and follicular lymphoma.

FL patients occupied less healthcare resources than DLBCL patients. During the first year after initial FL diagnosis, the average healthcare resource utilization PPPM included 0.10 inpatient admissions, 0.12 radiation therapy, 2.06 outpatient or office visits, 0.11 ED visits, 0.03 ICU admissions and 0.04 stem cell transplantation. During the

Table 2. Clinical characteristics at baseline.

Co-morbidities	DLBCL (n = 2794)		FL (n = 6021)	
	n	%	n	%
Cancer	743	26.6	1541	25.6
Diabetes without complications	560	20.0	1066	17.7
Chronic pulmonary disease	462	16.5	950	15.8
Mild liver disease	327	11.7	547	9.1
Metastatic carcinoma	285	10.2	476	7.9
Peripheral vascular disease	235	8.4	433	7.2
Cerebrovascular disease	206	7.4	385	6.4
Congestive heart failure	200	7.2	357	5.9
Renal disease	171	6.1	274	4.6
Connective tissue disease-rheumatic disease	147	5.3	230	3.8
Diabetes with complications	121	4.3	228	3.8
Peptic ulcer disease	84	3.0	89	1.5
Myocardial infarction	67	2.4	137	2.3
AIDS/HIV	30	1.1	40	0.7
Paraplegia and hemiplegia	16	0.6	23	0.4
Moderate or severe liver disease	14	0.5	16	0.3
Dementia	9	0.3	17	0.3
Time distribution from initial diagnosis to first-line treatment				
– <3 months	2211	79.9	3740	62.4
– 3–5 months	197	7.1	760	12.7
– ≥6 months	359	13.0	1489	24.9

DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma.

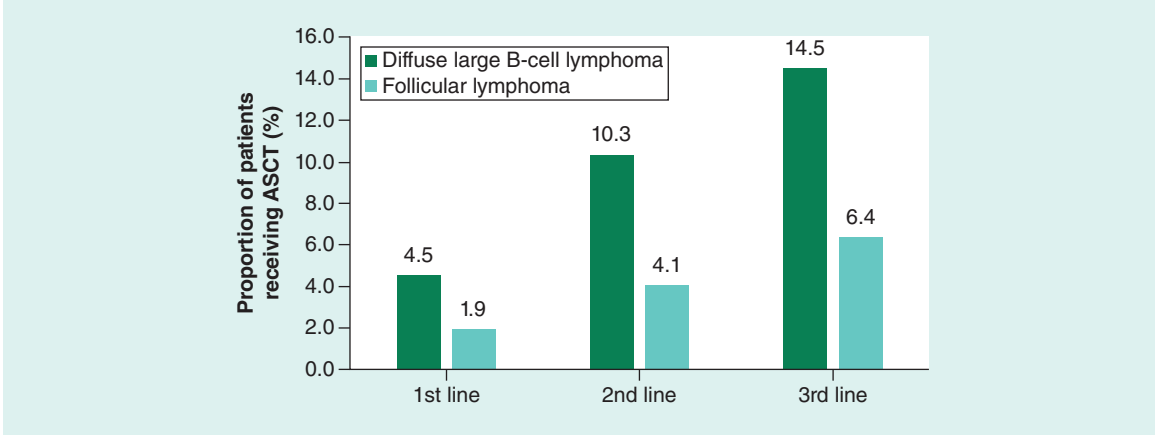

Figure 3. Autologous stem cell transplant therapy for follicular lymphoma and diffuse large B-cell lymphoma.
ASCT: Autologous stem cell transplant.

study period, the percentages of FL patients receiving at least once inpatient admission, radiation therapy, ICU or SCT were 59.4, 17.8, 22.8 and 4.9%, respectively.

Discussion

This observational study provides real-world evidence of treatment patterns, healthcare cost and healthcare resource utilization in patients with DLBCL and FL. The majority of DLBCL and FL patients were treated by rituximab or bendamustine either alone or in combination during frontline treatment, and more than a quarter of patients

Table 3. Healthcare costs during 1 year following frontline treatment in 2015 US dollars.

Categories	Diffuse large B-cell lymphoma		Follicular lymphoma	
	Mean PPPM	Standard deviation	Mean PPPM	Standard deviation
Average total costs	15,555	19,951	10,192	15,556
Drug costs	5157	6134	4462	6041
Medical costs	10,398	18,139	5731	13,626
– Inpatient	6257	15,806	2895	11,848
– Outpatient facility	1366	3721	982	2872
– Other outpatient	2298	2978	1513	2147
– Office visit	247	330	195	279
– Emergency room	230	700	145	791

PPPM: Per patient per month.

Table 4. Healthcare costs by regimen.

