Costs Associated with Adverse Events from Remission Induction for Children with Acute Lymphoblastic Leukemia (ALL)

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Abstract

Background

During remission induction (RI) treatment, adverse events (AEs) may require hospital treatment, causing partial or total suspension of the treatment protocol depending on their severity which delays the end of RI. We will follow up patients with AEs initiated in IR assuming that they may require several weeks of treatment before hospital discharge, which may represent a considerable cost for the hospital institution.

Objective

To estimate the incremental cost of the RI treatment protocol by the presence of AEs in children with ALL.

Methods

Children with a recent diagnosis of ALL, who are undergoing RI treatment. The AE experienced during remission were classified according to System Organ Class (SOC). With data available from the clinical records, we quantified and compared the direct medical costs generated between a group of patients who presented AE and another group that did not. Generalized linear models were developed to identify cost variations according to the frequency of events, which were associated with characteristics of the patient, such as sex, risk category and alive status.

Results

297 AEs were identified in 86.8% of the patients, 68.7% of the events were treated in hospital. The total incremental cost to treat a patient who has adverse events during induction exceeds $7,000 and for each additional adverse event the total cost increase $527 dollars.

Conclusion

The cost of a pediatric patient undergoing RI without adverse events is $3,078.36. The average incremental cost to treat a patient with AEs exceeds twice the cost of a patient without events and the frequency of inpatient AEs in RI exceeds that of outpatient by three to one. Generalized linear models show that variables such as sex, risk category and alive status are associated with the presence, frequency and cost of AE. This is the first study aiming to analyze the effect of ALL-related AEs on health care costs in pediatric population, so our results may help not only to local decision making but also it may contribute to the research agenda in this field.

Background

ALL is the most frequent hematological neoplastic disease reported at pediatric age. Standard chemotherapy at the RI phase include vincristine, L-asparaginase, one anthracycline and one glucocorticoid which are all administered during four weeks resulting in ALL remission in a short time favoring high survival rates [1]. In developed countries 96–99% of pediatric patients achieve disease remission [1–4] with a treatment regimen similar to the currently used at the Hospital Infantil de México Federico Gómez (HIMFG). AEs related to treatment toxicity are usually acute and not serious, but when they are serious the patients may die. Some AEs requiring hospital treatment such as bleeding, pancreatitis, febrile neutropenia, septic shock or pancytopenia, often occur during RI and may entail treatment interruption until the patient meets the clinical requirements for treatment completion, which may represent considerable costs for the hospital.

The estimated mortality during RI reported for USA is 1.12% [5], however in Mexico it ranges between 7% [6] and 15% [7] in patients who achieved complete remission, whereas chemotherapy-associated mortality in children is around 51.4% in developing countries [8], being the main causes infections, septic shock, bleeding [6–9], severe anemia, tumor lysis syndrome and hyper leukocytosis [10–14]. Some patients' characteristics have been associated with the occurrence of AEs such as sex, type of relapse [15] and early response to RI treatment [16–17]. Studies about cost of AEs in patients with ALL are scarce and adult population has been the most studied [18], where the cost of inpatient treatment of febrile neutropenia has been estimated in USD $33,189 [19, 20]. A systematic review found that hospital-acquired adverse drug reactions (ADR) translate into £380 million per year in UK while in Canada the overall cost of ADR- related admission to the emergency department and succeeding hospitalizations was quantified as approximately USD $13.6 million [21].

The current public program in Mexico that deliver financial support to oncologic children without social security has been funding ALL chemotherapy with a fixed amount, but the additional resources needed to treat any other disease related unexpected event must be taken from the budget of the oncologic health care providers, therefore our research purpose was to estimate the cost of AEs associated with ALL treatment in children.

Methods

The study design was retrospective, longitudinal, and observational; data were extracted from the clinical records of patients with ALL treated from 2015 to 2019 at the Hospital Infantil de México Federico Gómez. Not inclusion criteria were: treatment abandonment, death from causes other than neoplastic disease and missing information. The variables of interest were the occurrence of treatment-related AEs during RI phase, patient clinical features, drug regimens, diagnostic tests (lab and image), blood transfusions, surgical procedures, length of stay and any other medical inputs consumed during hospitalization. Adverse events were classified according to the SOC as well as the Common Terminology Criteria for Adverse Events (CTCAE) [22]. The study protocol was approved by the research committee of the Hospital Infantil de México Federico Gómez with the number HIM-DIC-SR-2020-004. This study was performed in accordance with research guidelines and regulations, national and international. Since the retrospective nature of our study no written or verbal consent was necessary. DURANTE TODA LA CONDUCCIÓN DEL ESTUDIO SE CUIDO LA CONFIDENCIALIDAD DE LOS PACIENTES

