Real-world expenditures and survival time after CAR-T treatment for large B-cell lymphoma in Switzerland: a retrospective study using insurance claims data

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Summary

AIM OF THE STUDY: Newly approved therapies with high and uncertain budget impact pose challenges to public health care systems worldwide. One recent example is chimeric antigen receptor T cell (CAR-T) therapies for adults with large B-cell lymphoma (LBCL). This study's primary objective is to examine the expenditures of Swiss public payers before, during, and after CAR-T cell therapy in patients with LBCL aged ≥30 years. Its secondary objective is to analyse 24-month survival rates.

METHODS: This retrospective observational data analysis used the administrative databases of the Swiss health insurers Concordia, CSS, Groupe Mutuel, Helsana, ÖKK, Sanitas, SWICA, Sympany, and Visana. These health insurers or groups provide mandatory health insurance to approximately 78% of Swiss residents in 2021. Using the relevant procedure codes, we identified CAR-T therapies administered between October 2018 (first approval) and June 2021 (treatment identification cut-off). Patients aged <30 years were excluded because they might be treated for pediatric acute lymphoblastic leukaemia. Expenditures were categorised as pre-infusion, peri-infusion (excluding CAR-T therapy acquisition costs), and post-infusion based on the time of service provision. Overall survival rates were estimated using the Kaplan–Meier method.

RESULTS: This study identified 81 patients aged ≥30 years, with a median follow-up period for censored observations of 27 months (interquartile range: 21–31 months). The median age group was 70–74, and 60% of patients were male. Mean healthcare expenditures per patient per month amounted to CHF 8,115–22,564 pre-infusion, CHF 38,490 peri-infusion, and CHF 5,068–11,342 post-infusion. For the total peri- and post-infusion period (i.e. 1-month before infusion to 23 months after infusion), mean healthcare expenditures amounted to CHF 215,737. The

24-month overall survival rate was 48% (95% confidence interval: 38–61%).

CONCLUSIONS: Healthcare expenditures after CAR-T cell infusion are relatively high compared to previous estimates of patients with LBCL in the last year of treatment. Further research is needed to understand the drivers behind these post-infusion expenditures. Especially, clinical data should be used to assess the time until disease progression. The analysis of 24-month overall survival is consistent with results from the pivotal trials. Our findings stress the importance of post-approval studies to monitor real-world expenditures and outcomes related to innovative therapies.

Introduction

In October 2018, tisagenlecleucel (tisa-cel, Kymriah®) was the first chimeric antigen receptor T cell therapy (CAR-T) approved by Swissmedic, the Swiss Agency for Therapeutic Products. Axicabtagene ciloleucel (axi-cel, Yescarta®) was subsequently approved in April 2019. Based on the positive results of the pivotal trials (JULIET for tisa-cel [1], and ZUMA-1 for axi-cel [2]), these therapies promised substantial survival benefits and even cure for patients with diffuse large cell lymphoma (DLBCL) whose disease was relapsed or refractory (r/r) after two or more previous treatments. Tisa-cel was also approved to treat pediatric acute lymphoblastic leukaemia (p-ALL), which is outside the scope of this study. This patient group previously had a poor prognosis, with estimated 24-month overall survival rates of 17% (95% confidence interval = 13–22%) to 24% (95% CI = 18–30%), depending on disease history [3].

While the need for effective treatment options for r/r DLBCL is undisputed, reimbursement of CAR-T cell therapies poses two critical challenges to Swiss public payers. First, the established process to include new services into the reimbursement system for inpatient care has proven in-

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adequate for highly-priced products with high unmet needs (see the Supplementary Material for details). Second, the high prices of CAR-T (average list price: CHF 373,000) raised questions about financial sustainability. Since CAR-T therapies are becoming more widespread (i.e. they are approved for new indications and earlier lines of treatment), their budget impact on public payers becomes even more relevant.

One hope was that cost offsets would reduce the budget impact of potentially curative CAR-T therapies because some subsequent treatments would be avoided [4]. The extent of these cost offsets remains highly uncertain. A pragmatic literature search on OVID found no real-world study analysing total healthcare expenditure (HCE) for patients over multiple years after CAR-T infusion. Several US studies analysed HCE during shorter post-infusion periods. Sahli et al. [5] identified 74 patients in a commercial insurance claims database and analysed the period between 30 days before and 56 days after CAR-T infusion. They estimated a mean HCE of $184,337 and a median HCE of $144,711, excluding CAR-T acquisition cost. Keating et al. [6] identified 191 patients in three US real-world databases. They estimated total HCE during the first three months after the CAR-T infusion to be $379,627 to $525,772 (including CAR-T acquisition cost). Total HCEs were generally higher among patients with cytokine release syndromes and neurological events; 27–29% of patients received subsequent salvage therapy after CAR-T infusion. Di et al. [7] analysed data for 305 patients with DLBCL in the Blue Cross Blue Shield Axis database between 41 days before and 154 days after CAR-T infusion and estimated a mean HCE of $611,900 and a median HCE of $573,300 (including CAR-T acquisition cost). Chihara et al. [8] found a median HCE of $352,572 (including CAR-T infusion costs) within 90 days after infusion among 445 Medicare patients aged ≥65; 106 patients who died or disenrolled during these 90 days were excluded from the HCE estimate. Chacim et al. [4] analysed HCE directly attributable to CAR-T cell therapy using data from 20 patients treated in a comprehensive cancer centre in Portugal. The mean HCE from referral to 150 days after infusion amounted to €358,809, including the CAR-T acquisition cost but excluding the cost of potential subsequent lines of treatment for relapsed patients and the cost of treatments for coexisting conditions.

We present a retrospective observational data study based on the administrative databases of several Swiss health insurers. This study's primary objective is to assess pre-, peri-, and post-CAR-T infusion real-world healthcare expenditures from a public payers' perspective. The estimates represent the total cost borne by mandatory health insurance and cantons in 2018–2022. This study's secondary objective is to describe 24-month overall survival, the number of deaths 0–14 days after infusion, and the hospital stay length of patients who received CAR-T therapies.

Methods

Data collection

This retrospective observational data analysis used anonymised patient data from the administrative databases

of Concordia, CSS, Groupe Mutuel, Helsana, ÖKK, Sanitas, SWICA, Sympany, and Visana. Other insurers asked to participate could not contribute data due to a lack of technical or human resources. These health insurance companies or groups provided mandatory health insurance to approximately 78% of Swiss residents in 2021 [9]. Personal information was limited to age in five-year groups and sex. Patients were included if they received CAR-T infusion before 30 June 2021 (treatment identification cut-off). CAR-T therapies were identified using the relevant procedure codes in the supplemental catalogue of the SwissDRG system. The catalogues are available at www.swissdrg.org. This identification only included patients who received a CAR-T infusion. The patient was excluded if T-cells were collected for genetic modification but not infused. Only patients aged ≥30 years at the time of infusion were included because younger patients could be treated for pediatric acute lymphoblastic leukaemia, which is outside the scope of this study.

Definition of the primary outcome (healthcare expenditure)

The primary outcome is direct healthcare expenditure (HCE) from a public payer's perspective. Public payers of direct medical costs in Switzerland are mandatory health insurance and cantons. Cantons pay 55% of all hospital inpatient claims, while mandatory insurance funds all other benefits. It is beyond the scope of this study to analyse non-medical costs (such as home help), indirect costs (such as loss of working capacity), or intangible costs (such as loss of well-being due to pain and grief). Acquisition costs for CAR-T therapies were not included due to strict confidentiality.

HCE data were collected at 30-day intervals, starting 300 days before the patient was admitted to a hospital for a CAR-T infusion and ending 720 days after the infusion or with death or censoring, whichever occurred first. For simplification, a 30-day interval will be called a "month" in the remainder of this article. The "per patient per month" metric is frequently used in analyses of total HCE. Because insurance premiums are calculated per month, actuaries, regulators, and the general population are familiar with this metric. Claims were included if they had been processed until 31 October 2022 (data cut-off).

In the results table, expenditures are shown for three-month periods and categorised into pre-, peri-, and post-infusion. The peri-infusion period was defined as one month before to two months after the infusion. Since the peri-infusion period began one month before infusion, it might have been too short to include apheresis for all patients. The University Hospital of Zurich reported a median duration of 41 days (range = 31–62) between order placement and CAR-T cell delivery to the treatment site for patients treated until mid-2020 [10]. Nonetheless, this definition ensured a low chance of including prior lines of therapy in CAR-T treatment costs. In addition, we classified those patients as "low-cost survivors" who survived the respective three-month period and had mean monthly expenditures below CHF 500 (i.e. total three-month HCE below CHF 1,500). The CHF 1,500 threshold is high enough to cover outpatient visits, including diagnostic services, but not inpatient stays or specialised post-progression treatments.

