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ORIGINAL RESEARCH

# Real-world costs of illness of Hodgkin and the main B-Cell Non-Hodgkin lymphomas in France

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## ABSTRACT

**Background:** Lymphomas are costly diseases that suffer from a lack of detailed economic information, notably in a real-world setting. Decision-makers are increasing the search for Real-World Evidence (RWE) to assess the impact, in real-life, of healthcare management and to support their public decisions. Thus, we aimed to assess the real-world net costs of the active treatment phases of adult Hodgkin Lymphoma (HL), Follicular Lymphoma (FL) and Diffuse Large B Cell Lymphoma (DLBCL).

**Methods:** We performed a retrospective cohort study using population-based data from a national representative sample of the French population covered by the health insurance system. Cost analysis was performed from the French health insurance perspective and took into account direct and sick leave compensation costs (€2,018). Healthcare costs were studied over the active treatment phase. We used multivariate modeling to adjust cost differences between lymphoma subtypes.

**Results:** Analyses were performed on 224 lymphoma patients and 896 controls. The mean additional monthly costs due to HL, FL and DLBCL patients were respectively €5,188, €3,242 and €7,659 for the active treatment phase. The main additional cost driver was principally inpatient stay (hospitalization costs and costly cancer-related drugs), followed by outpatient medication and productivity loss. When adjusted, DLBCL remains significantly the most costly lymphoma subtype.

**Conclusion:** This study provides an accurate assessment of the main lymphoma subtypes related cost with high magnitude of details in a real-world setting. We underline where potential cost saving could be realized via the use of biosimilar medication, and where lymphoma management could be improved with the early management of adverse events.

## KEY POINTS

- This is one of the first studies which assess the additional cost of lymphoma in Europe, according to the main sub-types of lymphoma and with real-world database.
- The additional monthly cost due to HL, FL and DLBCL patients were respectively €5,188, €3,242 and €7,659 for the active treatment phase and the main additional cost driver was principally inpatient stay (i.e. hospitalization costs and additional inpatient medicines, notably rituximab), followed by outpatient medication and productivity loss.
- This study provides an accurate and detailed lymphoma subtype cost description and comparison which supply data for efficiency evaluations and will allow French health policy to improve lymphoma management.

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## 1. Introduction

Lymphomas are malignant hemopathies separated into two main subtypes: Hodgkin Lymphoma (HL) and Non Hodgkin Lymphoma (NHL). They account together for approximately 3–4% of cancers worldwide, placing them to the 6th rank of cancers in 2011<sup>1</sup>. In France, the annual incidence of HL and NHL were respectively estimated to 1,757 and 11,512 new

cases in 2012<sup>2</sup>. HL are B-cell neoplasms and NHL are divided into B-cell and T/NK-cell neoplasms where B-cell NHL (B-NHL) are the most frequent, notably represented by Follicular Lymphoma (FL) and Diffuse Large B-Cell Lymphoma (DLBCL)<sup>3</sup>. The 5-years net survival of HL is equal to 85% and varies widely according to sub-types for B-NHL with 87% for FL and 57% for DLBCL<sup>4</sup>.

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The type and duration of treatment depend on lymphoma stages and sub-types. Treatment of lymphoma is mainly based on drug strategies combining conventional cytotoxic chemotherapy with monoclonal immunotherapy, rituximab, for B-NHL<sup>5</sup>. Lymphoma patients may be treated by immunotherapy, radiation therapy and surgery<sup>6,7</sup>. The active treatment phase is characterized by high toxicity with important magnitude of Adverse Events (AEs)<sup>8</sup>. The diagnosis, treatments and AEs may lead to important physical and psychological vulnerability<sup>8,9</sup>. Thus, the high consumption of care and the resulting number of hospitalizations lead to a significant cost supported by the social health insurance which should be assessed through a Cost-Of-Illness (COI) study.

The aim of a COI study is to identify and measure the costs of a particular disease. COI outcome tells how much society is spending on a particular disease and the amount that would be saved if the disease was eradicated<sup>10</sup>. They reveal the different cost components and their relative societal burden. COI studies help health policy makers to rationalize health care expenditure by identifying areas where potential economic savings can be realized<sup>11</sup>. Likewise, these studies supply useful economic information to assess innovation in healthcare management.