Cost estimations were done from the perspective of the health care provider (HIMFG) which is a tertiary referral hospital located in Mexico City that belongs to the National Institutes of Health, therefore the focus was on direct medical costs. A micro-costing approach was adopted for resources quantification and a time horizon lower than one year was utilized so no costs discounting was necessary. Information about prices and unit costs of inputs were taken from the hospital tariff payment system. Body weight or body surface area information was used for calculation of total cost of pharmacotherapy. All cost estimations were expressed in US dollars of 2020.

Descriptive statistics included calculation of central tendency and dispersion measures for continuous variables, while categorical variables were analyzed with relative frequency tables. Comparisons between groups were done by means of parametric or non-parametric tests according to the probability distribution of cost variables. To evaluate the effects of patient characteristics on total cost we tried some generalized linear models (GLM) because they allow dealing with biased data and directly modeling heteroscedasticity, giving the possibility of having a specification that approximates the real process of generating economic data in the health sector. Therefore, to select the link function and variance distribution family of the GLM model, specification tests were first performed with Akaike (AIC) and Bayesian (BIC) information criteria to select the model with the lowest values between both. For model fitting with the logarithmic and square root link functions, together with the Gaussian, Poisson and gamma variance distribution

families, six different models were obtained for which comparisons of the likelihood (log) values were performed. This was ordered by the application date throughout follow-up. All statistical procedures were performed with the STATA program, version 16.

Results

The sociodemographic and clinical characteristics of patients are shown in **Table 1**. Fifty- three medical records met inclusion criteria for review, of which 30 were high-risk category and 23 standard risk ALL. No adverse events were found in 7 patients, so this group was used as a reference for comparison purposes (Figure 1A).

Adverse Events

We identified 297 adverse events in the study sample. Forty patients (75.5%) accumulated 204 AEs requiring inpatient care as well as 81 AEs treated on an outpatient basis while 6 patients (11.3%) only experienced 12 AEs (4%) receiving outpatient care. The mean number of AEs per patient was 6.4 (median: 4, SD: 6.1). Gastrointestinal disease was the most frequent AEs category, and within this the most frequent conditions were abdominal pain (13 AEs), neutropenic colitis 11, mucositis 9 and pancreatitis 8. The second most frequent category was infection including 10 septic shock events and 4 events diagnosed as systemic inflammatory response syndrome. Bicytopenia and pancytopenia were assigned to the category investigations which accumulated 32 AEs, and was the third most important by frequency of events (Figure 1B). A wide variety of clinically important AEs were also found, which were classified into the following disease categories according to the SOC: cardiac, hepatic, immunological, skeletal muscle, nervous system, psychiatric, respiratory, thoracic, mediastinal, vascular, and urinary system. Within these categories febrile neutropenia was the most frequent in the sample (25 AEs) followed by tachycardia (21) and sepsis (15).

Costs results are displayed in **Table 2** divided by groups and by health care modality (inpatient or outpatient). Since only one patient in the group without AEs experienced hospitalizations no variability statistics were reported. The higher cost in the group with AEs was due to longer hospital stay which suggests the impact of AEs on resources consumption, considering that the only patient hospitalized without AEs needed it because diagnosis complications. But also, significant differences were observed when comparing both groups under outpatient health care linked to chemotherapy costs since AEs occurrence can lead to modifications in ALL scheme treatment protocol increasing so the total cost. Comparison of total costs between groups showed an incremental cost of $7,460 likewise attributable to adverse events. The correlations between total cost and number of AEs (Table 2) supported the mentioned result since the scatter plots showed increasing trends by sex, alive status, and ALL risk category (Figures 2A, B y C).

GLM Models

The **Table 3A** shows the results of the specification tests performed by means of the Akaike and Bayesian information criteria, denoting that the GLMs with the lowest values were those with gamma family and log-link function as well as square root link function; therefore, we decided to use the log-link function for GLM. We estimated two GLMs (Table 3B) to know the effect of AEs as a binary predictor as well as a discrete covariate. The GLM 1 estimated an incremental cost of AEs near $4,000 which suggests that the total cost difference calculated in **Table 2** (USD $7,460) may not be fully attributable to AEs occurrence, while for each additional adverse event the total cost increase $527 as we can see in the GLM 2. It is worth noting that the greatest effect was observed for death which suggests that cost of AEs increase as patients die from adverse events.