Post-infusion healthcare expenditure can be incomplete at data cut-off because of the lag between the treatment date and claim processing and data censoring. Our primary strategy to avoid bias and a sensitivity analysis are described in the appendix.

Definition of the secondary outcome (overall survival)

For survival analysis, the start date was the date of the CAT-T infusion. For technical reasons, it was not possible to determine the exact date in 23% of the cases. For these cases, the hospital admission date was used instead, which might have caused a slight overestimation of the survival time after CAR-T therapy. For patients with an observed infusion date, 85% received infusion 0–5 days after hospital admission, so the overestimation of overall survival (OS) was likely to be limited. A sensitivity analysis was conducted by excluding these individuals (see supplementary materials in the appendix).

Study administration

Ethical approval is not required for retrospective database studies on anonymised patient data. Potentially identifying variables such as the area of residence, treatment sites, or exact dates were not used in this study. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross sectional studies was followed.

Descriptive statistics were done using R version 4.2.1. OS was estimated applying the Kaplan-Meier method and using the R package "survival".

Results

Population

This study identified 49 male and 32 female patients who underwent CAR-T therapy for LBCL between November 2018 and June 2021. For censored patients, the median time from treatment to data cut-off was 27 months, with a minimum of 17 months (interquartile range = 21–31). In our data set, the median age group was 70–74 years, with a minimum of 30–34 years and a maximum of 80–84. These estimates do not represent the entire treated population in Switzerland because patients aged <30 years were excluded. For comparison, table 1 also includes information on the population in a Swiss real-world data analysis by Stolz et al. [10] and the pivotal trials (JULIET for tisa-cel/Kym-

riah® [1, 11], and ZUMA-1 for axi-cel/Yescarta® [2, 12]). The 62 years reported by Stolz et al. is the best available estimate for the median age in the entire treated population in Switzerland.

Previous lines of therapy could not be analysed, but all patients must have had at least two lines of therapy to be eligible for reimbursement of CAR-T therapy [13]. Most patients were treated for r/r DLBCL, but data might include some individuals treated for r/r primary mediastinal LBCL. Diagnostic information is not routinely available in claims data, so it could not be used as a direct inclusion criterion. Among the 81 patients, 66.7% (54/81) were treated with tisa-cel (Kymriah®) and 33.3% (27/81) were treated with axi-cel (Yescarta®).

Primary outcome: Total healthcare expenditure (HCE)

The HCE per patient per month in the pre-, peri-, and post-CAR-T cell infusion periods are shown in table 2. Each row represents a three-month period. Patients who were deceased or censored during the period account for less than the full three months. During the peri-infusion period (one month before infusion and two months after), the mean expenditure per month amounted to CHF 38,490 and the median to CHF 25,765 (interquartile range = CHF 18,884–38,170). The high mean compared to the median indicates a right-skewed distribution, which is confirmed in figure S1 in the appendix. Eighty-six per cent of these expenditures were billed for hospital inpatient services (DRG payments and additional fees).

The mean monthly HCE during the first post-infusion year amounted to CHF 8,696–11,342 (table 2), and the median monthly HCE to CHF 3,446–4,733. The proportion of low-HCE survivors increased with time since infusion and amounted to approximately 15% in months 15–17 after treatment. Inpatient expenditures, including drugs administered during hospital stays, accounted for approximately 40–50% of total expenditure in the post-CAR-T infusion period. Many patients required inpatient treatment in the months and years after CAR-T infusion.

For comparison, expenditures in the 10 months before CAR-T treatment are shown in the first rows in table 2. These expenditures are likely to include the costs of second and/or later lines of therapy because they often follow quickly after each other. A recent review reported the median treatment duration for patients with DLBCL in the second and third treatment lines as 2.3 and 3.4 months,

Table 1:

The patient population in the Swiss claims data study.

	Swiss claims data study	Stolz et al. (2022)	JULIET trial (tisa-cel)	ZUMA-1 trial (axi-cel)
N (patients who received infusion)	81	21	111	101
Median age (range), 5 yr group or yr	70–74 (30–34; 80–84)*	62 (20; 76)	56 (22; 76)	58 (23; 76)
Age ≥65 yr, no. (%)	54 (67%)*	nr	25 (23%)	24 (24%)
Male, no. (%)	49 (60%)	16 (76%)	nr	68 (67%)
Previous treatments				
Number of prior treatment lines, mean (range)	nr (2-nr)**	3.6 (2–7)	nr	nr
≥3 prior lines of therapy	nr	nr	57 (52%)	70 (69%)

* This number is not representative of the entire patient population treated in Switzerland because patients aged <30 years were excluded.

** the number of previous lines of therapy was not directly identifiable in claims data, but all patients must have had at least two lines of therapy to be eligible.

nr = not reported

respectively [14]. For patients with rapid disease progression, even the first line of treatment might be included in this period. The mean expenditure in months 10 to 5 before CAR-T therapy was CHF 8,115–11,353 (median = CHF 4,524–8,044). The mean expenditure in months 4 to 2 before CAR-T infusion was CHF 22,564 (median = CHF 17,509).

Table 3 shows the total HCE (excluding CAR-T acquisition costs) per patient during the entire observation period from 30 days before CAR-T cell infusion until death or censoring. The mean HCE, excluding CAR-T cell therapy, was CHF 215,737, with a median of CHF 151,539 and an interquartile range of 100,238 to 250,234.

In cost-effectiveness modelling, it is common to evaluate the costs for end-of-life care and curative treatments separately. A direct identification of end-of-life care was infeasible in our data. As an approximation, we calculated total healthcare expenditures in the last 30 days of life, excluding patients who died within 30 days of CAR-T infusion and patients who were admitted to the hospital more than 30 days before their death. The rationale behind this decision was a technical concern: Hospital inpatient services are billed per case in the DRG-based system. For patients who remained continuously hospitalised for more than 30 days before their eventual demise, the per-case hospital claim encompasses services rendered within and outside the specified 30-day window. Table 3 shows that mean expenditures in the last 30 days of life were CHF 29,193 (median = CHF 21,567). Most of these expenses were for hospital inpatient care.

Secondary outcome: overall survival

Figure 1 shows the Kaplan-Meier curve of overall survival during the first 30 post-infusion months. The curve descends with observed deaths, while vertical lines represent data censorings. The complete Kaplan-Meier data and the cumulative hazard plot are provided in the appendix. Four per cent of patients (3/81) died within 0–2 days after CAR-T infusion, and another died within the first 14 days after CAR-T infusion. The estimated 12-month OS rate was 59% (95% CI 49–71%), and the estimated 24-month OS rate was 48% (38–61%). For the deceased patients, the mean survival time after CAR-T infusion was 7.4 months.

A few other patient-relevant outcomes could be observed in the claims data: 11% of patients (9/81) died during the hospital stay for CAR-T infusion, and 2% (2/81) had to stay in the hospital for at least two months after the CAR-T infusion. The median hospital stay duration after CAR-T infusion was 20 days, and the mean duration was 23 days (see figure S6 in the appendix for the distribution). It is important to note that providers in Switzerland are obliged to monitor patients daily within the first 10 days after CAR-T infusion to detect symptoms of cytokine release syndrome, neurological events, or other toxicities. Nine per cent of patients (7/81) were discharged 10–14 days after CAR-T infusion.

Discussion

Primary outcome

Our study described direct medical expenditures from a Swiss public payer's perspective of patients with LBCL treated by CAR-T in 2019–2021. HCEs were categorised into pre-, peri-, and post-CAR-T infusion periods.

Table 2:
HCE pre- and post-CAR-T infusion.

| Period | Pat. N | Pat. months | HCE per month | | | | | | Low-HCE survivors (%) | Share inpatients | Share drugs outpatients |
			Mean	SE	25th percentile	50th percentile	75th percentile				
Pre: m 10–8	78	234	8,115	2,285	1,000	4,524	9,705		16 (21%)	56%	16%
Pre: m 7–5	78	234	11,353	3,007	2,130	8,044	15,207		4 (5%)	59%	12%
Pre: m 4–2	78	234	22,564	4,513	10,962	17,509	25,920		0 (0%)	61%	8%
Peri infusion*	78	230	38,490	6,874	18,884	25,765	38,170		0 (0%)	86%	3%
Post: m 3–5	67	186	8,696	2,276	2,231	4,733	11,900		1 (2%)	38%	17%
Post: m 6–8	56	162	11,342	3,482	1,823	3,970	11,312		3 (5%)	43%	19%
Post: m 9–11	50	150	10,643	4,696	1,196	3,465	8,945		5 (10%)	49%	23%
Post: m 12–14	46	132	9,722	6,262	1,290	3,446	10,801		6 (13%)	50%	24%
Post: m 15–17	40	105	6,981	3,451	464	2,265	5,288		6 (15%)	43%	27%
Post: m 18–20	29	80	5,068	2,216	1,222	2,603	6,963		2 (7%)	19%	31%
Post: m 21–23	22	57	7,455	5,565	1,547	2,493	3,593		1 (5%)	55%	14%

Pre/post = before or after CAR-T infusion; m = month; IQR = interquartile range; "Low-HCE survivors" are defined as patients who are alive and non-censored for the entire interval and have an average cost per month below CHF 500 during this interval.