Nowadays, decision makers are increasing interest for Real-World Evidence (RWE)<sup>12</sup>. It allows to assess the impact, in real-life, of healthcare management and to guide health authority in their public decisions. Nevertheless, only a few studies assessing the cost of lymphoma in real-world settings were found in Europe<sup>13</sup> or in North America<sup>14–18</sup>. They were focused on special treatments, particular line of treatments or AEs and they did not finely describe cost components of the active treatment phase. Only two cost-effectiveness studies have assessed lymphoma's costs in France, but not in real-world setting<sup>19,20</sup>.

In this context, our aims were to assess direct and sick leave compensation costs during the active treatment phase of HL, FL and DLBCL patients according to a population-based real-world database and to identify the most important cost components, notably rituximab as it is the main medication used for B-NHL.

## 2. Method

### 2.1. Study design, setting and population

We performed a population-based, retrospective, cohort study using a representative random sample of the French national health insurance database ("Système National des Données de Santé" (SNDS)), called the "Echantillon Généraliste des Bénéficiaires" (EGB).

The SNDS is a national medical and administrative database, allowing access to health care consumption and corresponding reimbursements for 98.8% of the French population<sup>21</sup>. The EGB database is a representative sample according to age and sex corresponding to 1/97 of SNDS population and includes demographic data, ambulatory care reimbursement (including drug dispensing), inpatient care data, medical data (Long-Term Diseases (LTD) diagnoses), and characteristics of healthcare providers<sup>22</sup>. Patients may be

enrolled in a special scheme called LTD which allows the reimbursement of 100% of disease-related costs.

This was an observational study on anonymous data. In accordance with French legislation, approval by an ethics committee was not required (French Law on Privacy: National Commission of Information Technology and Liberty Decision No. 89-117).

### 2.2. Identification of the study population

In France, most of lymphoma patients inevitably receive treatment in the frame of day hospital. Patients generally stay less than one night but generate a Diagnosis Related Group (DRG) related inpatient stay coded with the International Classification of Disease, 10th revision (ICD-10). Three different diagnoses could be coded, together or not, to define the purpose of the inpatient stay: the Main Diagnosis (MD), Related Diagnosis (RD) and Associated Diagnosis (AD). Study population was then identified using inpatient care data through these diagnoses according to a validated incident identification lymphoma case algorithm<sup>23</sup>. The algorithm considers a patient as lymphoma patient if he has at least a MD of lymphoma or an MD of chemotherapy in combination with a RD or AD of lymphoma. HL (ICD-10 code: C81), FL (ICD-10 code: C82) and DLBCL (ICD-10 code: C833) patients were considered. Exclusion period of prevalent lymphomas and inclusion period of incident lymphomas was ranged respectively from 01/03/2007 to 28/02/2009 and from 01/03/2009 to 28/02/2013. Data were available until 31/12/2015.

Study period was the active treatment phase identified during the maximum range of 01/03/2009 and 31/12/2015 and defined by: (1) an index date per patient as the first ICD-10 lymphoma discriminant code minus 21 days. (2) The end of the active treatment phase defined by the date of the last ICD-10 code of lymphoma management if there are no more discriminant ICD-10 codes of lymphoma management associated during the following 12 weeks. The 12 weeks period after the last ICD-10 discriminant code of lymphoma management will be identified as the "post-treatment period". This period allows us to define if the active treatment phase is over or if it always runs. Active treatment phase is fluctuant according to each lymphoma identified. [Online resource 1](#) summarizes how incident lymphoma and lymphoma active treatment period are identified. Lymphoma discriminant management codes correspond to a MD of lymphoma alone as those described above or a MD or RD code of chemotherapy, radiotherapy or a code of the main complication management associated with a MD, a RD or an AD code of lymphoma. These codes are described in the [Online resource 2](#). That allows notably labeling a large active treatment phase taking into account postpone treatment due to chemotherapy complications without considering surveillance alone. Index date was chosen 21 days before the first ICD-10 lymphoma code to take into account all potential clinical examinations related to diagnosis of lymphoma before the first lymphoma related hospitalization. The post-treatment period long were chosen to take into account the

different healthcare courses of lymphoma sub-types, notably the maintenance therapy for FL, and the variability of management according to patients.

