Cost drivers associated with diffuse large B-cell lymphoma (DLBCL) in Japan: A structural equation model (SEM) analysis

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin’s lymphoma of increasing prevalence in Japan. However, patients with relapsed or refractory disease to first line treatment (rrDLBCL) have been found to shoulder greater economic burden and have poor survival with subsequent lines of therapy. The relative impact of individual patient attributes on total medical cost among patients with rrDLBCL receiving second or third line (2L/3L) therapy was assessed. Structural equation modelling was used to identify potential cost drivers of total medical costs incurred by treatment and procedures in a Japanese retrospective claims database. From the database, rrDLBCL patients on 2L or 3L of treatment were grouped into respective cohorts. The mean [median] total medical cost of care for the 2L cohort was 73,296.40 [58,223.11] (58,409.79) US dollars (USD) and 75,238.35 [60,477.31] (59,583.66) USD for the 3L cohort. The largest total effect on medical cost in both cohorts was length of hospital stay (LOS) ($\beta$: 0.750 [95% CI: 0.728, 0.772] vs $\beta$: 0.762 [95% CI: 0.729, 0.794]). Length of hospital stay and potential heart disease complications due to line of treatment were the primary drivers of total cost for patients who had received at least 2L or 3L therapy for rrDLBCL.

Introduction

The incidence of aggressive non-Hodgkin lymphoma (NHL) has been increasing steadily in Japan. By 2008, NHL was responsible for 39.6% of all hematologic malignancies nationwide [1]. Diffuse large B-cell lymphoma (DLBCL) accounts for a large proportion of such lymphoid neoplasms in Japan (35.8%) and regional disease proportion varies between 25.7% to 39.5% [2]. The standard treatment for DLBCL is R-CHOP regimen (rituximab [R] + cyclophosphamide/doxorubicin/vincristine/prednisone) administered for 6–8 cycles. A United States (US) claims-based study found that 87.7% of DLBCL patients received combination therapies, and 69.7% had received R-CHOP [3]. A population-based cancer registry in Japan reported the 5-year overall survival for DLBCL patients to be 57% in 2003–2006, a 13% increase from 1993–
1997 [4]. However, after stopping treatment, up to 50% of patients may become relapse or become refractory to further treatment [5].

Patients with relapsed or refractory (rrDLBCL) have poor prognosis and unstandardized treatment regimens across subsequent treatment lines [6]. A large study of pooled patient level data in the US demonstrated rrDLBCL patients had an overall response rate of 26% to further treatment and a median survival of 6.3 months [7]. Even after autologous stem cell transplantation (auto-SCT), median OS for rrDLBCL patients was 9.9 months [8]. While it is critical to understand not only the real-world course of treatment, but also the drivers of those medical costs for patients, there is a paucity of research on the economic burden of rrDLBCL in Japan.

Even with poor survival outcomes, the economic burden of DLBCL is high. The average DBLCL-related cost per patient per year in the first year of treatment was reported to be significantly higher for second line (2L) DLBCL patients (210,488 USD) compared to first line (1L) patients (25,044 USD) in the US [9]. A separate analysis of the economic burden for matched 1L and 2L DLBCL cohorts in the US highlighted clinical services as the main incremental cost drivers (outpatient (50%) and inpatient (36%) services) [10]. The relationship between the direct and indirect drivers of medical costs for rrDLBCL in Japan, as well as any intermediate effects, remain unclear.

In this study, structural equation modeling (SEM) was used to explore the relationship between patient characteristics, healthcare resource utilization (HCRU) and medical costs for rrDLBCL. Identifying drivers of medical cost may provide insights into how to reduce the economic burden for Japanese patients.

Materials and methods
Study design and study population
An administrative retrospective claims database (2008–2020) provided by Medical Data Vision Co., Ltd. (MDV; Tokyo, Japan) was used in this study. Covering approximately 23% of acute hospitals and 30 million patients, the MDV database is a large database of anonymized medical claims from over 400 acute care hospitals in Japan.

The identified patients had at least one DLBCL-related treatment claim between October 1, 2008 and June 30, 2019. The first treatment date was defined as the date of first DLBCL-related treatment (1L) during this period with the appropriate International Classification of Disease 10th revision (ICD-10) diagnosis code (C83.3x, C85.2x or receipt code 8847286). Records must have had a 6-month lookback period from index date with at least 1 claim (for any disorder) as used in a previous database study [11]. Minimum follow-up period for inclusion was 12 months and patient records that did not have at least 2 claims (1 claim every 6-month period for any disorder) were excluded in order to capture sufficient cost for this study to conduct SEM. Remaining patients were included in further analysis if they had received either 2L or 3L during the identification period. Two separate cohorts (with overlapping patients) were analyzed; one for patients who initiated 2L and one for patients who initiated 3L. Index date was defined as the first administration of second line for the 2L cohort and third line for the 3L cohort. Database was downloaded on 5th Oct 2020.

Patient characteristics
Patient demographics tabulated of which include gender, age, and age group. Clinical characteristics including year of index date, prior treatment regimen, potential complications due to treatment, duration of therapy (1L-3L), baseline Charlson Comorbidity Index (CCI) score
with breakdowns of each comorbidities, including a modified index excluding diagnosis of DLBCL itself, were analyzed to describe the study cohorts.

Potential complications from 2L/3L treatment, including heart disease [12], kidney disease [13], and liver disease [14], were defined as new events after index date among those without these conditions during any prior lines of therapy. Prior or concurrent cancers during the look-back period were also assessed (C00-C96 except for C77-89, i.e. exclude secondary neoplasms and lymphomas). The average duration of each line of therapy was calculated (1L-3L) as months from the first treatment date to the last treatment date records. CCI scores were calculated using the look-back period (prior to start of 2L/3L treatment) based on the ICD-10 codes associated with the modified CCI [15].

DLBCL-related treatment was summarized for drugs received within ±30 days of first line treatment initiation so to also include patients in the middle of their treatment cycle. Subsequent line of treatment for all included patients were extracted up to 5L+. Treatment lines were grouped in a hierarchical order based on their regimen components: DeVIC-based (dexamethasone, etoposide, ifosfamide, carboplatin) with or without rituximab, R-CHASE-based (rituximab, cyclophosphamide, cytarabine, etoposide, dexamethasone), GDP-based (gemcitabine, dexamethasone, cisplatin) with or without rituximab, R-Bendamustine-based, R-EPOCH-based (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), R-ESHAP-based (rituximab, etoposide, cytarabine, cisplatin, methylprednisolone), ESHAP-based, R-ICE-based (rituximab, ifosfamide, carboplatin, etoposide), R-DHAP-based (rituximab, dexamethasone, cytarabine, cisplatin), other R-based, and other chemotherapy without rituximab. Lastly, patients receiving conditioning regimens before auto-SCT were also extracted (including MINE, LEED, MCEC, MEAM followed by auto-SCT). Patients who received combination of rituximab and other immunotherapy were excluded as they generally were not indicated for treatment of rrDLBCL.