* Expenditures for CAR-T therapies are not included (list price = CHF 373,000).

Table 3:
Total HCE from treatment to the end of the observation period: HCE in the last 30 days of life.

| Period | Pat. | HCE peri- and post-infusion** | | | | | Share inpatients | Share drugs |
		Mean	SE	25th percentile	50th percentile	75th percentile		
Peri- and post-infusion*	78	215,737	21,279	100,238	151,539	250,234	66%	12%
Last 30 days of life	34	29,193	4,947	12,189	21,567	39,682	83%	7%

* 24 months or until death/earlier censoring.

** HCE excluded the cost of CAR-T therapy (average list price = CHF 373,000).

The observed post-infusion costs of CHF 5,068 to CHF 11,342 per month or CHF 215,000 over two years are higher than previous cost estimates for non-Hodgkin lymphoma in Switzerland. Wieser et al. [15] translated US estimates by Mariotto et al. [16] into Switzerland and estimated that patients with non-Hodgkin lymphoma incurred direct medical costs of CHF 33,429 to CHF 51,269 in the last treatment year. The high mean cost in a population treated with a potentially curative CAR-T therapy is remarkable. This patient population was expected to include many patients with durable responses whose low healthcare expenditures impact the grand mean. This point is best illustrated by an example. It is assumed that 20% of patients treated with CAR-T experience durable responses, and the 12-month overall survival is 60%. In this scenario, the patient population after 12 months can be divided into two groups: One-third of patients will be in a state of remission, while two-thirds will have experienced disease progression. The healthcare expenditures of the first group are expected to be low, significantly impacting the grand mean.

Two primary factors can explain the escalated cost per patient with disease progression. Firstly, many novel treatment alternatives have become accessible since the previous cost estimations. Secondly, patients with LBCL who received CAR-T therapy represent more severe cases than the average non-Hodgkin lymphoma case.

Our observed real-life expenditure over two years also exceeds the estimated lifetime expenditures of infused patients of CHF 139,000 in a recent cost-effectiveness study [17]. This cost-effectiveness study reported a total lifetime cost of CHF 403,470, but CHF 264,821 were attributable to CAR-T therapy costs, which were excluded in our study (see [18] and table 10 in the appendix). However, these costs are not directly comparable since our estimates include total healthcare expenditure, while cost-effectiveness studies focus on treating one specific disease. See appendix, section 6, for a discussion on the decomposition of healthcare expenditure.

Our findings of considerable total care costs relating to CAR-T infusion are consistent with several US real-world data analyses cited in the introduction. Jalbert et al. provided one possible explanation for high post-infusion expenditures [19]. They analysed 129 patients with DLBCL treated with CAR-T and estimated the risk of receiving radiation or systemic treatment as 36% (95% CI = 27–46%) after six months and 48% (95% CI = 44–71%) after 12 months.

Figure 1: Kaplan–Meier estimates of overall survival; vertical line = censoring mark; grey band = 95% confidence interval.
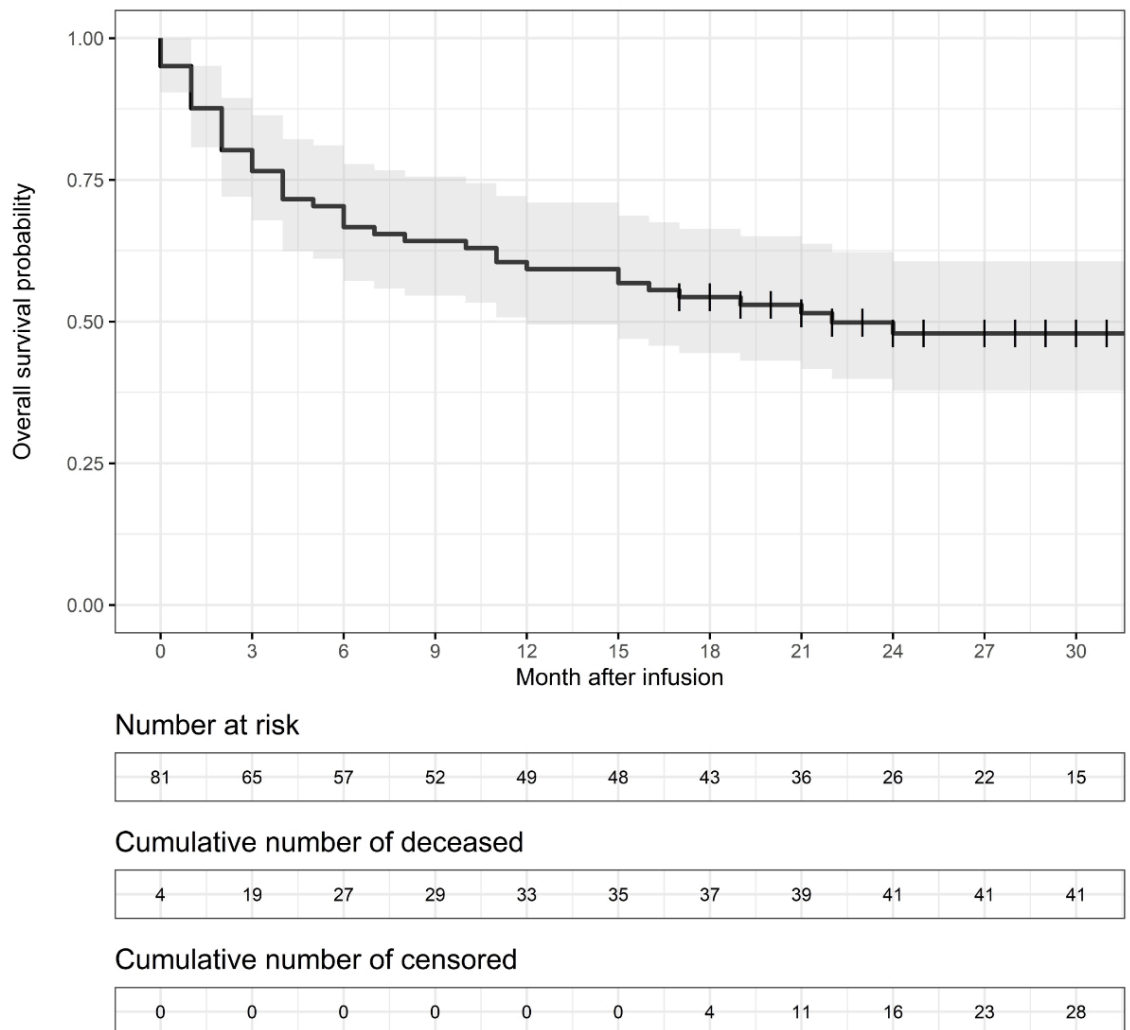
Secondary outcome

Our study estimated overall survival rates as 59% (95% CI = 49–71%) after 12 months and 48% (95% CI = 38–61%) after 24 months. These estimates are comparable to other recent real-world data studies. Using data for 408 patients registered in the retrospective French DESCAR-T registry study, Bachy et al. [18] estimated 12-month overall survival at 64% (95% CI = 55–71%) with axi-cel and 49% (95% CI = 40–47%) with tisa-cel. In an analysis of cases enrolled in the German Registry for Stem Cell Transplantation, Bethge et al. [20] estimated 12-month survival at 52%, but their real-world population included patients with poor performance status who would not have been eligible for the ZUMA-1 trial. Using data for 149 patients in the Center for International Blood and Marrow Transplant Research (CIBMTR) database, Shadman et al. [21] estimated a 24-month OS rate of 47% (95% CI = 33–60%).

However, our estimates are less optimistic than a recent cost-effectiveness study that estimated an average life expectancy of 9.24 years after infusion [17]. In our real-world data, deceased patients had a mean survival time after CAR-T infusion of 7.4 months. In order to attain an average of 9.24 years in the entire dataset, the censored patients would have to attain a mean survival time of 17 years. This residual life expectancy is longer than the 16 years of 70-year-old male members of the Swiss general population [22], which seems implausible given the disease history and frailty of patients given CAR-T therapy.