**Q3** We did not consider T-cell lymphoma because algorithm cannot identify them correctly given their particular healthcare management. Besides, we have not considered others B-Cell lymphoma to avoid misclassification bias and because FL and DLBCL are globally representatives of B-NHL management (i.e. indolent and aggressive lymphomas). For each case, we have randomly selected from the EGB 4 controls among patients not suffering from lymphoma to estimate the net cost of lymphoma. Controls were matched on gender and age. We did not use a propensity score to match our control according the low number to socio-demographic data we had. Control patients had the same index date of their associated cases and we have identified their healthcare consumptions during identical follow-up.

### 2.3. Costs estimates

Cost analysis was performed from the French health insurance perspective and included direct and sick leave compensation costs. Direct medical costs corresponded to the cost of health care consumption, represented by inpatient care and outpatient care. Inpatient stays cost take into account costs of hospitalization and costs of medicine delivered in inpatient setting. Outpatient care cost corresponds to the cost of visits, medical and paramedical procedures, outpatient drugs and medical equipment. Direct non-medical costs were limited to transportation costs and are detailed in the database according to the type of transport used. Sick leave compensation costs are represented by the patient's earning lost because of the illness. These costs are represented by daily allowance and disability pension. These costs are compensated to the patient by the French health insurance according to the amount of day absence of work. Daily allowance corresponds to the cost associated to short term sick leave and disability pension correspond to the cost associated to long term sick leave. All these data are available in the EGB databases with detailed fees (classification codes, quantities, unit costs, reimbursement costs...). Costs were estimated by multiplying the number of resources used by the corresponding reimbursement tariff given by the French health insurance ([Online resource 3](#)).

In France, public and private hospital fees are based on DRG tariffs which can be added by various supplements as expensive drugs like rituximab or medicine with special constraints of distribution, dispensation or administration which are hospital-reserved drugs. Expensive drugs are delivered only during inpatients stay. Hospital-reserved drugs are dispensed in outpatient setting by hospital pharmacy. Nevertheless, we have classified this medication within inpatient category. According to the huge weight of expensive medication in B-NHL management (i.e. rituximab), inpatient care was disaggregated into hospitalization costs and additional medicines (expensive and hospital-reserved drugs), which are funded in addition to hospitalization cost. DRG tariffs include also price of medication administered (i.e.

chemotherapies) when it is not included as additional medicines.

Outpatient cares were valued according to the French Common Classification of Medical Acts (CCAM). Medication and medical equipment were valued with the French health insurance tariffs. Transportations, paramedical acts and visits were valued using the General Classification of Professional Act (NGAP). Costs linked to productivity loss were valued using the daily benefits given by the health insurance for short absences in the workplace and using disability pension for long-term sick leave.

Additional medicines were divided into rituximab and other medicines to allow rituximab weight assessment in the B-NHL management cost. DRG were split into 4 classes: lymphoma's diagnoses, lymphoma's treatments, lymphoma's complications and other hospitalizations. All inpatient stays combining both lymphoma's treatments and lymphoma's complications or diagnoses are grouped in lymphoma's treatments category. Outpatient medications were categorized using the main ATC (Anatomical Therapeutic Chemical) classification groups<sup>24</sup>.

All costs were inflated to corresponding 2018 prices using the French Consumer Price Index (CPI) from the Organization for Economic Co-operation and Development (OECD) website<sup>25</sup>.

### 2.4. Others data

We have derived baseline comorbidities and Charlson Comorbidity Index (CCI) from Bannay et al. paper during the year before index date for both cases and controls<sup>26</sup>. They use medical procedures, drugs and discharge diagnosis in hospital in addition to LTD scheme to identify the comorbidities and the CCI. Finally, they apply new weights to a better assessment of CCI. The related comorbidities identification algorithm and the new weights are described in Bannay et al. and were implemented in the EGB for cases and controls. Length of the active treatment phase and place of management (i.e. private vs public) were also described for lymphoma patients. Place of management was defined according to where the patient is treated. This information is known in the EGB database.