Patients were considered to be the same line of therapy if they were on the same regimen without a gap. Thus, a treatment regimen was considered a new line of therapy if the patient took a drug not included in their initial treatment regimen more than 30 days after treatment initiation date, or had a gap in treatment for >90 days (Fig 1). Patients who had a record of

![Fig 1. Line of therapy diagram indicating identification of treatment lines.](https://doi.org/10.1371/journal.pone.0269169.g001)
SCT (allogeneic (allo)- or auto-) were also considered part of the same line of therapy if the transplant occurred prior to a next line of therapy as described above. The approach for defining lines of therapy has also been previously described [16].

**Healthcare resource utilization**

Healthcare resources used during follow-up were assessed and included: number of patients receiving each line of therapy (i.e. 2, 3, 4, 5+), hospitalizations, ICU admissions, emergency room visits, any imaging (positron emission tomography (PET) scans, magnetic resonance imaging (MRI), computerized tomography (CT) scans), allogenic SCT (allo-SCT), auto-SCT, and radiation therapy. Mean (SD), median (Q1, Q3) and minimum and maximum values were calculated for continuous data and categorical data was calculated as the number of patients and proportion of the cohort.

**Medical costs**

Medical costs were the main outcomes of interest of the SEM. Total medical cost of care was calculated to include both DLBCL-related and DLBCL non-related costs, which occurred during each patient’s follow-up (from the 2L/3L treatment). The components of total costs were: inpatient cost, intensive care unit (ICU) cost, outpatient cost, cancer treatment costs, and other pharmacy costs (for drugs prescribed other than cancer treatment). SCT costs, including any allo-SCT and auto-SCT. In addition to the SEM, all of these cost components were described as the number of patients, mean (SD), median (Q1, Q3), as well as minimum and maximum values.

Nominal direct medical costs were obtained in Japanese yen (JPY) directly from the database. Direct unadjusted (nominal) medical costs were presented after converting from JPY to USD using the exchange rate based on the first month of every year [17]. Direct unadjusted (nominal) medical costs were then adjusted to direct adjusted medical costs with regard to Japanese inflation rate based on the calendar year average of Consumer Price Index (reference year: 2020) [18].

**Statistical analysis**

The primary outcome for this study was the drivers of total medical cost. A SEM with path analysis was constructed to assess medical cost drivers as the associations with and between patient profile components (e.g. treatment regimen received, demographics, clinical conditions and HCRU) and total medical cost. The SEM is a measurement model used to define complex relationships between observed variables and their underlying concepts [19]. SEM includes two major components, a measurement model assessing confirmatory factor analysis and structural model for multiple regression/path analysis [20]. As the input parameters were not conceptual and defined from claims data, the model was constructed as path analyses, and due to the skew of medical cost and sample size under 5000, non-normality was accounted for with robust standard error [21, 22].

All effects observed upon analysis with SEM are presented as direct, indirect and total effects for each cohort. The results of each effect category are presented as coefficients (B), standardize coefficients (β) with 95% confidence intervals (95%CI), and a two-sided test for significance (p-value). As the conventional of presentation of parameter estimates are the standardized coefficients its level of significance (p<0.05 or p<0.01) [23, 24], threshold for all SEM coefficients was therefore set at 5%. The goodness of fit was tested for both SEMs using the standardized root mean square residual (SRMR), in which a value less than 0.08 is considered a well-fitted model [25]. The SEM pathway diagram showing the hypothesized
relationships between variables is presented in Fig 2. Based on prior literature on covariates related to medical cost found in literature, patient clinical characteristics, treatment regimen, comorbidities, and complications were theorized to be direct effects on total healthcare cost in the SEM. Given the nature of the retrospective database, as medical cost is directly derived from an associated procedure or treatment, HCRU was also specified as a direct effect. Index treatment regimen was additionally specified as a mediator, as patient characteristics and comorbidities may also affect treatment regimen, and thus indirectly the medical cost. Similarly, complications and HCRU were also specified as mediators, as comorbidities and index regimen may indirectly impact total medical cost due to certain complications and high HCRU. Total effect for each predictor was subsequently calculated as the sum of the direct and indirect effects.

Direct effects.
- Total healthcare cost (THCC) = w \cdot \text{Patient Characteristics} + x \cdot \text{Comorbidities} + y \cdot \text{index treatment regimen (ITR)} + v \cdot \text{Complications} + z \cdot \text{HCRU}

Mediators.
- ITR = a \cdot \text{Patient Characteristics} + b \cdot \text{Comorbidities}
- HCRU = k \cdot \text{ITR} + m \cdot \text{Complications}
- Complications = c \cdot \text{Comorbidities} + d \cdot \text{ITR}

Indirect effects.
- Patient characteristics (indirect): = a \cdot y + a \cdot k \cdot z + a \cdot d \cdot v + a \cdot d \cdot m \cdot z
- Comorbidities (indirect): = b \cdot y + b \cdot k \cdot z + b \cdot d \cdot m \cdot z + c \cdot v + c \cdot m \cdot z
- ITR (indirect): = k \cdot z + d \cdot m \cdot z + d \cdot v
- Complications (indirect): = m \cdot z
**Total effects.**

- Total, Patient characteristics: \( w + \text{patient characteristics (indirect)} \)
- Total, Comorbidities: \( x + \text{comorbidities (indirect)} \)
- Total, ITR: \( y + \text{ITR (indirect)} \)
- Total, Complications: \( v + \text{complications (indirect)} \)
- Total, HCRU: \( z \)

The DLBCL analytical dataset was obtained from SAS® version 9.4 or higher, and all SEM data analyses were performed using the Lavaan package in R [26].

**Results**

There were 4,208 patient records included in the 2L cohort and 1,702 patient records in the 3L cohort (Fig 3).

**Patient profile of 2L cohort**

Patient profiles for both cohorts are presented for several key characteristics in Table 1. In the 2L cohort 55.7% were male and the mean [median] (SD) age was 68.9 [70.0] (12.4) years. The largest age group proportion was those under 66 years old (32.9%). The index year of treatment for the 46.9% of the 2L patients was on or after 2017. Mean [median] (SD) follow-up time was 916.2 [685.0] (694.1) days.

Nearly one third of patients had prior radiation therapy (32.7%), and a small proportion had prior SCT (13.5%). The mean [median] (SD) duration of 2L regimen was 3.7 [2.4] (5.5) months (S1 Table in S1 File). There were 20.3% and 22.0% of patients with congestive heart failure and chronic pulmonary disease, respectively. The proportion of the 2L group with baseline CCI score of 5 or greater decreased from 31.0% to 27.9% after removing DLBCL diagnosis from the calculation of the CCI score.

![Selection flow for patients with rrDLBCL in each cohort](https://doi.org/10.1371/journal.pone.0269169.g003)
Patient profile of 3L cohort

In the 3L cohort, 55.8% were male and the mean [median] (SD) age was 67.7 [69.0] (12.4) for the entire population. A minority of patients were aged 71 years or above (45.1%). The index year of treatment for the 49.5% of these patients was on or after 2017. Mean [median] (SD) follow-up time was 820.6 [581.5] (650.0) days. A large minority of patients had prior radiation therapy (36.7%) or prior SCT (23.1%). The mean [median] (SD) duration of 2L in the 3L cohort was 2.6 [1.9] (3.1) months (S1 Table in S1 File). Comorbidities were identified in many 3L patient records, including 24.5% and 25.8% of patients with congestive heart failure and chronic pulmonary disease, respectively. Mild liver disease and metastatic solid tumors were also found in 27.4% and 18.2% of patients, respectively. Almost one third of patients had a CCI score of 5 or greater (31.5%) even after removing DLBCL diagnosis from the calculation.