An interesting question is how the survival rates of patients after CAR-T therapies compare to those of patients treated with other therapy options. It is beyond this study's scope to indirectly compare our patient population with historical controls. An often-cited historical comparison is the SCHOLAR-1 study, which performed a patient-level pooled retrospective analysis of a population of patients with refractory DLBCL. For the subgroup refractory to second or greater line therapy, 24-month OS was 17% (95% CI = 13–22%) [3].

Maziarz et al. [23] indirectly compared tisagenlecleucel (tisa-cel; Kymriah®) and historical treatments for r/r DLBCL. Using standardised mortality ratio weights, they found an overall survival hazard ratio of 60% (95% CI = 44–77%) in favour of tisagenlecleucel in the intention-to-treat (ITT) population. In the same analysis, they found 24-month OS rates in the ITT population of 34% (95% CI = 26–42%) with tisa-cel compared to 16% (95% CI = 12–22%) with the other treatments, also favouring tisagenlecleucel. Salles et al. [24] conducted a matching-adjusted indirect comparison of another CAR-T therapy (lisocabtagene maraleucel) and salvage chemotherapy for r/r DLBCL. After matching and adjusting, they found an overall survival hazard ratio of 50% (95% CI = 40–60%) in favour of lisocabtagene maraleucel and a median overall survival of 20.5 months (95% CI = 12.1–unreached) with CAR-T therapy compared to 6.0 months (95% CI = unreported) with salvage chemotherapy, also favouring the CAR-T therapy (lisocabtagene maraleucel). Using real-world data from one clinical centre in the US, Sermer et al. [25] compared the outcomes of 69 patients treated with CAR-T therapy with a historical population of 146 patients treated with alternative therapies. Observed 12-month OS rates were 64% (95% CI = 54–77%) in the CAR-T group and 39% (95% CI = 31–48%) in the alternative treatment group. In a multivariate analysis adjusting for pre-treatment characteristics, the treatment type was not a significant predictor of OS.

Limitations

Our analysis of HCE (primary outcome) had several limitations. First, some pre- and post-CAR-T treatments are not recorded in insurance claims data because they are part of clinical trials or early access programs. Those new treatments might be covered by mandatory health insurance in the future, leading to higher expenditure for public payers. Second, pre- and post-CAR-T treatment patterns are not standardised and are rapidly changing, further reducing the future generalizability of our results. Third, patient selection and optimal treatment timing remain under evaluation [10], and our study population might not represent future patients. Fourth, three patients had to be excluded from the sample because their insurers could not report complete data on expenditures. Fifth, our estimates are a lower bound for actual expenditures because of possible delayed claims and censoring. Based on the sensitivity analyses shown in the appendix, we expect our mean post-infusion HCE estimates to be underestimated by 3–4%.

The main limitation in measuring overall survival was the relatively short follow-up period. With less than 20% of patients still at risk after 30 months, long-term estimates are too uncertain. Two other limitations are common to most observational studies. The first is the absence of a control group. We could not assess how similar patients would have done after other treatment settings and were, therefore, unable to analyse cost-effectiveness. The second limitation is the presence of many post-infusion therapies, often also novel approaches, which make it difficult to assess the effectiveness of CAR-T therapies alone.

A general caveat of our study is its limited scope, which leaves unanswered many questions that are highly relevant to patients, physicians, and society. First, we could not describe the treated patient population in detail. Because Swiss health insurance data does not contain diagnostic information, neither the patient's disease history nor relevant comorbidities could be analysed. Second, we could not analyse the duration of progression-free survival or the time to the next treatment. Data from registries or treatment sites should be used to analyse these highly relevant issues.

Conclusions

Two years after the introduction of CAR-T therapies for relapsed or refractory DLBCL, much uncertainty remains around the budget impact on public payers. We conducted a retrospective insurance claims data analysis and found high mean healthcare expenditure peri- and post-infusion (excluding CAR-T acquisition cost). Further research is needed to understand the drivers behind these expenditures. Data from registries and treatment sites should be used to analyse progression-free survival and post-infusion treatment patterns and relate them to prognostic factors.

The challenges of high and uncertain costs and uncertain long-term benefits are not limited to CAR-T therapies and apply to many newly approved therapies. For example, a

recent study found that less than 40% of drugs approved through accelerated approval or conditional marketing authorisation pathways in Europe and the US from 2007 to 2021 were rated by official health technology assessment agencies in Germany, France, or Canada as providing at least moderate therapeutic value compared to existing therapies [26]. The authors concluded that post-approval studies should be given more importance in the decision-making process. Registries and administrative databases provide valuable sources of information for such studies. From a societal perspective, balancing fast access to therapies with sustainable public financing will be very challenging. Monitoring expenditures and benefits in the real world is an essential step towards creating transparency and finding new pathways for societal-decision making.

Acknowledgments

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Most authors and contributors work for health insurers providing mandatory health insurance in Switzerland. The companies didn't directly influence the conceptualization or results presented, but the study was written from the perspective of a public payer. The academic experts Mark Pletscher and Niklaus Meier regularly advise different Swiss Health insurers in topics related health technology assessment and pricing.

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Appendix

S1: Approval and reimbursement of new therapies in Switzerland

Approval

Swissmedic is the national authorization and supervisory authority for drugs and medical products. Approval is granted only if high levels of quality and safety are proven and if the risk-benefit balance is positive.[1]

Reimbursement of new therapies in the outpatient sector

The Federal Office for Public Health (FOPH) issues positive lists of drugs ("Spezialitätenliste") that are reimbursed by mandatory insurance. The FOPH determines the maximum reimbursement price and possible limitations. To be included, pharmaceuticals must be approved by Swissmedic, and proven to be effective, appropriate and economical.[2]

Under strict criteria, reimbursement by mandatory insurance is possible for therapies that are not listed on the "Spezialitätenliste" or that are used outside their listed labels or limitations.[3] This requires pre-utilization review by medical officers and health insurers. The criteria include that a high therapeutic benefit is to be expected against an illness that leads to severe chronic impairments or death and no effective alternative treatment options are available.

Reimbursement of new therapies in inpatient care

Inpatient care in Switzerland is reimbursed by a system of Diagnosis Related Groups (DRGs). Diagnostic codes and procedures are used to group patients in around 1'000 DRGs. Each group is assigned a "cost weight" based on the average amount of resources it takes to care for a patient assigned to that DRG. Additional fees ("Zusatzentgelte"/"Rémunerations supplémentaires") are put in place to reimburse complex procedures or expensive drugs. The catalogues of DRGs and additional fees are issued by SwissDRG AG, a joint organization of providers, cantons and insurers.

The introduction of new DRGs or new additional fees to the respective catalogues follow an administrative process ("Antragsverfahren"). The process can be initiated by providers or payers. Newly approved drugs

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[1] Source: https://www.swissmedic.ch/swissmedic/en/home/about-us/swissmedic--swiss-agency-for-therapeutic-products/patients-and-users.html, accessed May 17, 2023.
[2] Source:https://www.bag.admin.ch/bag/en/home/versicherungen/krankenversicherung/krankenversicherung-leistungen-tarife/Arzneimittel.html, accessed May 17, 2023.
[3] Verordnung über die Krankenversicherung, KVV, Art. 71 a.-d.

or medicinal products are usually first used within the current reimbursement system, and then added to the catalogues based on previous experiences and observed cost.

Reimbursement for CAR-T cell treatments

At the time of their first approval, it became evident that CAR-T cell treatments did not fit into the reimbursement systems and using the established "Antragsverfahren" would not give patients access in due time. Therefore, a group of hospitals and health insurers entered price negotiations with manufacturers. Confidential rebates on the list price were agreed upon.

Treatments or diagnostic procedures that are associated with CAR-T cell therapy are reimbursed using the standard framework. In particular, hospitals stays are paid by DRGs and additional payments which are not specific to CAR-T cell treatment (e.g. based on procedures and ICU use).

S2: Data specification: Data Cut-offs for treatment and claim settlement date

An important issue in the analysis of expenditure is the lag between treatment date and claim settlement date. Table S2 shows the cumulative share of expenditures that have been settled 0-12 months after treatment during the years relevant for this study. In 2021, 15 percent of expenditures were settled during the treatment month, 85 percent after three months, and 95 percent after six months. Still, treatments that are carried out shortly before data cut-off have a considerable likelihood of being underreported. For this reason, different cut-offs were applied for the analysis of expenditures and the analysis of survival. All claims that have been registered until October 2022 can be included in the analysis, but they are only counted as "valid information on expenditure" if the treatment took place at least six months before this date (May 22). In consequence, some observations are regarded as censored in the analysis of expenditures, but not in the survival analysis. The duration of the lag was chosen at six months because at least 90 percent of expenditures are expected to be reported in this time (see Table S2). Still, the reported expenditures are a lower bound of actual expenditures.