Patients who died during the active treatment phase have been maintained in the analysis and we did not stop active treatment phase before date of death. Indeed, we aimed to assess real-world cost due to lymphoma. If death occurs during the active treatment phase, it occurs during the last inpatient stay with a discriminant code of lymphoma. If the death occurs after the end of the active treatment phase, costs of end of life were not taken into account in the cost calculation. Nevertheless, the death variable will be used as adjustment variable to take into account the high costs due to end of life.

### 2.5. Statistical analysis

Descriptive statistics were used to summarize the data and included mean  $\pm$  Standard Deviation (SD) or quantiles, for

continuous variables and occurrences with percentages for qualitative variables. Baseline characteristics were compared between lymphoma patients and controls using the Z-test for quantitative variables and Fisher's exact test for qualitative variables.

Lymphoma patient's costs were compared to those of the controls to estimate the additional cost of different lymphoma subgroups. Costs were monthly standardized to take into account the variability within the active treatment phases through lymphoma subtypes. Costs were described in terms of mean per patient and their Bias-Corrected and accelerated (BCa) bootstrap 95% Confidence Intervals (CI) which adjusts for skewness distribution of cost. Depending on cost distribution, cost differences between lymphoma patients and their controls were tested using a statistical Z-Test or a Mann Whitney Wilcoxon non-parametric test.

A Generalized Linear Model (GLM) with gamma distribution and log link was implemented to adjust the cost differences between lymphoma subgroups with covariates. Age in quantile, gender, CCI, state of life at the end of active treatment phase identified and the place of care were used as adjustments covariables. Age and gender were maintained in the model despite if they were non-significant. Statistical analyses were performed using R software (version 3.1.2).

### 3. Results

#### 3.1. Patient characteristics

Lymphoma patients and controls identification are summarized in [Figure 1](#) and descriptive statistics according to lymphoma sub-types are synthesized in [Table 1](#). All comorbidities are summarized in the [Supplementary files \(Online resource 4\)](#).

The mean age of HL, FL and DLBCL patients was respectively  $46.9 \pm 19$ ,  $63 \pm 13.2$  and  $65.9 \pm 16.1$  years with 40.4%, 46.9% and 55.3% of women. HL and DLBCL patients had not significantly higher CCI than controls ( $p = .172$ ,  $p = .084$ ) contrary to FL patients ( $p < .01$ ). This significant difference principally came from the important number of others cancer types in FL group ([Online resource 3](#)). Furthermore, DLBCL controls have higher proportion of diabetes than cases. The mean follow-up with the first and third quantile were respectively 199 days [155; 253], 419 days [104; 860] and 186 [126; 232] for HL, FL and DLBCL patients. Management by private hospital structures accounted between 9% for FL and 13.5% for DLBCL. We observed that 16.5% of DLBCL patients are dead between the last inpatient stay related to code of lymphoma and the 3 following months.

#### 3.2. Cost analysis

Mean additional costs due to HL, FL and DLBCL patients were respectively €32,832, €44,539 and €46,708 for the active treatment phase. When monthly standardized, mean additional costs due to HL, FL and DLBCL patients were respectively equal to €4,478, €3,820 and €7,526 ([Table 2](#)). The main cost drivers were inpatient stay, medication, and productivity

loss. All significant cost differences between lymphomas and controls are detailed in the online [Supplementary material \(Online resource 5\)](#).

Inpatient stay was the most important cost driver amounted to a significant mean additional cost per month per patient ( $p < .001$ ) of respectively €2,980, €3,115 and €5,931 for HL, FL and DLBCL patients. These additional costs were mainly led by: (1) hospitalization costs (DRG tariffs) arising from the treatment, especially for DLBCL with €2,167 and for HL patients with €1,124; (2) additional medicine coming from rituximab for FL and DLBCL patients with respectively €1,511 and €2,284.

The second most important cost driver was outpatient medication which amounted to a significant mean additional cost per month per patient ( $p < .001$ ) of respectively €560, €365 and €858 for HL, FL and DLBCL patients. These additional costs were firstly led by antineoplastic and immunomodulators drug costs which were mainly composed by the three following growth factor drugs (ATC code: L03AA): filgrastim, lenograstim and pegfilgrastim. Secondly, drug costs were explained by blood and hematopoietic organs drugs which are driven by the antianemic preparations (ATC code: B03).