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| Table 1. Characteristics of rrDLBCL patient cohorts. |
|---------------------------------|-----------------|-----------------|
| **Number of patients, N**      | **2L Cohort**   | **3L Cohort**   |
| Female                         | 1864 (44.3)     | 752 (44.2)      |
| Male                           | 2344 (55.7)     | 950 (55.8)      |
| **Age**                        |                 |                 |
| Mean (SD)                      | 68.9 (12.4)     | 67.7 (12.4)     |
| Median (Q1, Q3)                | 70.0 (62.0, 78.0)| 69.0 (61.0, 77.0)|
| Min, max                       | 6.0, 97.0       | 17.0, 95.0      |
| **Age groups, n (%)**          |                 |                 |
| <66                            | 1386 (32.9)     | 628 (36.9)      |
| 66–80                          | 2133 (50.7)     | 848 (49.8)      |
| >80                            | 689 (16.4)      | 226 (13.3)      |
| **Index year, n (%)**          |                 |                 |
| 2008–2010                      | 96 (2.2)        | 28 (1.7)        |
| 2011–2015                      | 1527 (36.3)     | 584 (34.3)      |
| 2016–2019                      | 2585 (61.4)     | 1090 (64.1)     |
| **Follow-up time (from index date until death or last patient record), n (%)** | | |
| Mean (SD)                      | 916.2 (694.1)   | 820.6 (650.0)   |
| Median (Q1, Q3)                | 685.0 (381.0, 1279.0)| 581.5 (331.0, 1132.0)|
| Min, max                       | 182.0, 4109.0   | 182.0, 4062.0   |
| **Complications, n (%)**       |                 |                 |
| Heart disease                  | 670 (15.9)      | 246 (14.5)      |
| Kidney disease                 | 220 (5.2)       | 95 (5.6)        |
| Liver disease                  | 680 (16.2)      | 252 (14.8)      |
| Prior SCT                      | 570 (13.5)      | 394 (23.1)      |
| Prior radiation therapy        | 1376 (32.7)     | 625 (36.7)      |
| **Modified baseline CCI†, n (%)** |                 |                 |
| 0–2                            | 1945 (46.2)     | 708 (41.6)      |
| 3                              | 479 (11.4)      | 201 (11.8)      |
| 4                              | 609 (14.5)      | 257 (15.1)      |
| 5+                             | 1175 (27.9)     | 536 (31.5)      |

CCI, Charlson Comorbidity Index
*New diagnosis after index date, with no history of disease any prior respective lines
†Modified by removing DLBCL as a comorbidity

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While proportions of patients receiving multiple lines of treatment differed slightly, the most common treatment categories for the 2L and 3L cohorts followed similar patterns (Table 2). In both cohorts, gemcitabine, dexamethasone, cisplatin/carboplatin (GDP)-based with or without rituximab was the most common specific regimen across all treatment lines (range: 7.7%-9.0%). The largest minority of the 2L cohort (44.4%) of patients received other R-based therapy in 2L. This proportion decreased to 21.6% by 5L for the 2L cohort and 22.7% for the 5L of the 3L cohort. During 3L for the 2L cohort, 24.9% received other R-based therapy and 28.1% received other chemotherapy without R. The 3L regimen for 3L cohort, in contrast, was comprised evenly of other R-based (32.7%) therapies or other chemotherapy without rituximab (30.4%). The proportion of patient receiving other R-based regimens switched to other chemotherapy without rituximab by 3L and steadily increased as patients progressed to through 5L.

Very few patients received induction regimens prior auto-SCT, detailed in S2 Table in S1 File. HCRU for 2L and 3L cohorts was relatively similar with the exception of transplantation outcomes. For example, the mean [median] (SD) number of hospitalizations for the 2L cohort was 5.0 [4.0] (3.8) with a mean [median] (SD) length of hospital stay (LOS) of 122.9 [100.0] (100.5) days. For mean [median] (SD) number of hospitalizations, the 3L cohort had 5.0 [4.0] (3.9) with a mean [median] (SD) LOS of 126.3 [100.5] (103.0) days. ICU admissions and emergency room visits were rare at less than 5% for both cohorts. It was notable that 13.3% of 2L cohort patients received an auto-SCT but 21.4% of 3L cohort patients received the same kind of transplantation during the follow-up period.

Medical costs for the cohorts were comparable (Table 3), with the 3L cohort having slightly higher total follow-up costs compared to 2L (by less than 2,000 USD). The mean [median] (SD) total medical cost of care for the 2L cohort was 73,296.40 [58,223.11] (58,409.79) USD. Inpatient costs were the highest component of total cost (mean [median]; 60,941.71 [47,026.10] USD). The mean [median] (SD) total medical cost of care for the 3L cohort was 75,238.35 [60,477.31] (59,583.66) USD where inpatient costs were also the highest component of total cost (mean [median]; 64,081.09 [49,795.46] USD). Total costs as well as relative follow-up time stratified by age and gender are shown in S3 Table in S1 File. While older age correlated less follow-up time and subsequently lower unadjusted total cost, female patients had comparable follow-up time with male patients, yet accrued lower total cost.

**SEM outcomes**

Estimates of total effects on medical cost, and its component indirect and direct effects, are presented for the 2L and 3L cohorts (Table 4).

LOS had the largest total effect on medical cost in the 2L cohort ($\beta$: 0.750 [95%CI: 0.728, 0.772]). The other largest cost drivers were heart disease complications ($\beta$: 0.218, [95%CI: 0.184, 0.252]), having R-CHASE treatment regimen as an index regimen ($\beta$: 0.191 [95%CI: 0.157, 0.225]) and induction regimens with auto-SCT ($\beta$: 0.156, [95%CI: 0.133, 0.178]). The largest protective drivers were all older age groups compared to those under 66 years, increasing index year ($\beta$: -0.113 [95%CI: -0.131, -0.094]), female gender ($\beta$: -0.036 [95%CI: -0.053, -0.019]), and a CCI score of 4 ($\beta$: -0.022 [95%CI: -0.042, -0.002]). The 81–85 age group had the strongest negative relationship with medical cost ($\beta$: -0.101 [95%CI: -0.116, -0.085]). This model fit the data well with a SRMR of 0.060.