Figure S2 shows two examples of the treatment date cut-off. Patient 1 had CAR-T cell infusion in May 2020. Her post-infusion expenditures are observes for the full two years. Patient 2 had CAR-T cell infusion in May 2021. Her post-infusion expenditures are observed for one year, until May 22. Even though some claims were registered for the treatment period June 22 – October 22, this information is not analyzed because of the lag.

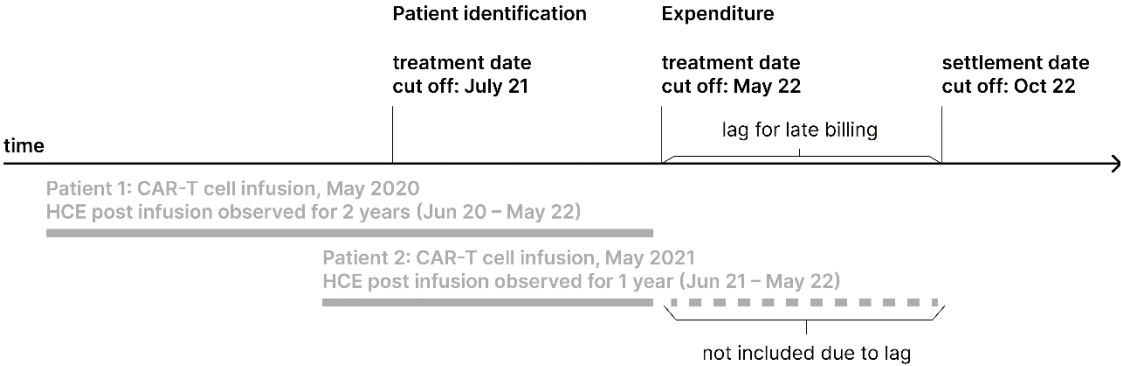*Figure S1 Lag period for expenditure data*

Table S1 Cumulative share of expenditures that where settled 0-12 months after treatment

Months between treatment and claim settlement	2019	2020	2021	2022
0	13	15	15	15
1	54	59	57	59
2	75	79	76	78
3	84	87	85	87
4	89	91	90	92
5	92	94	93	95
6	93	95	95	97
7	94	96	96	98
8	95	97	97	99
9	96	98	97	100
10	96	98	98	100
11	97	98	98	100
12	97	99	99	100

Source: SWICA Health Services Research

S3: Distribution of health care expenditure

All distributions are truncated at the 90th percentile. If high outliers are included, the rest of the distribution is barely visible.

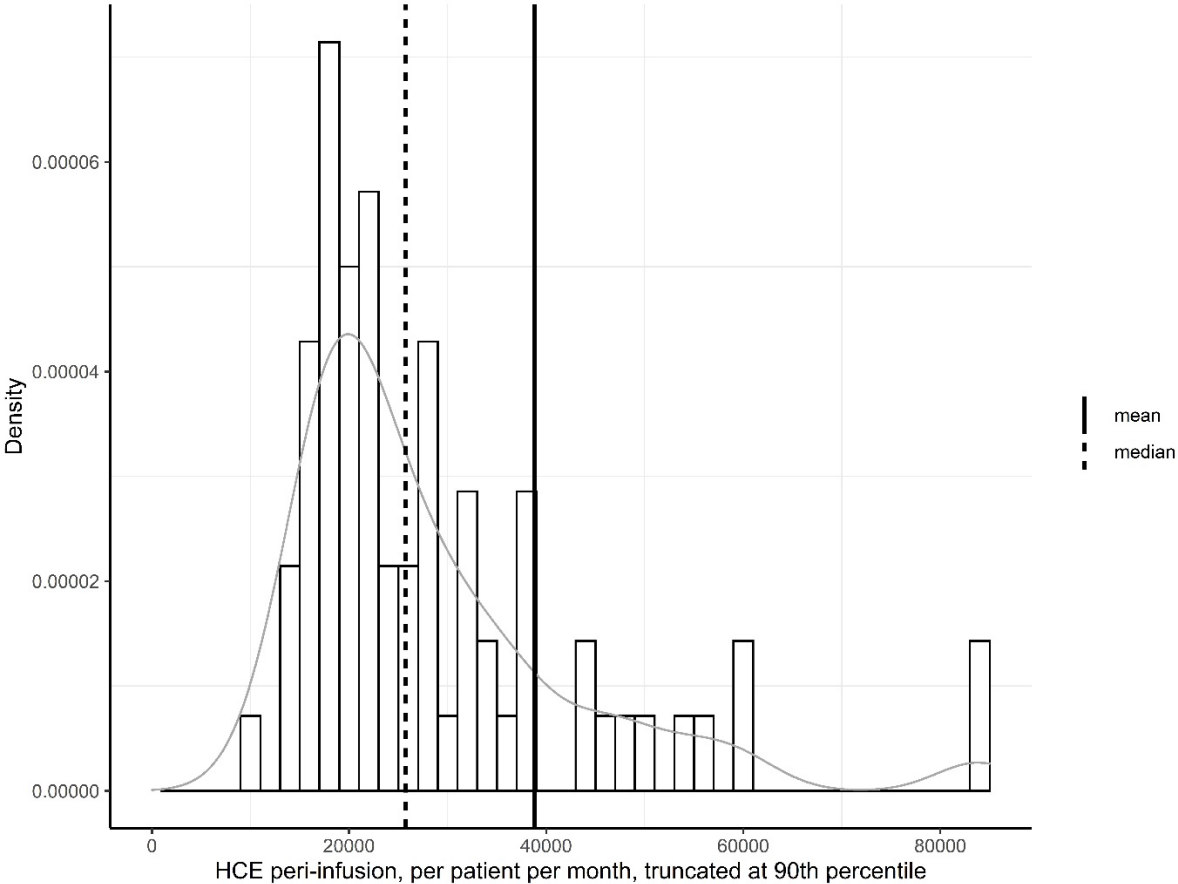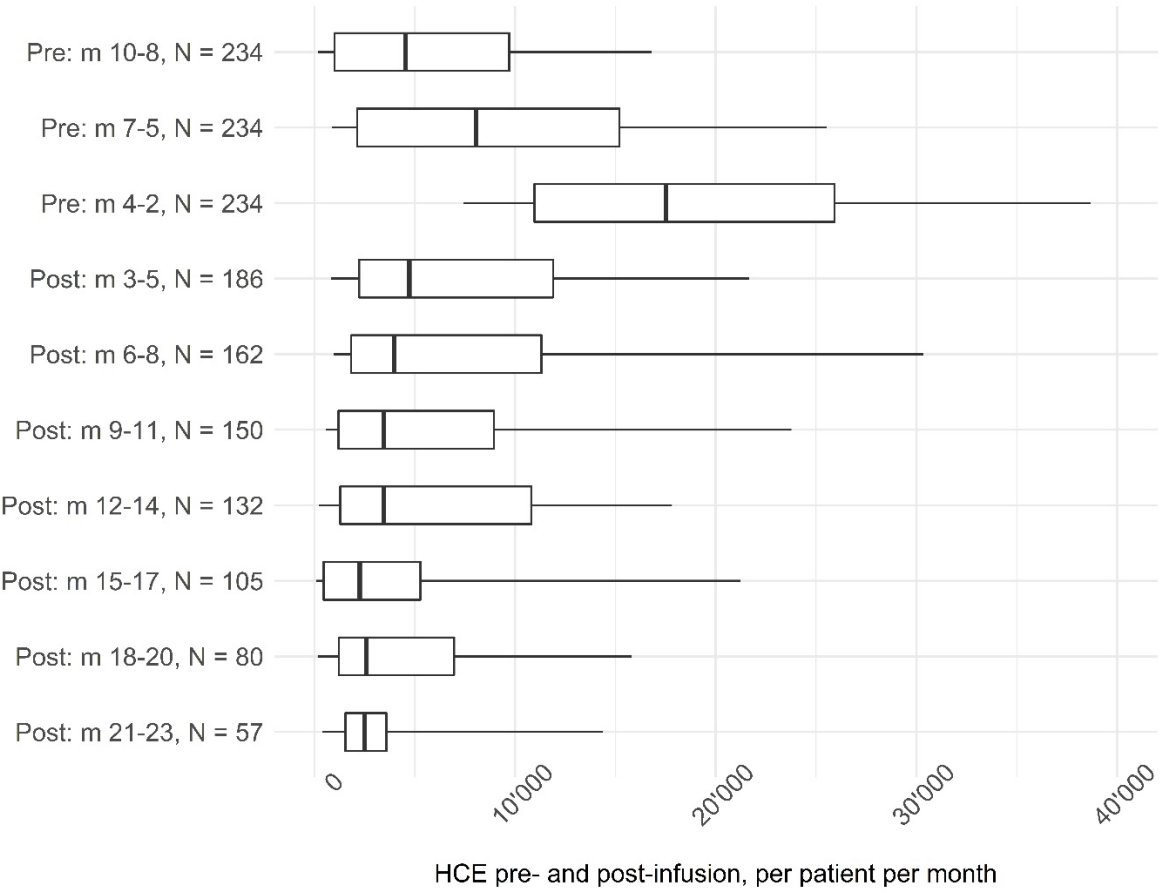*Figure S2 Distribution of HCE per patient and month, peri-infusion*

Figure S3 HCE per patient and month, pre- and post-infusion, truncated at the 90th percentile

The whiskers go from the 10th to the 90th percentile, the box goes from the 25th to the 75th percentile, the vertical line inside the box is the median.