Discussion

As far as we know, this is the first study aiming to analyze the effect of ALL-related AEs on health care costs in pediatric population, so our results may help not only to local decision making but also it may contribute to the research agenda in this field. At local level these results should alert both the health care providers that deliver oncologic treatment to pediatric patients with ALL as well as the government officers in charge of the program that grant financial support to the families to alleviate the burden of cancer, since according to our GLM the cost of AEs may be as large as the cost of chemotherapy.

Worth it emphasize how frequent was the occurrence of AEs in this sample, which not only have an economic importance as we have already seen, but from clinical and humanistic perspectives it is regrettable notice in these children a deterioration in their quality of life which is susceptible of economic estimation. This is a pending taskin health economics since the difficulties faced in assigning an economic value to suffering in children. We also could recognize that although the high frequency of AEs in these patients, the target of ALL remission was not impeded in the most of them. The percentage of remitted patients was comparable to the remission rates observed in developed countries [1–4].

Our results must be taken with caution since this study had some methodological narrows. Our main limitation was the source of information because the medical records we used were not designed to collect detailed data about resources consumption, so we had to make some assumptions during the data collection to derive the production function needed to micro-costing. This issue also limited the research of additional factors that could impact on the cost of AEs, so we only included information about the covariates displayed in the GLMs. We also recognize that a matched case-control prospective study should be used to estimate the attributable cost of AEs, so our retrospective design could be another limitation. However, despite these limitations we could not only apply a micro-costing methodology, but we could evaluate the effect of relevant factors on the total health care cost in Mexican children treated for ALL and adverse events.

Our cost estimates resulted higher than those reported by Perez J, et al. for patients attended in a hospital located at the northern region of Mexico with lower doses of chemotherapy; whose estimations were for inpatient neutropenia febrile $1,512 and for inpatient adverse drug reaction $1,070 [23]. However these costs for similar conditions may appear too high in other countries, for example in a sample of pediatric patients with ALL treated in a hospital in Finland, the mean charges estimated for treatment of infections were $5,872 in standard risk, $13,718 in intermediate risk and $33,430 in high risk patients [24]. Similar evidence have been reported in China, where the cost of severe complications in children with ALL was estimated around $21,000 [25].

Conclusions

The variability of the cost of a pediatric patient undergoing RI ranges from $3,078.36 to $10,538.59 because of AEs. The cost of a pediatric patient undergoing RI without adverse events is $3,078.36. The average incremental cost to treat a patient with AEs exceeds twice the cost of a patient without events and the frequency of inpatient AEs in RI exceeds that of outpatient by three to one. Generalized linear models show that variables such as sex, risk category and alive status are associated with the presence, frequency and cost of AE. This is the first study aiming to analyze the effect of ALL-related AEs on health care costs in pediatric population, so our results may help not only to local decision making but also it may contribute to the research agenda in this field.

Abbreviations

RI- remission induction, **AEs**- adverse events, **ALL**- Acute Lymphoblastic Leukemia, **SOC**- System Organ Class, **USD ($)**- United States Dollar, **HIMFG**- Hospital Infantil de México Federico Gómez, **ADR**- adverse drug reactions, **£**- pound sterling, **UK**- United Kingdom, **CTCAE**- Common Terminology Criteria for Adverse Events, **GLM**- generalized linear models.

Declarations

Ethics approval and consent to participate: The clinical research committee of Hospital Infantil de México Federico Gómez, reviewed the protocol and it was approved with the number HIM-DIC-SR-2020-004 and indicated that this protocol was considered as a documentary research; therefore, it was not necessary to obtain informed consent from the patients. The participating investigators are obliged to protect the identity and personal data of the research subjects, both during the development of the protocol and in the phases of publication or dissemination of the results of the same.

Consent for publication: Not applicable

Availability of data and materials: The Raw Data is available in the supplementary file. If you required more information this is available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: These authors contributed equally to this work. Mejía-Aranguré, Reyes-López, Yosef Olaf performed statistical analysis of economics data and adverse events, prepared tables and graphs, wrote and designed the manuscript. These authors contributed equally to this work. Barajas-Nava, Martínez Valverde, Garduño-Espinosa supported the design of the economic analysis, edited the manuscript. These authors contributed equally to this work. Juárez-Villegas, Saucedo Campos, Hernández-Pliego supported the analysis and classification of adverse events, edited the manuscrip.

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Tables

Table 1. Sociodemographic and clinical characteristics of patients with and without AEs.