The total effect of LOS on medical cost was also the largest for the 3L cohort ($\beta$: 0.762 [95% CI: 0.729, 0.794]). The next largest driver of total cost was having heart disease as a complication ($\beta$: 0.176 [95%CI: 0.122, 0.230]), with a large part due to the indirect effects ($\beta$: 0.118 [95% CI: 0.075, 0.161]) and any SCT ($\beta$: 0.154 [95%CI: 0.120, 0.187]). Unlike the 2L cohort where it was third largest, R-CHASE as an index regimen was associated with the fourth largest
Table 2. Treatment patterns for rrDLBCL patients.

|                                      | 2L Cohort | 3L Cohort |
|--------------------------------------|-----------|-----------|
| Number of treatment patients, N      | 4208      | 1702      |
| Total lines, mean (SD)               | 3.5 (1.7) | 4.8 (1.8) |
| 2, n (%)                             | 1432 (34.0) | - | - |
| 3, n (%)                             | 1096 (26.0) | 485 (28.5) |
| 4, n (%)                             | 714 (17.0) | 424 (24.9) |
| 5+, n (%)                            | 966 (23.0) | 793 (46.6) |
| **Second line regimen (2L), n (%)**  |           |           |
| R+/−DeVIC-based                      | 250 (5.9) | - | - |
| R-CHASE-based                        | 280 (6.7) | - | - |
| GDP-based with or without R          | 323 (7.7) | - | - |
| R-Bendamustine-based                 | 98 (2.3) | - | - |
| R-EPOCH                              | 143 (3.4) | - | - |
| R-ESHAP-based                        | 70 (1.7) | - | - |
| ESHAP-based                          | 24 (0.6) | - | - |
| R-ICE-based                          | 21 (0.5) | - | - |
| R-DHAP-based                         | 3 (0.1) | - | - |
| Other R-based                        | 1868 (44.4) | - | - |
| Before an auto-SCT regimens (MEAN, LEED, MCEC, MEAM) | 52 (1.2) | - | - |
| Other chemotherapy without R         | 1076 (25.6) | - | - |
| **Third line regimen (3L), n (%)**   |           |           |
| R+/−DeVIC-based                      | 186 (6.7) | 111 (6.5) |
| R-CHASE-based                        | 112 (4.0) | 74 (4.3) |
| GDP-based with or without R          | 234 (8.4) | 140 (8.2) |
| R-Bendamustine-based                 | 71 (2.6) | 47 (2.8) |
| R-EPOCH                              | 114 (4.1) | 104 (6.1) |
| R-ESHAP-based                        | 52 (1.9) | 40 (2.4) |
| ESHAP-based                          | 31 (1.1) | 19 (1.1) |
| R-ICE-based                          | 22 (0.8) | 15 (0.9) |
| R-DHAP-based                         | 0 (0.0) | 0 (0.0) |
| Other R-based                        | 691 (24.9) | 557 (32.7) |
| Before an auto-SCT regimens (MEAN, LEED, MCEC, MEAM) | 89 (3.2) | 78 (4.6) |
| Other chemotherapy without R         | 781 (28.1) | 517 (30.4) |
| Not otherwise specified              | 393 (14.2) | NA |
| **Fourth line regimen (4L), n (%)** |           |           |
| R+/−DeVIC-based                      | 124 (7.4) | 87 (7.1) |
| R-CHASE-based                        | 66 (3.9) | 52 (4.3) |
| GDP-based with or without R          | 152 (9.0) | 108 (8.9) |
| R-Bendamustine-based                 | 45 (2.7) | 34 (2.8) |
| R-EPOCH                              | 56 (3.3) | 43 (3.5) |
| R-ESHAP-based                        | 29 (1.7) | 16 (1.3) |
| ESHAP-based                          | 10 (0.6) | 7 (0.6) |
| R-ICE-based                          | 10 (0.6) | 9 (0.7) |
| R-DHAP-based                         | 3 (0.2) | 3 (0.2) |
| Other R-based                        | 362 (21.5) | 294 (24.2) |
| Before an auto-SCT regimens (MEAN, LEED, MCEC, MEAM) | 26 (1.5) | 24 (2.0) |
| Other chemotherapy without R         | 530 (31.5) | 386 (31.7) |
| Not otherwise specified              | 267 (15.9) | 154 (12.7) |

(Continued)
increase in cost burden in the 3L cohort (β: 0.116 [95%CI: 0.059, 0.172]). Parameters associated with significant decrease in burden of cost included female gender (β: -0.034 [95%CI: -0.061, -0.007]), older age groups (71 years or older) compared to those under 66 years, and increasing index year of treatment (β: -0.117 [95%CI: -0.144, -0.090]). CCI score was not significantly associated with total effect on medical cost. This model fit the data well with a SRMR of 0.065.

Other prior or concurrent primary cancers besides DLBCL did not have a total effect on cost for either 2L or 3L cohort.

Discussion

Total medical cost during follow-up was relatively similar between 2L and 3L cohorts with average costs for 2L of 73,296 USD and 75,238 USD for 3L patients. The two treatment cohorts of rrDLBCL patients had similar baseline characteristics, HCRU, cost and cost drivers, except a few notable exceptions in terms of relative cost driver size. LOS and heart disease complications were consistently the largest drivers of medical costs was for both 2L and 3L cohorts. In 3L, the effect of LOS was about four times larger than heart disease complications and LOS was about three times larger than the effect of heart disease complications in 2L. The 2L cohort had about one third fewer auto-SCT than the 3L cohort and SCT was the third largest cost driver in the 3L cohort compared to R-CHASE regimen in the 2L cohort. These differences may reflect complex clinical decision-making about curative treatments based on the baseline characteristics of patients who have rrDLBCL refractory to more than one line of salvage chemotherapy in Japan.

The biggest cost driver was LOS followed by heart disease complications for both cohorts. In 3L, the effect of LOS was about four times largest than heart disease complications and in

Table 2. (Continued)

| Subsequent regimen (5L), n (%) | 2L Cohort | 3L Cohort |
|-------------------------------|-----------|-----------|
| R+/DeVIC-based                | 70 (7.2)  | 55 (6.9)  |
| R-CHASE-based                 | 24 (2.5)  | 22 (2.8)  |
| GDP-based with or without R   | 84 (8.7)  | 67 (8.4)  |
| R-Bendamustine-based          | 19 (2.0)  | 16 (2.0)  |
| R-EPOCH                       | 17 (1.8)  | 17 (2.1)  |
| R-ESHAP-based                 | 11 (1.1)  | 10 (1.3)  |
| ESHAP-based                   | 11 (1.1)  | 10 (1.3)  |
| R-ICE-based                   | 5 (0.5)   | 4 (0.5)   |
| R-DHAP-based                  | 0 (0.0)   | 0 (0.0)   |
| Other R-based                 | 209 (21.6)| 180 (22.7)|
| Before an auto-SCT regimen (MEAN, LEED, MCEC, MEAM)* | 13 (1.3) | 10 (1.3) |
| Other chemotherapy without R  | 349 (36.1)| 293 (36.9)|
| Not otherwise specified       | 154 (15.9)| 109 (13.7)|

R, rituximab; DeVIC, dexamethasone, etoposide, ifosfamide, carboplatin; CHASE, cyclophosphamide, cytarabine, etoposide, dexamethasone; GDP, gemcitabine, dexamethasone, cisplatin/carboplatin; Bendamustine; EPOCH, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin; ESHAP, etoposide, cytarabine, cisplatin, methylprednisolone; ICE, ifosfamide, carboplatin, etoposide; DHAP, dexamethasone, cytarabine, cisplatin; MINE, mitoxantrone, ifosfamide, mesna, etoposide; LEED, melphalan, cyclophosphamide, etoposide, dexamethasone; MCEC, ranimustine, carboplatin, etoposide, cyclophosphamide; MEAM, ranimustine, etoposide, cytarabine, melphalan