Figure S4 Total HCE peri- and post infusion period (max. 24 months), truncated at the 90th percentile
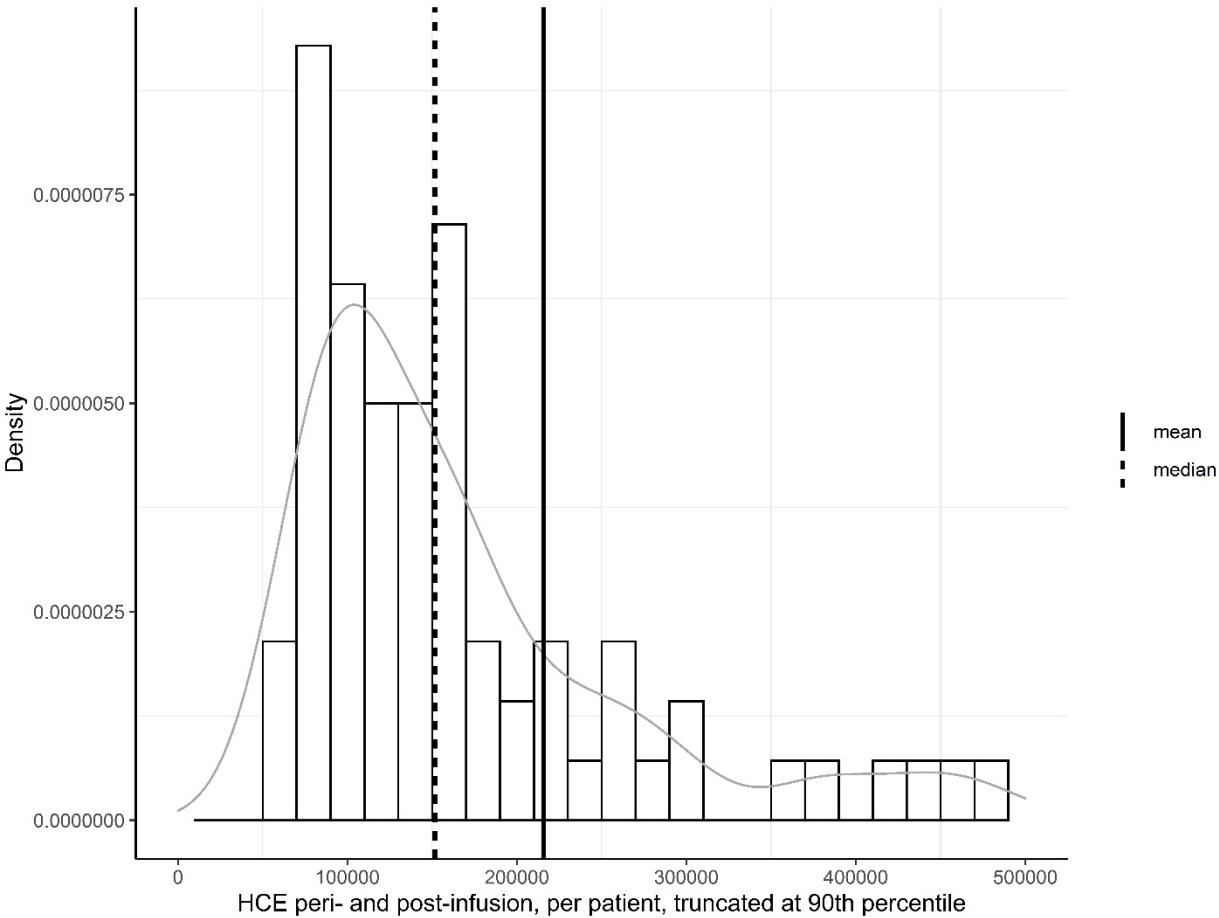
Figure S5 HCE in the last 30 days of life, truncated at the 90th percentile
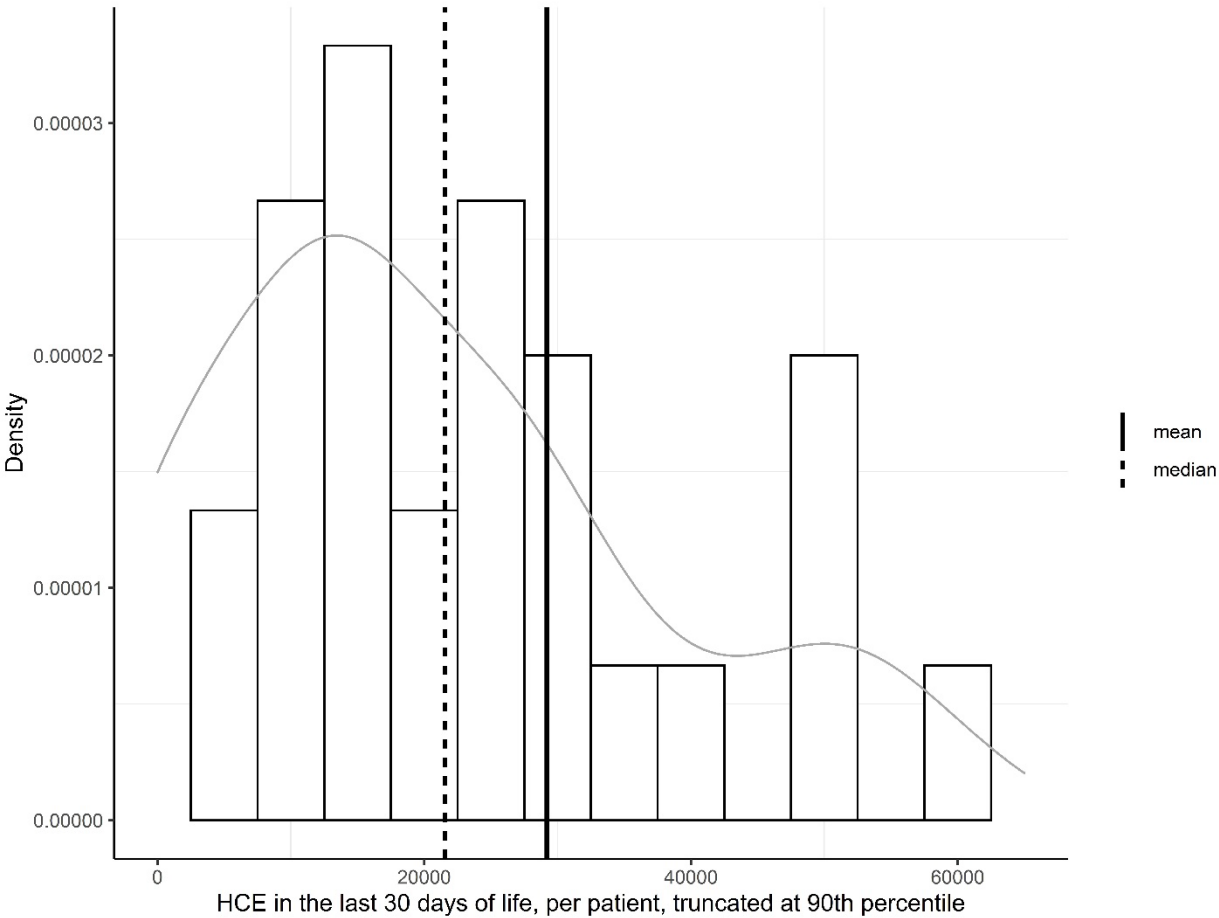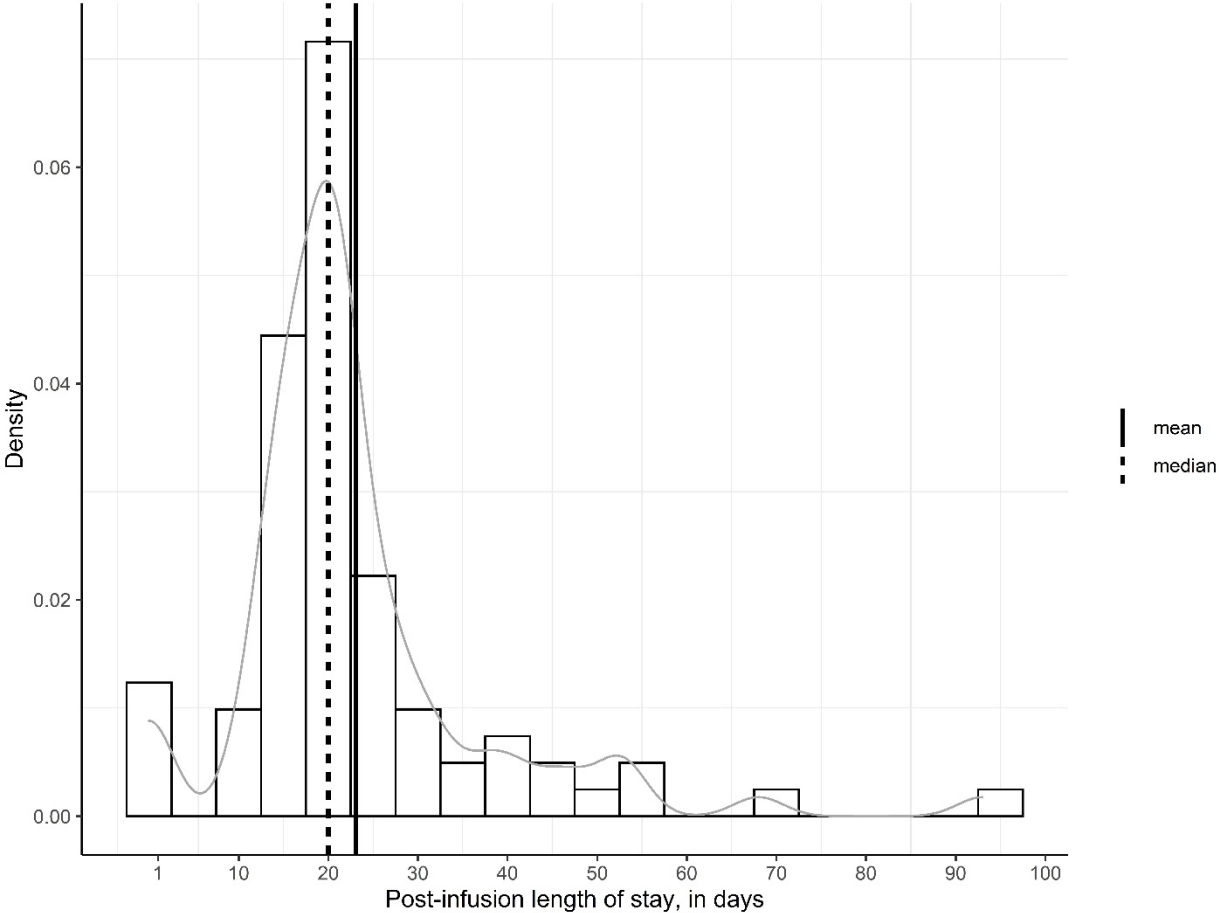
Figure S6 Length of inpatient stay after CAR-T cell infusion.