Variables	Patients with AEs (n= 46)	Patients without AEs (n= 7)
Age (years)	7 (4.4)	6 (2.6)
Weight (kg)	27 (18.2)	22.4 (11.4)
Height (cm)	115.6 (26.7)	111 (16.3)
Female, n (%)	25 (54.3)	3 (42.8)
High risk ALL, n(%)	27 (58.7)	3 (42.8)
Standard risk ALL, n (%)	19 (41.3)	4 (57.2)
Completed remission induction treatment, n (%)	43 (93.5)	7 (100)
ALL remission, n (%)	45 (97.8)	7 (100)
Deaths, n (%)	4 (8.7)	0 (0)
Time to ALL remission (days)	14 (5.9)	14 (3.3)
First hospital length of stay (days)	9 (13.6)	1.86(4.9)
Second hospital length of stay (days)	7 (9.7)	0.14(0.38)
Third hospital length of stay (days)	1.35 (6.25)	0(0)
Amount of AEs	6.46(6.06)	0(0)
AEs: adverse events. The values shown are mean and standard deviations except for percentages		

Table 2. Estimations of inpatient and outpatient costs for patients with and without adverse events during IR.

Inpatient care costs (USD)							
	patients with AEs (n=39)			patients without AEs (n=1)			
Variable (costs)	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	***p*-value**
Hospital stay	$1,558.73	$1,362.94	$1,078.67	$1,078.67	not calculable	$1,078.67	not calculable
Surgery	$126.24	$378.61	$0.00	$0.00	not calculable	$0.00	not calculable
Special procedure	$280.53	$946.49	$0.00	$0.00	not calculable	$0.00	not calculable
Laboratory test	$836.76	$1,924.00	$396.42	$0.00	not calculable	$0.00	not calculable
Diagnostic radiology test	$36.10	$75.13	$0.00	$0.00	not calculable	$0.00	not calculable
Blood products	$479.51	$1,272.79	$27.12	$0.00	not calculable	$0.00	not calculable
Interconsultation	$755.93	$938.69	$415.82	$178.21	not calculable	$178.21	not calculable
General medications	$3,095.64	$5,939.04	$901.74	$1,296.78	not calculable	$1,296.78	not calculable
Total hospital stay	$7,169.45	$11,117.75	$2,964.22	$2,553.66	not calculable	$2,553.66	not calculable
Outpatient care cost (USD)							
	patients with AEs (n=7)			**patients without AEs (n=6)**			
Variable (costs)	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	***p*-value**
Laboratory test	$23.13	$61.20	$0,00	$14.55	$35.65	$0.00	1.0000
Blood products	$3.87	$10.25	$0.00	$0.00	$0.00	$0.00	0.3545
Consultation	$82.03	$24.06	$79.20	$69.30	$41.06	$69.30	0.4223
Chemotherapy	$4,893.91	$1,630.34	$4,424.06	$2,788.57	$1,315.28	$2,331.12	0.0321
Total outpatient	$5,002.95	$1,589.53	$4,483.46	$2,872.42	$1,340.27	$2,453.99	0.0321
Total and incremental costs (USD)							
Total cost	$10,538.59	$10,419.96	$7,360.90	$3,078.36	$1,339.06	$3,168.42	0.0002
Incremental cost	$7,460.23						
SD: standard deviation, USD: United States Dollar, AEs: adverse events							

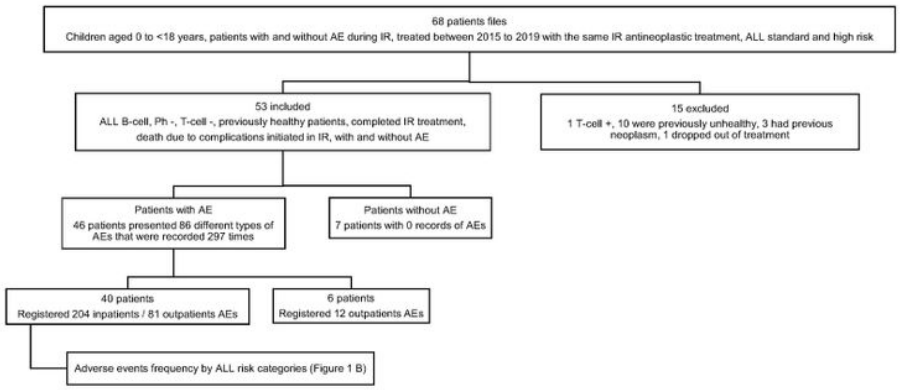
Table 3A. Results of specification tests based on Akaike and Bayesian information criteria.