* Includes only patients who underwent auto-SCT after regimen; patients who underwent the following therapies but did not undergo auto-SCT after the regimen were counted as ‘Other chemotherapy without R’

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2L LOS was about three times larger than the effect of heart disease complications. This large effect of LOS is distinct from other studies using SEM to calculate effects on medical cost. For example, an SEM path analysis of respiratory syncytial virus in Japanese children found the effect of LOS on medical cost to be high but approximately 10 times lower than the effect of blood transfusions [27]. In the present study there were also SEM parameters for cohorts where direct effects were positive and the indirect effects were negative or vice versa. Indirect

Table 3. Healthcare costs (USD) during follow-up.

|                        | 2L Cohort | 3L Cohort |
|------------------------|-----------|-----------|
| Total medical cost of care, N | 4208      | 1702      |
| Mean (SD)              | 73296.40 (58409.79) | 75238.35 (59583.66) |
| Median (Q1, Q3)        | 58223.11 (32898.90, 94623.89) | 60477.31 (33081.40, 98382.96) |
| Min, Max               | 1842.95, 528090.15 | 1893.19, 449778.98 |
| Cost subcategories     |           |           |
| Inpatient cost, n      | 3965      | 1596      |
| Mean (SD)              | 60941.71 (53470.41) | 64081.09 (54397.09) |
| Median (Q1, Q3)        | 47026.10 (22754.39, 82425.81) | 49795.46 (25324.70, 87557.80) |
| Min, Max               | 488.50, 415774.22 | 466.74, 382401.46 |
| Intensive care unit (ICU) cost | 112     | 42        |
| Mean (SD)              | 4282.24 (4184.19) | 3553.31 (3656.36) |
| Median (Q1, Q3)        | 2510.72 (866.34, 6485.93) | 2015.99 (938.02, 5198.07) |
| Min, Max               | 791.53, 16611.09 | 791.53, 16611.09 |
| Outpatient cost        | 4101      | 1661      |
| Mean (SD)              | 16288.06 (22139.76) | 15522.13 (22552.28) |
| Median (Q1, Q3)        | 9806.97 (4434.62, 20371.38) | 8807.34 (3904.47, 18604.34) |
| Min, Max               | 6.76, 364765.41 | 8.64, 361559.02 |
| Cancer treatment costs | 4208      | 1702      |
| Mean (SD)              | 16027.24 (19331.29) | 14979.17 (20362.97) |
| Median (Q1, Q3)        | 11909.82 (5896.15, 20001.11) | 9921.29 (4487.80, 18916.99) |
| Min, Max               | 6.43, 398654.49 | 10.17, 365816.51 |
| Other pharmacy costs   | 4206      | 1702      |
| Mean (SD)              | 17709.69 (23990.57) | 19601.32 (24941.91) |
| Median (Q1, Q3)        | 9985.52 (4407.57, 21099.57) | 11206.48 (4713.06, 23497.90) |
| Min, Max               | -9874.54, 309876.04 | 8.99, 254909.73 |
| Any SCT costs          | 566       | 366       |
| Mean (SD)              | 3214.07 (1084.62) | 3161.93 (1100.12) |
| Median (Q1, Q3)        | 2840.14 (2758.10, 3091.32) | 2840.14 (2666.34, 3091.32) |
| Min, Max               | 2234.19, 12090.71 | 2234.19, 12090.71 |
| Allo-SCT costs         | 32        | 12        |
| Mean (SD)              | 6235.67 (1130.49) | 6690.51 (1773.38) |
| Median (Q1, Q3)        | 6117.58 (5842.05, 6149.83) | 6149.83 (6029.23, 6149.83) |
| Min, Max               | 5618.75, 12090.71 | 5618.75, 12090.71 |
| Auto-SCT costs         | 558       | 364       |
| Mean (SD)              | 3164.70 (1014.60) | 3130.08 (1041.24) |
| Median (Q1, Q3)        | 2840.14 (2758.10, 3091.32) | 2840.14 (2666.34, 3091.32) |
| Min, Max               | 2234.19, 12090.71 | 2234.19, 12090.71 |

*Direct unadjusted (nominal) medical costs are presented after converting from JPY to USD using the exchange rate based on the first month of every year.

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2L LOS was about three times larger than the effect of heart disease complications. This large effect of LOS is distinct from other studies using SEM to calculate effects on medical cost. For example, an SEM path analysis of respiratory syncytial virus in Japanese children found the effect of LOS on medical cost to be high but approximately 10 times lower than the effect of blood transfusions [27]. In the present study there were also SEM parameters for cohorts where direct effects were positive and the indirect effects were negative or vice versa. Indirect
Table 4. Standardized estimates from structural equation model of 2L and 3L cost drivers.