The graph includes patients who died during the hospital stay for CAR-T cell infusion.

S4: Survival analysis

Table S2 Survival data

time	n.risk	n.event	Cum. n.event	n.censor	Cum. n.censor	OS KM estimate	std.err	OS KM CI upper	OS KM CI lower
0	81	4	4	0	0	95%	3%	100%	90%
1	77	6	10	0	0	88%	4%	95%	81%
2	71	6	16	0	0	80%	6%	89%	72%
3	65	3	19	0	0	77%	6%	86%	68%
4	62	4	23	0	0	72%	7%	82%	62%
5	58	1	24	0	0	70%	7%	81%	61%
6	57	3	27	0	0	67%	8%	78%	57%
7	54	1	28	0	0	65%	8%	77%	56%
8	53	1	29	0	0	64%	8%	76%	55%
9	53	1	29	0	0	64%	8%	76%	55%
10	52	1	30	0	0	63%	9%	74%	53%
11	51	2	32	0	0	60%	9%	72%	51%
12	49	1	33	0	0	59%	9%	71%	49%
13	49	1	33	0	0	59%	9%	71%	49%
14	49	1	33	0	0	59%	9%	71%	49%
15	48	2	35	0	0	57%	10%	69%	47%
16	46	1	36	0	0	56%	10%	68%	46%
17	45	1	37	1	1	54%	10%	66%	44%
18	43	0	37	3	4	54%	10%	66%	44%
19	40	1	38	2	6	53%	10%	65%	43%
20	37	0	38	1	7	53%	10%	65%	43%
21	36	1	39	4	11	51%	11%	64%	42%
22	31	1	40	2	13	50%	11%	62%	40%
23	28	0	40	2	15	50%	11%	62%	40%
24	26	1	41	1	16	48%	12%	61%	38%
25	24	0	41	2	18	48%	12%	61%	38%
26	24	0	41	2	18	48%	12%	61%	38%
27	22	0	41	5	23	48%	12%	61%	38%
28	17	0	41	1	24	48%	12%	61%	38%
29	16	0	41	1	25	48%	12%	61%	38%
30	15	0	41	3	28	48%	12%	61%	38%
31	12	0	41	2	30	48%	12%	61%	38%
32	12	0	41	2	30	48%	12%	61%	38%
33	12	0	41	2	30	48%	12%	61%	38%
34	12	0	41	2	30	48%	12%	61%	38%
35	10	0	41	2	32	48%	12%	61%	38%
36	10	0	41	2	32	48%	12%	61%	38%
37	8	0	41	1	33	48%	12%	61%	38%
38	7	1	42	0	33	41%	20%	60%	28%
39	6	0	42	1	34	41%	20%	60%	28%
40	5	0	42	1	35	41%	20%	60%	28%
41	4	0	42	3	38	41%	20%	60%	28%

Figure S7 Overall Survival, Cumulative hazard
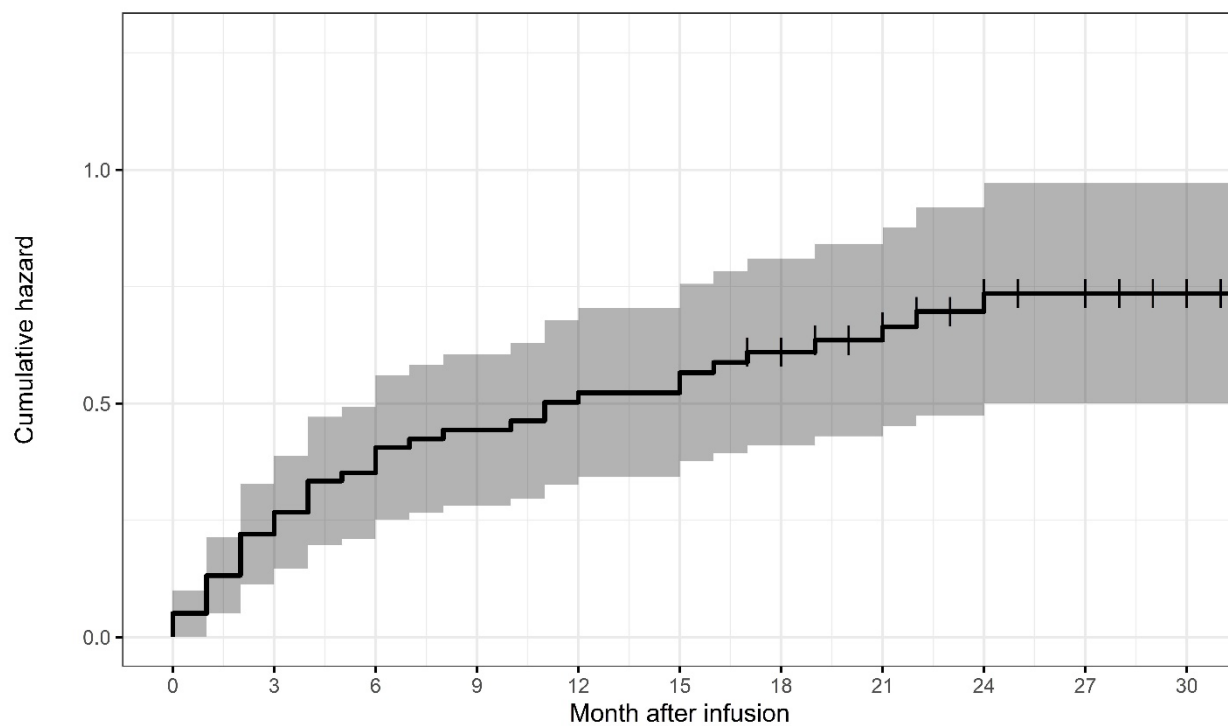
S5: Sensitivity analyses

<u>Survival Analysis</u>

For technical reasons, the exact infusion date was not observed in 23% of the cases. For these cases, the date of hospital admission was used instead. A sensitivity analysis was run excluding these individuals. The 12-month overall survival rate was 60% [49%-73%], the 24-month overall survival rate was 46% [35%-61%], very close to the ones in the main dataset (12 month: 59% [49% – 71%], 24-month OS 48% [38% – 61%]).