Healthcare cost ($)†	Diffuse large B-cell lymphoma			Follicular lymphoma		
	Regimen with rituximab	Regimen without rituximab	Adjusted p-value	Regimen with rituximab	Regimen without rituximab	Adjusted p-value
–Total costs	12,021	11,083	0.036	10,865	9365	<0.001
– Pharmacy costs	5473	2118	<0.001	6387	2406	<0.001
– Medical costs	6417	8782	<0.001	4740	7138	<0.001

received second-line therapies within 1 year from the initial date of frontline treatment. The healthcare costs and healthcare resource utilizations were considerable, especially for DLBCL patients. The medical costs were nearly twice as much as the drug costs for DLBCL patients during frontline treatment. Our findings also demonstrated that patients receiving rituximab had lower medical costs than those who did not receive rituximab for both DLBCL and FL patients, although they had relatively higher pharmacy costs.

Healthcare costs for NHL could be affected by numerous types of lymphoma, different treatment therapies, diverse side effects from various treatment, complicated prognoses and the growing emergence of new drugs. Patients with aggressive NHL tended to accrue higher costs compared with those with indolent lymphomas [2]. In our study, the healthcare costs of DLBCL patients were more than $5000 PPPM higher than FL patients during the first year of frontline treatment. Previously studies have demonstrated that rituximab has a favorable economic profile in both DLBCL and FL patients [12–14]. However, this result is not consistent with the findings from Griffiths *et al.* that reported rituximab could result in higher 4-year total costs of $23,097 in DLBCL patients, although rituximab was associated with survival benefits [15]. Our study demonstrated that DLBCL patients receiving rituximab had higher pharmacy costs ($3355 PPPM) and lower medical costs (save $2365 PPPM) than those who did not receive rituximab. Aside from costs, the use of rituximab as a maintenance therapy for DLBCL continues to be a point of controversy [16], although a recent Phase III clinical trial reported that rituximab maintenance therapy improved survival in male patients with DLBCL [17]. On the other hand, growing evidence demonstrates that rituximab maintenance therapy could significantly prolong progression-free survival for patients with FL, but without an improvement in overall survival or quality of life after first-line induction chemoimmunotherapy [18–20]. Also, NHL patients receiving myelosuppressive chemotherapy often take G-CSF agents, such as pegfilgrastim and filgrastim, in order to reduce the risk of febrile neutropenia. Our study found that 35.8% of DLBCL patients and 35.6% of FL patients received G-CSF agents during frontline treatment. Lyman *et al.* reported that the incremental cost–effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis was $2167 per febrile neutropenia episode avoided [21]. In addition, allogeneic SCTs in DLBCL and FL patients could significantly increase their economic burden [22].

It is not surprising that DLBCL patients consume more healthcare resources than FL patients because of the aggressive tendency of DLBCL. In our study, 34.5% of DLBCL patients and 22.8% of FL patients required ICU admission prior to or during chemotherapy. According to the findings reported in a recent study, hemodynamic (37.8%) or respiratory failure (24.3%) may be the primary reasons for requiring ICU treatments in DLBCL patients [23]. Our study also found that advanced DLBCL patients were more likely to receive SCT (10.3 and

14.5% in second-line and third-line treatment, respectively). This might be, at least in part, attributed to the fact that the efficacy and feasibility of SCT have recently become confirmed in DLBCL patients, even among elderly patients [24–26]. However, there is no evidence suggesting that adding SCT as part of FL initial treatment could improve overall survival [27].

As a claim-based analysis, some inherent limitations are unavoidable. First, the data may incompletely capture the conditions and outcomes documented in the medical records when filing a claim or reimbursement. Since no validated approach could be used to identify nonresponses and relapses in this database, we did not report these clinical outcomes in our paper. Second, as survival data were not available in our analysis, we did not adjust average costs when utilizing the Kaplan–Meier Sample Average estimator approach. To minimize bias associated with censored data, we only analyzed healthcare costs and healthcare resource utilization during the first year after initial diagnosis. Finally, the diagnosis was based upon ICD-9 coding system that might not correspond to histologic diagnosis. Despite its limitations, this study adds to the body of research in economic burden and treatment patterns for DLBCL and FL patients. Our findings may be useful for relevant patients, health providers, stakeholders and researchers in this field.

Conclusion

The healthcare costs and health resources utilized were considerable in non-Hodgkin's lymphoma, especially among DLBCL patients.

Summary points

- Given the rapid evolution in diagnostic subtyping as well as treatment regimens, it is important to examine economic burden, treatment patterns and outcomes among non-Hodgkin's lymphoma patients, including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).
- The majority of DLBCL and FL patients were treated with rituximab or bendamustine either alone or in combination during frontline treatment, and more than a quarter of patients received second-line therapies within 1 year from the initial date of frontline treatment.
- The total healthcare costs were US $15,555 and $10,192 per patient per month within 1 year following their initial diagnosis for DLBCL and FL, respectively. The medical costs were almost twice as much as the drug costs for DLBCL patients during frontline treatment.
- DLBCL patients occupied more health resources than FL patients. During the first year following initial diagnosis, inpatient admissions per patient per month were 0.21 for DLBCL and 0.10 for FL.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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•• **This meta-analysis suggests that high-dose therapy and autologous stem cell transplantation treatment as part of follicular lymphoma does not improve overall survival.**