| THCC drivers | Direct effect (USD) | Indirect effect* (USD) | Total effect (USD) |
|--------------|---------------------|------------------------|-------------------|
|              | $\beta$ 95%CI $p$   | $\beta$ 95%CI $p$     | $\beta$ 95%CI $p$  |
| **2L**       |                     |                       |                   |
| Patient characteristics |                     |                       |                   |
| Gender (reference: male) |                     |                       |                   |
| Female       | -0.036 -0.052 -0.020 <0.001 | 0 -0.007 0.007 0.927 | -0.036 -0.053 -0.019 <0.001 |
| Age (reference: <66) |                     |                       |                   |
| 66–70        | -0.030 -0.047 -0.013 0.001 | -0.009 -0.017 0 0.043 | -0.038 -0.057 -0.020 <0.001 |
| 71–75        | -0.052 -0.068 -0.036 <0.001 | -0.013 -0.023 -0.004 0.004 | -0.065 -0.083 -0.048 <0.001 |
| 76–80        | -0.063 -0.078 -0.047 <0.001 | -0.016 -0.025 -0.007 0.001 | -0.079 -0.096 -0.061 <0.001 |
| 81–85        | -0.081 -0.096 -0.066 <0.001 | -0.02 -0.028 -0.011 <0.001 | -0.101 -0.116 -0.085 <0.001 |
| 85+          | -0.063 -0.075 -0.052 <0.001 | -0.023 -0.030 -0.017 <0.001 | -0.086 -0.099 -0.073 <0.001 |
| Index year   | -0.119 -0.136 -0.102 0 0.006 -0.002 0.014 0.128 | -0.113 -0.131 -0.094 <0.001 |
| Comorbidities |                     |                       |                   |
| CCI score (reference: 0–2) |                     |                       |                   |
| 3            | 0.017 0 0.034 0.051 -0.009 -0.021 0.003 0.127 | 0.008 -0.013 0.029 0.454 |
| 4            | 0.018 0.001 0.034 0.035 -0.040 -0.051 -0.028 <0.001 | -0.022 -0.042 -0.002 0.028 |
| 5+           | 0.062 0.044 0.081 <0.001 -0.059 -0.073 -0.045 <0.001 | 0.003 -0.019 0.026 0.768 |
| Prior/concurrent non-lymphoma neoplasms (reference: No) | 0.024 0.006 0.041 0.009 -0.003 -0.014 0.008 0.554 | 0.020 0 0.041 0.054 |
| Complications |                     |                       |                   |
| Heart disease (reference: No) | 0.064 0.042 0.085 <0.001 | 0.155 0.128 0.181 <0.001 | 0.218 0.184 0.252 <0.001 |
| Liver disease | 0.012 -0.007 0.03 0.210 | 0.108 0.081 0.134 <0.001 | 0.119 0.088 0.150 <0.001 |
| Kidney disease | 0.053 0.029 0.078 <0.001 | 0.062 0.033 0.090 0.007 | 0.115 0.074 0.156 <0.001 |
| **Index treatment regimen** |                     |                       |                   |
| R±-DeVIC-based | -0.002 -0.017 0.13 0.796 | 0.110 0.083 0.136 <0.001 | 0.108 0.078 0.137 <0.001 |
| R-CHASE-based | 0.016 -0.005 0.307 0.136 | 0.175 0.150 0.20 <0.001 | 0.191 0.157 0.225 <0.001 |
| GDP-based without or without R | -0.006 -0.019 0.008 0.404 | 0.07 0.043 0.097 <0.001 | 0.064 0.038 0.091 <0.001 |
| R- Bendamustine -based | 0.076 0.050 0.102 0 | 0.014 -0.015 0.044 0.340 | 0.091 0.054 0.127 <0.001 |
| R-EPOCH | -0.005 -0.020 0.011 0.556 | 0.080 0.054 0.107 <0.001 | 0.076 0.044 0.108 <0.001 |
| R-EHAP-based | 0.004 -0.012 0.019 0.640 | 0.068 0.043 0.092 <0.001 | 0.071 0.040 0.102 <0.001 |
| ESHAP-based | -0.006 -0.025 0.012 0.505 | 0.046 0.021 0.072 <0.001 | 0.04 0.002 0.078 0.040 |
| R-ICE-based | 0.001 -0.009 0.010 0.911 | 0.059 0.023 0.095 0.001 | 0.059 0.020 0.098 0.003 |
| R-DHAP-based | 0.002 -0.009 0.013 0.720 | 0.009 0.003 0.015 0.002 | 0.011 -0.002 0.025 0.091 |
| Other R-based | 0.033 0.017 0.049 <0.001 | 0.002 -0.024 0.028 0.871 | 0.035 0.005 0.065 0.022 |
| Induction therapy before auto-SCT regimens† | -0.026 -0.044 -0.007 0.007 | 0.023 0 0.045 0.046 | -0.003 -0.031 0.025 0.826 |
| HCRU |                     |                       |                   |
| Number of hospitalizations (reference: No) | 0.088 0.064 0.112 <0.001 | - - - - | 0.088 0.064 0.112 <0.001 |
| Any ICU admission | 0.050 0.027 0.072 <0.001 | - - - - | 0.050 0.027 0.072 <0.001 |
| Any PET scans | 0.022 0.005 0.040 0.013 | - - - - | 0.022 0.005 0.040 0.013 |
| Any MRI scans | 0.029 0.013 0.046 0.001 | - - - - | 0.029 0.013 0.046 0.001 |
| Any CT scans | 0.005 -0.008 0.017 0.449 | - - - - | 0.005 -0.008 0.017 0.449 |
| Any emergency room visits | 0.002 -0.012 0.017 0.760 | - - - - | 0.002 -0.012 0.017 0.760 |
| Any SCT | 0.156 0.133 0.178 <0.001 | - - - - | 0.156 0.133 0.178 0 |
| Any radiation therapy | 0.005 -0.011 0.021 0.572 | - - - - | 0.005 -0.011 0.021 0.572 |
| LOS | 0.750 0.728 0.772 <0.001 | - - - - | 0.750 0.728 0.772 <0.001 |

(Continued)
### Table 4. (Continued)

| THCC drivers                                      | Direct effect (USD) | Indirect effect * (USD) | Total effect (USD) |
|---------------------------------------------------|---------------------|-------------------------|--------------------|
|                                                   | β                   | 95%CI                   | p                  |
|                                                   | β                   | 95%CI                   | p                  |
|                                                   | β                   | 95%CI                   | p                  |
| Age (reference: <66)                              |                     |                         |                    |
| 66–70                                             | -0.027              | -0.054 0.001 0.057      | 0.003 -0.009 0.015 0.15 0.608 | -0.023 -0.053 0.006 0.119 |
| 71–75                                             | -0.048              | -0.077 -0.018 0.001     | 0.003 -0.010 0.016 0.16 0.648 | -0.045 -0.075 -0.014 0.004 |
| 76–80                                             | -0.076              | -0.100 -0.052 <0.001    | 0.003 -0.011 0.017 0.664 | -0.073 -0.099 -0.048 <0.001 |
| 81–85                                             | -0.054              | -0.079 -0.03 <0.001     | -0.001 -0.013 0.012 0.919 | -0.055 -0.082 -0.028 <0.001 |
| 85+                                               | -0.063              | -0.087 -0.039 <0.001    | -0.009 -0.018 -0.001 0.037 | -0.072 -0.096 -0.049 <0.001 |
| Index year                                        | -0.116              | -0.141 -0.091 <0.001    | -0.001 -0.013 0.010 0.823 | -0.117 -0.144 -0.090 <0.001 |
| Comorbidities                                     |                     |                         |                    |
| CCI score (reference: 0–2)                        |                     |                         |                    |
| 3                                                 | 0.008               | 0.022 0.037 0.612       | -0.013 -0.028 0.003 0.103 | -0.005 -0.038 0.028 0.772 |
| 4                                                 | 0.017               | 0.009 0.042 0.203       | -0.036 -0.053 -0.018 <0.001 | -0.019 -0.049 0.011 0.213 |
| 5+                                                | 0.056               | 0.025 0.088 <0.001      | -0.055 -0.077 -0.033 <0.001 | 0.001 -0.035 0.037 0.950 |
| Prior/concurrent non-lymphoma neoplasms (reference: No) | 0.037               | 0.008 0.066 0.012       | -0.019 -0.034 -0.004 0.013 | 0.018 -0.015 0.051 0.281 |
| Complications                                     |                     |                         |                    |
| Heart Disease (reference: No)                     | 0.058               | 0.027 0.089 <0.001      | 0.118 0.075 0.161 <0.001 | 0.176 0.122 0.230 <0.001 |
| Liver Disease                                     | 0.021               | -0.009 0.051 0.167      | 0.098 0.054 0.141 <0.001 | 0.119 0.067 0.171 <0.001 |
| Kidney Disease                                    | 0.046               | 0.011 0.08 0.009        | 0.063 0.017 0.108 0.007 | 0.108 0.049 0.168 <0.001 |
| Index treatment regimen                           |                     |                         |                    |
| R+/−DeVIC-based                                   | 0                   | -0.022 0.022 0.991      | 0.082 0.041 0.122 0 0.082 0.034 0.129 0.001 |
| R-CHASE-based                                     | 0.008               | -0.019 0.035 0.546      | 0.107 0.065 0.15 0 0.116 0.059 0.172 <0.001 |
| GDP-based without or without R                    | -0.007              | -0.031 0.018 0.603      | 0.043 0.001 0.086 0.046 | 0.037 -0.004 0.077 0.076 |
| R- Bendamustine -based                            | 0.058               | 0.023 0.094 0.001       | -0.026 -0.063 0.012 0.184 | 0.033 -0.014 0.079 0.169 |
| R-EPOCH                                          | -0.020              | -0.040 0 0.048          | 0.018 -0.018 0.054 0.323 | -0.002 -0.043 0.039 0.918 |
| R-ESHAP-based                                     | -0.001              | -0.020 0.018 0.892      | 0.043 0.018 0.069 0.001 | 0.042 0.009 0.074 0.011 |
| ESHAP-based                                       | 0.001               | -0.027 0.030 0.932      | 0.015 -0.012 0.042 0.262 | 0.017 -0.029 0.063 0.475 |
| R-ICE-based                                       | 0.046               | 0.008 0.084 0.018       | 0.079 0.020 0.137 0.008 | 0.125 0.050 0.200 0.001 |
| Other R-based                                     | 0.047               | 0.020 0.074 0.001       | -0.049 -0.091 -0.007 0.024 | -0.002 -0.052 0.048 0.939 |
| Induction therapy before auto-SCT regimens†       | -0.023              | -0.051 0.005 0.106      | 0.015 -0.019 0.049 0.381 | -0.008 -0.053 0.037 0.727 |
| HCRU                                              |                     |                         |                    |
| Number of hospitalizations (reference: No)        | 0.121               | 0.085 0.157 <0.001      | 0.121 0.085 0.157 <0.001 |
| Any ICU admission                                 | 0.049               | 0.012 0.087 0.010       | 0.049 0.012 0.087 0.010 |
| Any PET scans                                     | 0.023               | -0.004 0.051 0.100      | 0.023 -0.004 0.051 0.100 |
| Any MRI scans                                     | 0.025               | -0.001 0.052 0.062      | 0.025 -0.001 0.052 0.062 |
| Any CT scans                                      | 0.014               | -0.003 0.031 0.104      | 0.014 -0.003 0.031 0.104 |
| Any emergency room visits                         | 0.009               | -0.017 0.036 0.490      | 0.009 -0.017 0.036 0.490 |
| Any SCT                                           | 0.154               | 0.120 0.187 <0.001      | 0.154 0.120 0.187 <0.001 |
| Any radiation therapy                             | 0.005               | -0.021 0.030 0.722      | 0.005 -0.021 0.030 0.722 |
| LOS                                               | 0.762               | 0.729 0.794 <0.001      | 0.762 0.729 0.794 <0.001 |