Figure S8 Kaplan-Meier estimates of overall survival
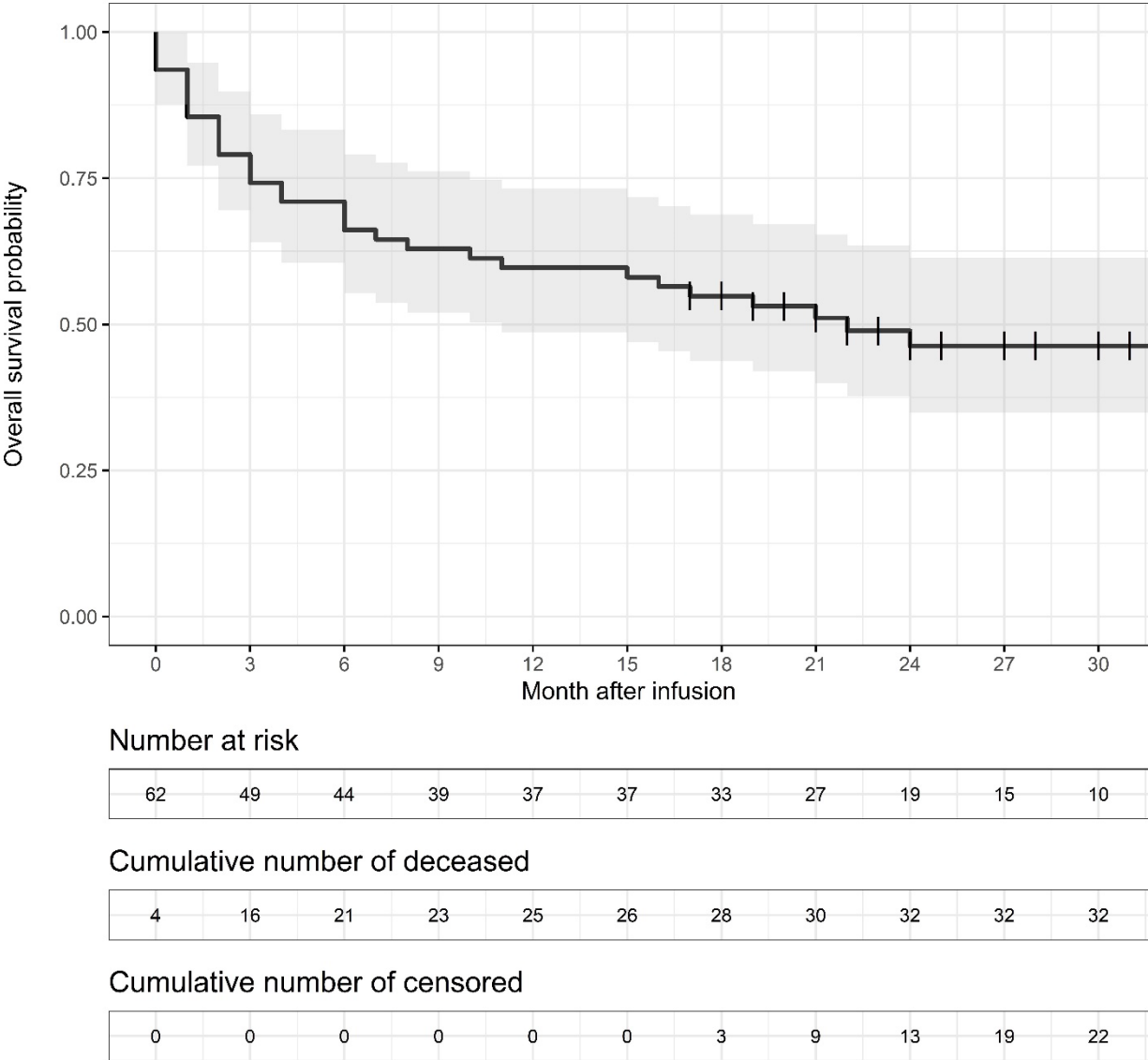
vertical line = censoring mark; gray band: 95% confidence interval.

Underreported Health Care Expenditures

HCE can be underreported because of the lag between the treatment date and claim settlement. We conducted two sensitivity analyses to assess the expected magnitude of the effect on mean peri- and post-infusion HCE (CHF 215'737 see Table 3 in the main text). In the first analysis, we imputed missing data of censored patients by the average of uncensored patients. If the patient was censored in the survival analysis (which does not have the additional six months lag described in S2), the mean was weighted by the survival probability. This leads to an increase in mean HCE of CHF 8'169, or 3.7%. In the second analysis, we augmented mean monthly HCE in the months 18-20 post-infusion by 3 percent, and mean monthly HCE in months 21-23 by 5 percent. Because these periods are closest to data-cut-off, HCE of have the highest chance of being underreported. This second estimation leads to an increase in HCE of CHF 8'779 or 4 percent.

S6: Decomposition of health care expenditure

This study presents an estimation of mean HCE during the peri- and post-infusion periods, amounting to CHF 215'000 over a span of two years. It is beyond the scope of this study to provide a decomposition analysis to identify disease-specific and non-disease-specific factors that influence health care expenditure. In this section, we discuss two hypothetical reference points.

During the peri-infusion period, 86% of financial resources were allocated towards hospital inpatient services, as indicated in Table 2 of the main text. These resources include Diagnose Related Group (DRG) payments and additional fees known as "Zusatzentgelte" / "Rémunerations supplementaires" . DRG payments depend significantly on the primary cause of hospitalization or the primary mode of treatment. The additional fees primarily pertain to cancer-specific therapies or intensive care unit services. If inpatient services are specific to the treatment of LBCL, the maximum proportion of expenditure for non-disease specific services is limited to 14%. As outpatient expenditures also contain bills for disease-specific services, the expected proportion is even lower.

In order to discuss the expected magnitude of non-disease specific cost in the post-infusion period, it is helpful to consider some contextual information. Table S3 displays mean annualized HCE incurred by the Swiss general population, categorized by different age groups. The final column presents the relative frequency weight of each age group in the study population. The weighted mean HCE for a general population with a comparable age profile would be CHF 7'525 per year. This amounts to CHF 15'050 over two years, or about 7 percent of the HCE observed in the study population. Using this benchmark, it is plausible to anticipate that not more than 7-10% of the observed real-life HCE were caused by non-disease-specific medical services. Should the study population exhibit substantially higher non-disease-specific morbidity rates[4] compared to the general population, the aforementioned reference point might lose its validity. Nonetheless, there are two reasons to suggest that this scenario is improbable: Firstly, CAR-T patients must have received at least two prior lines of therapy, a circumstance typically uncommon among the most vulnerable patients.[5] Secondly, CAR-T treatments, known for their severe side effects, are less likely to be prescribed for the frailest patients.

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[4] It should be noted that the distribution of health care expenditure exhibits a significant right skewness. Consequently, a considerable proportion (> 75 percent) of the population experiences health care expenditures that fall below the arithmetic mean. If health care expenditure in a subpopulation are above the arithmetic mean of their age group, morbidity rates within this subpopulation must be substantially elevated when compared to the general population.

[5] Very vulnerable patients often do not survive long enough to receive several lines of therapy. See among others: Prasad, Vinayak K. 2020. Malignant: How Bad Policy and Bad Evidence Harm People with Cancer. Baltimore: Johns Hopkins University Press.

Table S3: Mean cost per member per month general Swiss population

Age group	Mean annualized expenditure per member and patient year, general Swiss population	weight
31-40	2'630	5%
41-50	2'995	4%
51-60	4'284	12%
61-70	6'307	28%
71-80	9'583	47%
80-90	12'651	4%
Weigthed average per patient year	7'525	

Source: Statistik Risikoausgleich 2021[6]

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[6] https://www.kvg.org/versicherer/risikoausgleich/rundschreiben-statistiken/, downloaded 19.07.2023