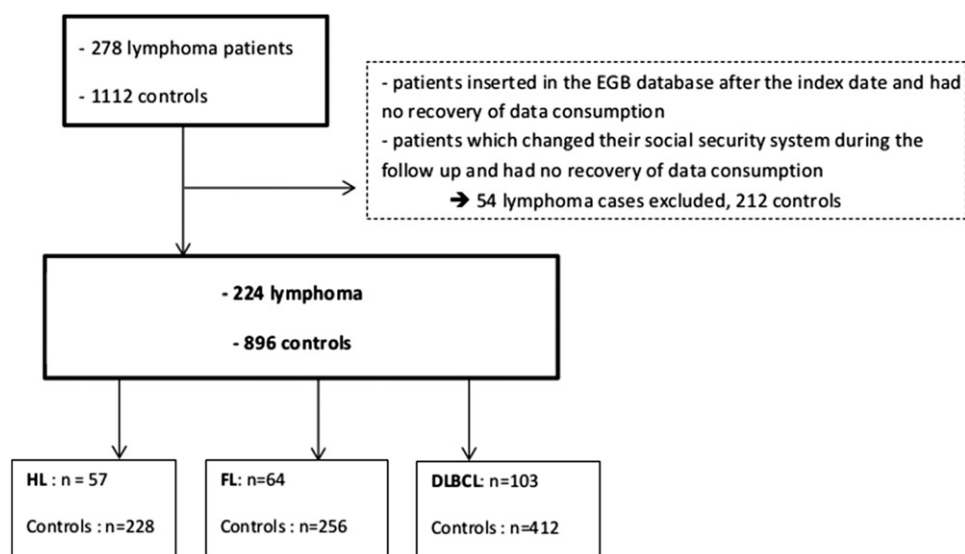
The third main cost driver comes from productivity loss which amounted to a significant mean additional cost per month per patient ( $p < .001$ ) equal to €464, €136 and €229 for respectively HL, FL and DLBCL and led by the daily allowance.

[Table 3](#) shows the cost variations associated to lymphoma subtypes. The CCI was not significant in both univariate and multivariate analysis and was excluded from the model. DLBCL patients are associated with a significant higher monthly cost of healthcare management than FL patients (RR = 1.87; 95% CI: 1.53; 2.28,  $p < .001$ ). Patients who are managed in private hospital are associated with a 26% cost decrease than patients who are managed in public hospital (RR = 0.74; 95% CI: 0.57; 0.95,  $p = .020$ ) and patients who died at the end of the active treatment phase incur a cost increase of 78% (RR = 1.78, 95% CI: 1.37; 2.32,  $p < .001$ ).

### 4. Discussion

This is the first study which assesses the lymphoma related cost in France, using French health insurance databases. Mean additional costs due to HL, FL and DLBCL patients were respectively €32,832, €44,539 and €46,708 for the active treatment phase. When monthly standardized, mean additional costs due to HL, FL and DLBCL patients were respectively equal to €4,478, €3,820 and €7,526. The main cost drivers were inpatient stays, medication, and productivity loss. When adjusted we observed that DLBCL incurs the most important cost per month.

Only few data are available on the COI of lymphoma subtypes using population based data. Five studies were found in North America and one in Europe. American studies were focused on HL, DLBCL or FL patients according to special treatments or line of treatments<sup>14–18</sup>. Moreover, the healthcare system in the US or Canada is considerably different



**Figure 1.** Identification of lymphoma and controls population. Abbreviations. HL, Hodgkin Lymphoma; FL, Follicular Lymphoma; DLBCL, Diffuse Large B-Cell Lymphoma.