Standardized Root Mean Square Residual (SRMR): 0.065

β, standardized coefficient; 95%CI, 95% confidence interval; ICU, intensive care unit; ITR, index treatment regimen; LOS, length of hospital stay; THCC, total health care cost; HCRU, healthcare resource utilization; USD, US dollars.

*Represents the total indirect effect of variable on THCC via all specified mediators. Paths and mediators for the variables under each category are described in Fig 2 and methods section.

Reference treatment group = other chemotherapy without rituximab

†Includes only patients who underwent auto-SCT after regimen; patients who underwent induction therapies but did not undergo auto-SCT after the regimen were counted as "Other chemotherapy without R".

‡Hu and Bentler,1999: SRMR of <0.08 represents a well-fitted model.

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The intersection of cohort patient characteristics and their treatment patterns are one suggestion that there are differences in how more advanced rrDLBCL patients are treated in Japanese real-world practice. The 2L cohort was only slightly older in age than 3L cohort, however a large proportion of 3L patients had more comorbidities than 2L. SCT is considered to be the optimal treatment option for eligible patients with rrDLBCL [28], but within the follow-up period of the current analysis, the 2L cohort had about one third smaller proportion of auto-SCT than the 3L cohort. This may potentially be due to patients receiving their high-dose chemotherapy (HDC) more than 30 days after second line initiation or with a 90-day treatment gap, thus were counted as third line treatment and resulting in slightly higher proportion of SCTs counted in the 3L cohort. Due to the complexity of claims data and the high heterogeneity of salvage regimen drugs, HDC drugs, as well as timing of HDC, explicit separation between salvage chemotherapy and HDC was not further conducted. On the other hand, in spite of their comorbidities, the poorer prognosis of the 3L cohort may have required intensive therapy as conditioning for auto-SCT to further prolong survival. For example, a study of rrDLBCL patients in a single center in the UK found a considerable drop in complete response rates for rrDLBCL with 2L (27.0%), to 3L (17.5%), to 4L (2.4%) [29]. HCST also had one of largest effects on medical cost for both cohorts, though it was relatively higher in 3L. A study of Canadian patients similarly found that SCT had a larger impact on medical cost for patient’s receiving more than one treatment DLBCL [30].

There were several protective factors for medical costs. Increasing age was associated with decreases in cost, mostly due to the shorter survival time (thus observation period) of older patients. Similarly, patients with later index years had a shorter observation period, thus index year was adjusted for in the model, but its coefficient should be interpreted with caution. Exploratory analysis of medical costs for each age group shows decreasing cost with age outside of the SEM, as well as decreasing follow-up time with age. The total effects from SEM results showed that females had significantly less cost burden. Outside of the SEM, females also had lower costs with comparable follow-up time.

The real world treatment patterns used to treat rrDLBCL in Japan are diverse and have different impact on overall medical cost. This treatment has been shown to have some efficacy in rrDLBCL in a phase II study (overall response rate 67%) [31] but this treatment has not been studied in detail from an economic perspective [28].

This study poses a few limitations. First, due to the nature of retrospective claims studies, patients cannot be traced longitudinally and each exact line of therapy assigned may be subject to bias. Additionally, medical costs accrued outside of the facilities captured by the database are not accounted for, which may contribute to an underestimation of the total medical costs. Lastly, due to the complex paths used and the large number of predictors, statistical significance should be interpreted with caution and should be interpreted holistically.

This study is the first in Japan to investigate the relationship between patient attributes, healthcare utilization, and total medical cost in rrDLBCL patients. Our study positioned a holistic model of the predictors of medical drivers in a complex disease with poor prognosis. The findings suggest that although age and gender have direct impact on total cost in both 2L and 3L, complications and treatment regimen also impact total cost, largely through indirect effects.
Supporting information

S1 File.