GLM Model	AIC	BIC
Gamma family log-link function	1,079.45	1,081.42
Gamma family square root link function	1,079.45	1,081.42
Gaussian family log-link function	1,128.05	1,130.02
Gaussian family square root link function	1,128.05	1,130.02
Poisson family log-link function	346,506.70	346,508.70
Poisson family square root link function	346,506.70	346,508.70
GLM: generalized linear models, AIC: Akaike, BIC: Bayesian		

Table 3B. Results of GLMs to assess the effects of patient characteristics on the total cost of AEs.

GLM 1				
Covariates	**Estimates (USD)**	**p-value**	**95% confidence interval (USD)**	
Adverse events ocurrence	$3,750.06	0.013	$802.89	$6,697.22
Sex	$3,601.37	0.002	$1,302.69	$5,900.04
Age	$1,289.68	0.263	-$966.69	$3,546.06
High risk ALL	$12.95	0.938	-$313.52	$339.43
Time to get ALL remission	$2,430.59	0.043	$80.94	$4,780.24
Hospitalized patients	$330.50	0.004	$105.31	$555.69
Deaths	$6,273.87	0.028	$693.88	$11,853.87
GLM 2				
Number of adverse events	$526.59	0.000	$257.54	$795.63
Sex	$409.58	0.673	-$1,490.15	$2,309.32
Age	$17.79	0.870	-$196.10	$231.70
High risk ALL	$2,040.07	0.046	$40.69	$4,039.45
Hospitalized patients	$241.15	0.000	$132.33	$349.98
Time to get ALL remission	$2,448.66	0.025	$300.69	$4,596.62
GLM: generalized linear models, USD: United States Dollar				

Figures



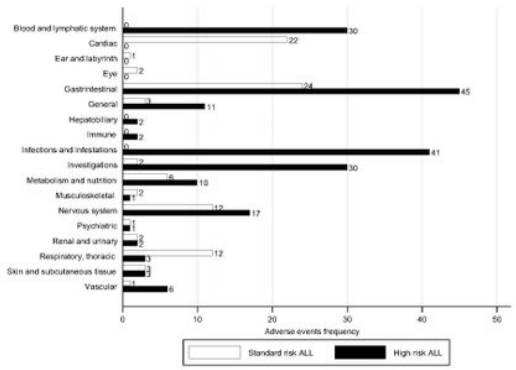


Figure 1

A. Patient selection flowchart

B. Adverse events frequency by ALL risk categories.

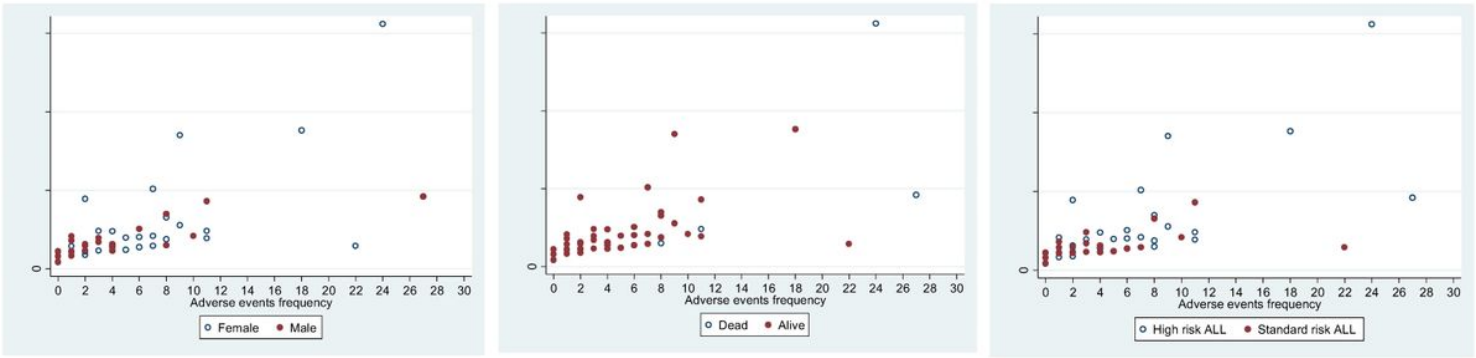


Figure 2

A. Correlation between number of AEs and total cost of care by sex.

B. Correlation between number of AEs and total cost of care by mortality.

C. Correlation between number of AEs and total cost of care by ALL risk category.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFile.dta