**Table 1.** Baseline characteristics according to lymphoma subgroups (HL and B-NHL).

	HL			FL			DLBCL		
	Cases (n = 57)	Controls (n = 228)	p	Cases (n = 64)	Controls (n = 256)	p	Cases (n = 103)	Controls (n = 412)	p
Age (mean, (sd))	46.9 (19.0)	46.9 (19.0)	1	63 (13.2)	63 (13.2)	1	65.9 (16.1)	65.9 (16.1)	1
Gender (women, (%))	23 (40.4)	92 (40.4)	1	30 (46.9)	120 (49.6)	1	57 (55.3)	228 (55.3)	1
CCI (n, (%))									
0	47 (82.5)	201 (88.2)	.172	41 (64.1)	204 (79.7)	.009	75 (72.8)	337 (81.8)	.084
1–2	7 (12.3)	23 (10.1)		18 (28.1)	43 (16.8)		20 (19.4)	57 (13.8)	
3–4	1 (1.8)	3 (1.3)		3 (4.7)	9 (3.5)		5 (4.9)	15 (3.6)	
5	2 (3.5)	1 (0.4)		2 (3.1)	0 (0)		3 (2.9)	3 (0.7)	
Management by Private	6 (10.5)			6 (9)			14 (13.5)		
Death* (n (%))	3 (5.3)			4 (6.3)			17 (16.5)		
Follow-up (mean, [Q1–Q3])		199 [155; 253]			419 [104; 860]			186 [126; 232]	

Abbreviations. HL, Hodgkin Lymphoma; FL, Follicular Lymphoma; DLBCL, Diffuse Large B Cells Lymphoma; CCI, Charlson Comorbidity Index; p, p-value; \*Death 3 months after the end of active treatment phase.

than the French healthcare system especially because of health care organization, reimbursement conditions and different unit prices used to value healthcare resources which makes harder the comparison between studies. According to the European context, Wang et al. used decision model to predict cost of DLBCL patient based on the UK’s population based database<sup>13</sup>. They were focused on costs of diagnosis, treatment, supportive care, follow-up and end-of-life care. They have estimated life time costs of patient treated with first line treatment to £22,122. Our results are higher despite the lower follow up we used. That may be explained by the larger part of cost component we took into account. Unfortunately, authors did not detail all inpatient cost components and we cannot compare our results.

There is a lack of economic evaluation of lymphoma in France. We reviewed only two studies on the topic<sup>19,20</sup>. These studies are cost effectiveness studies which mainly focus on rituximab cost. Best et al. in 2005 assessed the cost of DLBCL patients from the French payer perspective and treated by rituximab to €41,952 over 15 years with 33.6% due to rituximab. Our results are quite similar considering that we took into account larger magnitude of cost component while they considered a larger follow-up period.

Deconinck et al. in 2010 estimated the cost of FL treated with Rituximab during maintenance therapy. Nowadays maintenance therapy with rituximab is considered as a standard of care and we consider it as a part of active treatment phase<sup>27</sup>. Furthermore, both of these studies have considered French healthcare perspective but they did not only use French data.

Our study is the first which assesses HL, FL and DLBCL related cost in France, using real-world population-based data. In a context where decision makers are increasing interest for RWE, our study provides detailed economic information about HL and the main NHL subtype’s management. Our finding spotlight where management could be improved in terms of quality of care and cost saving.

According to our model, we have identified a 26% cost decrease if the patient is managed in private hospital. Firstly, private hospitals attract generally patients with higher socio-economic level, better survival prognosis and less complicated management. In private hospital setting, patients spend less, meet fewer and less critical AEs. Furthermore, private and public hospitals are not subject to the same funding rules<sup>28</sup>. Finally, we have to be caution because of the lack of statistical power depending to the small proportion

Table 2. Mean costs per patient of lymphoma cases, controls, and additional costs according to lymphoma.