(DOCX)

Author Contributions

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References

1. Chihara D, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S, et al. Differences in incidence and trends of haematological malignancies in Japan and the United States. Br J Haematol. 2014; 164 (4):536–45. https://doi.org/10.1111/bjh.12659 PMID: 24245986

2. Miyoshi H, Oshimia K. Epidemiology of malignant lymphoma and recent progress in research on adult T-cell leukemia/lymphoma in Japan. Int J Hematol. 2018; 107(4):420–7. https://doi.org/10.1007/s12185-018-2430-6 PMID: 29502313

3. Morrison VA, Bell JA, Hamilton L, Ogbonnaya A, Shih HC, Hennenfent K, et al. Economic burden of patients with diffuse large B-cell and follicular lymphoma treated in the USA. Future Oncol. 2018; 14 (25):2627–42. https://doi.org/10.2217/fon-2018-0267 PMID: 29911900

4. Chihara D, Ito H, Izutsu K, Hattori M, Nishino Y, Ioka A, et al. Advance and stagnation in the treatment of patients with lymphoma and myeloma: Analysis using population-based cancer registry data in Japan from 1993 to 2006. Int J Cancer. 2015; 137(5):1217–23. https://doi.org/10.1002/ijc.29477 PMID: 25694231

5. Gisselbrecht C, Schmitz N, Mounier N, Singh Gill D, Linch DC, Tmeny M, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. J Clin Oncol. 2012; 30(36):4462–9. https://doi.org/10.1200/JCO.2012.41.9416 PMID: 23091101

6. Zelenetz AD, Gordon LI, Abramson JS, Advani RH, Bartlett NL, Caimi PF, et al. NCCN Guidelines Insights: B-Cell Lymphomas, Version 3.2019. J Natl Compr Canc Netw. 2019; 17(6):650–61. https://doi.org/10.6004/jnccn.2019.0029 PMID: 31200358

7. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017; 130 (16):1800–8. https://doi.org/10.1182/blood-2017-03-769620 PMID: 28774879

8. Nagle SJ, Woo K, Schuster SJ, Nasta SD, Stadtmueller E, Mick R, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. Am J Hematol. 2013; 88(10):890–4. https://doi.org/10.1002/ajh.23524 PMID: 23813874

9. Purdum A, Tieu R, Reddy SR, Broder MS. Direct Costs Associated with Relapsed Diffuse Large B-Cell Lymphoma Therapies. Oncologist. 2019; 24(9):1229–36. https://doi.org/10.1634/theoncologist.2018-0490 PMID: 30850561

10. Huntington S, Keshishian A, McGuire M, Xie L, Baser O. Costs of relapsed diffuse large B-cell lymphoma among Medicare patients. Leuk Lymphoma. 2018; 59(12):2880–7. https://doi.org/10.1080/10428194.2018.1459613 PMID: 29936866
11. Tsutsue S, Tobinai K, Yi J, Crawford B. Nationwide claims database analysis of treatment patterns, costs and survival of Japanese patients with diffuse large B-cell lymphoma. PLoS One. 2020; 15(8): e0237509. https://doi.org/10.1371/journal.pone.0237509 PMID: 32810157

12. Mizia-Stec K, Elżbieciak M, Wybraniec MT, Różewicz M, Bodys A, Braksator W, et al. Chemotherapy and echocardiographic indices in patients with non-Hodgkin lymphoma: the ONCO-ECHO study. Med Oncol. 2017; 35(1):14. https://doi.org/10.1007/s12032-017-1075-2 PMID: 29274027

13. Javaugue V, Debiais-Delphe C, Nouvier M, Gand E, Chauvet S, Ecotiere L, et al. Clinicopathological spectrum of renal parenchymal involvement in B-cell lymphoproiferative disorders. Kidney Int. 2019; 96 (1):94–103. https://doi.org/10.1016/j.kint.2019.01.027 PMID: 30987838

14. Shi Q, Shen R, Wang CF, Fan X, Qian Y, Ou-Yang BS, et al. Pretreatment Liver Injury Predicts Poor Prognosis of DLBCL Patients. Mediators Inflamm. 2017; 2017:7960907. https://doi.org/10.1155/2017/ 7960907 PMID: 29109622

15. Quan H, Li B, COURIS CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011; 15(173):676–82. https://doi.org/10.1093/aje/kwq433 PMID: 21330339

16. Tsutsue S, Makita S, Yi J, Crawford B. Economic burden in treated Japanese patients with relapsed/ refractory large B-cell lymphoma. Future Oncol. 2021; 17(33):4511–25. https://doi.org/10.2217/fon-2021-0400 PMID: 34414783

17. Bank of Japan. Foreign Exchange Rates (Daily) 2020 [https://www.boj.or.jp/en/statistics/market/forex/ fxdaily/index.htm/.

18. Statistical Bureau of Japan. 2015-Base Explanation of the Consumer Price Index [https://www.stat.go.jp/english/data/cpi/1589.html.

19. Rosseel Y. lavaan: an R package for structural equation modeling. J Stat Softw. 2012; 48:1–36.

20. Orimo H, Sato M, Kimura S, Wada K, Chen X, Yoshida S, et al. Understanding the factors associated with initiation and adherence of osteoporosis medication in Japan: An analysis of patient perceptions. Osteoporos Sarcopenia. 2017; 3(4):174–84. https://doi.org/10.1016/j.afos.2017.10.002 PMID: 30775527

21. Bentler PM. Some contributions to efficient statistics in structural models: Specification and estimation of moment structures. Psychometrica. 1983; 48:493–517.

22. Lai K. More Robust Standard Error and Confidence Interval for SEM Parameters Given Incorrect Model and Nonnormal Data. Struct Equ Modeling. 2019; 26(2):260–79.

23. Bryan A, Schmiege SJ, Broaddus MR. Mediation analysis in HIV/AIDS research: estimating multivariate path analytic models in a structural equation modeling framework. AIDS Behav. 2007; 11(3):365–83. https://doi.org/10.1007/s10461-006-9150-2 PMID: 16917669

24. Rijnhart JJM, Twisk JWR, Chinapaw MJM, de Boer MR, Heymans MW. Comparison of methods for the analysis of relatively simple mediation models. Contemp Clin Trials Commun. 2017; 7:130–5. https://doi.org/10.1016/j.conctc.2017.06.005 PMID: 29696178

25. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Struct Equ Modeling, 1999; 6(1):1–55.

26. Rosseel Y, Jorgensen TD, Rockwood N, Oberns D, Bynes J, Vanbrabant L, et al. Package ‘lavaan’: CRAN; 2021 [https://cran.r-project.org/web/packages/lavaan/lavaan.pdf.

27. Sruamsiri R, Kubo H, Mahlich J. Hospitalization costs and length of stay of Japanese children with respiratory syncytial virus: A structural equation modeling approach. Medicine (Baltimore). 2018; 97(29): e11491. https://doi.org/10.1097/MD.0000000000011491 PMID: 30024527

28. Kondo E. Autologous Hematopoietic Stem Cell Transplantation for Diffuse Large B-Cell Lymphoma. J Clin Exp Hematol. 2016; 56(2):100–8. https://doi.org/10.3960/j.sjlt.56.100 PMID: 27980299

29. Radford J, White E, Castro FA, Chaturvedi A, Spieweoy N, Gibb A, et al. Treatment Patterns and Outcomes in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma: Experience from a Single UK Centre. Blood. 2019; 134:2917.

30. Lee RC, Zou D, Demetrick DJ, Difrancesco LM, Fassbender K, D S. Costs associated with diffuse large B-cell lymphoma patient treatment in a Canadian integrated cancer care center. Value Health. 2008; 11 (2):221–30. https://doi.org/10.1111/j.1524-4733.2007.00227.x PMID: 18380634

31. Oki Y, Ogura M, Kato H, Kikuchi A, Taji H, Kagami Y, et al. Phase II study of a salvage regimen using cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, and rituximab in patients with relapsed or refractory B-cell non-Hodgkin’s lymphoma. Cancer Sci. 2008; 99(1):179–84. https://doi.org/10.1111/j.1349-7006.2007.00662.x PMID: 17991293