	Inpatient stays	Medical visits	Medical acts	Paramedical acts	Medication	Medical equipments	Transportation	Productivity loss	Total
<b>HL</b>									
Cases (n=57)	3075 [2325; 4580]	26 [21; 35]	188 [140; 280]	36 [24; 57]	592 [449; 812]	15 [10; 25]	255 [192; 337]	499 [337; 671]	4690 [3845; 5981]
Controls (n= 228)	95 [38; 284]	11 [8; 18]	16 [12; 31]	7 [4; 13]	32 [22; 63]	7 [3; 17]	7 [2; 21]	35 [22; 61]	212 [142; 432]
ΔCost	2980	15	172	29	560	8	248	464	4478
p	<.001	<.001	<.001	<.001	<.001	.055	<.001	<.001	<.001
<b>FL</b>									
Cases (n= 64)	3188 [2733; 3716]	26 [21; 32]	118 [96; 148]	27 [16; 54]	427 [302; 613]	21 [11; 58]	92 [66; 129]	200 [114; 318]	4101 [3591; 4731]
Controls (n= 256)	73 [46; 122]	18[14; 24]	24 [20; 31]	24[13; 45]	62 [48; 88]	9[6; 15]	3 [2; 9]	64 [36; 124]	281 [212; 395]
ΔCost	3115	8	94	3	365	12	89	136	3820
p	<.001	.027	<.001	.767	<.001	.182	<.001	.011	<.001
<b>DLBCL</b>									
Cases (n= 103)	5999 [5400; 6849]	28[23; 35]	181 [152; 238]	63[46; 96]	908 [803; 1027]	30[21; 45]	244 [200; 304]	261 [176; 374]	7745 [7071; 8518]
Controls (n= 412)	68 [43; 113]	12[11; 14]	20 [18; 24]	23[14; 39]	50 [43; 64]	8 [5; 15]	5 [3; 8]	32 [18; 58]	219 [180; 273]
ΔCost	5931	16	161	40	858	22	239	229	7526
p	<.001	<.001	<.001	.002	<.001	.001	<.001	<.001	<.001

Abbreviations: HL, Hodgkin Lymphoma; FL, Follicular Lymphoma; DLBCL, Diffuse Large B Cells Lymphoma; p, p-value.

Table 3. Gamma multivariate regression model on additional cost of lymphoma.

Variable	RR	CI (95%)	p
Age			
[18; 55]	1		
[56; 70]	1.00	[0.81; 1.24]	.983
[71; 89]	0.85	[0.68; 1.05]	.136
Gender			
Female	1.01	[0.86; 1.19]	.869
Life State			
Death	1.78	[1.37; 2.32]	<.001**
Place of management			
Private	0.74	[0.57; 0.95]	.020*
Lymphoma subtype			
FL	1		
HL	1.11	[0.88–1.4]	.383
DLBCL	1.87	[1.53–2.28]	<.001**

Abbreviations: HL, Hodgkin Lymphoma; FL, Follicular Lymphoma; DLBCL, Diffuse Large B-Cell Lymphoma; RR, Relative Risk; p, p-value. \*p &lt; .05; \*\*p &lt; .001.

of patients treated in private hospital. Thus, this variable has to be considered rather an adjustment covariable than a covariable of interest.

We noticed that DLBCL are significantly the most costly lymphoma. Related expenditures are mainly lead by rituximab. This cost could be largely reduced in the future, especially with the recent availability of two biosimilars in France, truxima® and rixathon® in 2017. According to the European Society for Medical Oncology (ESMO), biosimilar medications present a necessary and timely opportunity for physicians, patients and healthcare systems<sup>29</sup>. This medication could lead to an important cost saving but naturally depending on the extent of biosimilar adoption<sup>30</sup>. Physicians and patients express reservations regarding biosimilar efficacy, safety and cost saving<sup>31</sup>. In this context, RWE provided in our study will be helpful to assess the budget impact or cost-effectiveness associated with these biosimilars. Findings associated may help to convince stakeholders about biosimilar benefit in real-world setting and to enhance product uptake<sup>32</sup>. As a comparison, an Italian study has investigated the 5-year budget impact of rituximab biosimilars<sup>33</sup>. Using the hospital perspective, they have estimated produce savings of respectively €79.2 and €153.6 million over 3 and 5 years. Furthermore, in France biosimilar of growth factor as filgrastim are available since 2013. Nevertheless, according to the French National Agency for Medicines and Health Products Safety, only 28% of administrated growth factors were biosimilar in 2015<sup>34</sup>. It could be an important way to optimize lymphoma management, medication lead by these drugs being the second cost driver in our study.

We have observed a high inpatient's DRG cost related to hospitalization stay for treatment, notably for DLBCL patients (€2,167). This cost is mainly determined by the duration of hospital stay that is longer than one night (€1,742), while chemotherapy is generally administered in day hospitalization setting. Chemotherapy is toxic and the resulting complications occur frequently during a cycle of chemotherapy. Nevertheless, they are managed at the following admission for chemotherapy administration, which explains these results and justifying the low cost related to complications alone. That highlights the need to prevent avoidable



697 complications to reduce this cost with promoting telemedi-  
 698 cine programs or improving therapeutic patient educa-  
 699 tion<sup>35-37</sup>. In this context, a better management of AEs could  
 700 leads to improve of patient quality of life, reduce day  
 701 absence from work and decrease productivity loss related  
 702 cost, the third cost driver in our study<sup>38</sup>. In addition, subcuta-  
 703 neous rituximab instead intravenous rituximab could reduce  
 704 treatment burden for B-NHL patient and improve resource  
 705 utilization<sup>39</sup>.

706 The main strength of our study is the use of real-life data  
 707 with a population-based reimbursement database. The  
 708 French health insurance databases are the best population  
 709 based data source for performing economic studies in  
 710 France<sup>22</sup>. It provides exhaustive reimbursement data of the  
 711 healthcare consumption of a large part of French population  
 712 with detailed inpatient and outpatient financial data which  
 713 allows thorough analysis. The second main strength of our  
 714 work is the use of a validated algorithm to select our popula-  
 715 tion. The validation study shows a great sensibility of the  
 716 algorithm allowing a correct identification of cases. In addi-  
 717 tion, false negative may concern patients never hospitalized  
 718 for their lymphoma because different disease management  
 719 or a gap between diagnosis and treatment<sup>23</sup>. Thus, according  
 720 to the exhaustiveness of health care consumption in the  
 721 EGB, the use of validated algorithm to these data are a great  
 722 of interest to conduct economic evaluation.

723 Our results present some limitations. The first one is due  
 724 to the high misclassifications rate on lymphoma sub-types:  
 725 approximately 20% of diagnoses change after an expert  
 726 review and the most frequent discrepancies were among  
 727 lymphoma sub-types (i.e. 41.3%)<sup>40</sup>. We have defined which  
 728 subgroups of lymphoma patient belongs according to type,  
 729 number and recency of ICD-10 code found to avoid it. In  
 730 addition, we have arbitrary chosen 12 week's long for the  
 731 post-treatment period to conclude about the end of active  
 732 treatment phase. That allows taking into account the large  
 733 gaps between guidelines and the practice arising from  
 734 patient and hospital characteristics and affecting treatment  
 735 adherence<sup>41</sup>. Nevertheless, we cannot point out and exclude  
 736 relapsed patients who have switched to second/salvage ther-  
 737 apy during the post-treatment period. That could lead to  
 738 consider few patients which early relapsed and started a  
 739 second active treatment phase and an overestimation of our  
 740 results. However, overestimation is small according to the  
 741 limited number of relapsed lymphoma patients during the  
 742 post-treatment period and according to the monthly standar-  
 743 dized cost we used in analysis<sup>42-44</sup>. Identification algorithm is  
 744 based on inpatient stay for diagnosis or treatment. Thus, we  
 745 could have missed untreated patient or patient with gap  
 746 between diagnosis and treatment as FL in observation  
 747 phase<sup>23</sup>. It is the main reason why we did not take into  
 748 account T-NHL and chronic lymphocytic leukemia which are  
 749 sometimes not managed in inpatient setting. Nevertheless  
 750 HL, DLBCL and treated FL are mainly managed in inpatient  
 751 setting and algorithm used present good performances  
 752 according detection of these pathologies.  
 753 In a context where decision maker increasing interest for  
 754 RWE, our study provide important information with high

755 magnitude of details on lymphoma related costs that will  
 756 help health policy to better understand the healthcare man-  
 757 agement of lymphoma<sup>12</sup>. Our results highlight the huge  
 758 weight of rituximab in the total cost of B-NHL. This cost com-  
 759 ponent can be largely reduced with upcoming biosimilars.  
 760 We have notably planned to assess economic impact of  
 761 these drugs with our results to develop a cost-minimization  
 762 analysis using an agent-based simulation model. In addition,  
 763 we highlight the crucial need to improve adverse event man-  
 764 agement by preventing avoidable complications. This study  
 765 shows the strength to work with a powerful tool as the  
 766 health insurance database using validated algorithm to sup-  
 767 ply useful RWE information for assessing novelties in health-  
 768 care management.

## 770 Transparency

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777 The authors declare that they have no conflict of interest. JME peer  
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### 780 Author contributions

781 All authors have participated in the work and have reviewed and  
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