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Economic implications of step-down outpatient management for fever and neutropenia episodes in pediatric cancer patients: a cost minimization analysis

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Abstract

Background The management of febrile neutropenia (FN) in pediatric cancer patients has traditionally been conducted in a hospital setting. However, recent evidence has indicated that outpatient management of FN can be equally effective compared to inpatient care. Based on this evidence, we conducted a cost-minimization analysis (CMA) specifically focused on pediatric cancer patients in Mexico.

Methods A piggy-back study was conducted during the execution of a non-inferiority clinical trial that compared outpatient treatment to inpatient treatment for FN in children with cancer. A CMA was performed from a societal perspective using patient-level data. In the previous study, we observed that step-down oral outpatient management of low-risk FN was as safe and effective as inpatient intravenous management. Direct and indirect costs were collected prospectively. The costs were adjusted for inflation and converted to US dollars, with values standardized to July 2022 costs. Statistical analysis using bootstrap methods was employed to obtain robust estimations for decision-making within the Mexican public health care system.

Results A total of 117 FN episodes were analyzed, with 60 in the outpatient group and 57 in the inpatient group; however, complete cost data were available for only 115 FN episodes. The analysis revealed an average savings of $1,087 per FN episode managed on an outpatient basis, representing a significant 92% reduction in total cost per FN episode compared to inpatient treatment. Length of hospital stay and inpatient consultations emerged as the primary cost drivers within the inpatient care group.

Conclusion This CMA demonstrates that the step-down outpatient management approach is cost-saving when compared to inpatient management of FN in pediatric cancer patients. The mean difference observed between the treatment groups provides support for decision-making within the public health care system, as outpatient management of FN allows for substantial cost savings without compromising patient health.

Keywords Neutropenia, Febrile neutropenia, Outpatient management, Cost-minimization analysis, Cost analysis, Economics, Pediatrics

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Background

Febrile neutropenia is the most frequent complication that entails hospitalization among cancer patients undergoing chemotherapy [1]. Over the past few decades, emerging evidence has indicated that certain low-risk patients may achieve positive outcomes through less aggressive FN management approaches, including the potential for outpatient management employing oral or intravenous antibiotics [1–5]. Despite these advancements, the management of pediatric FN remains heterogeneous across countries and institutions.

According to the 2020 Mexican census, malignant lymphatic tissue and hematopoietic organ tumors are the leading cause of death among children between 6 and 11 years of age. Most children with catastrophic illnesses, including cancer, are covered by the Mexican public health care system. A health care program that provides coverage for all Mexicans with catastrophic illnesses regardless of employment status, called Seguro Popular, was created in 2003, but in 2020, it was replaced with the Institute of Health for Welfare (Instituto de Salud para el Bienestar, INSABI). The Seguro Popular aimed to provide healthcare services to individuals without medical insurance. Its focus was to expand coverage and reduce financial barriers to accessing healthcare. However, INSABI aims to offer free healthcare to the entire Mexican population, including those with other forms of health insurance. Seguro Popular operated on a mixed financing model, with contributions from beneficiaries and the government. In contrast, INSABI is fully financed by public resources. This shift in the financing model has prompted discussions about the long-term financial sustainability of INSABI. The establishment of INSABI has encountered logistical and administrative challenges, including the proper integration of state healthcare systems and the procurement of medications, exacerbating their scarcity.

Clinical practice guidelines recommend considering initial or step-down outpatient management for low-risk febrile neutropenia (FN) in children with cancer. This recommendation is supported by a systematic review of pediatric FN randomized clinical trials, which found comparable clinical outcomes for both strategies. However, the choice of management approach should be made considering the unique resources and preferences of each institution [6]. Subsequent studies have further validated the safety and efficacy of outpatient management [7], highlighting the importance of considering cost.

High hospital costs associated with FN treatment have been reported in various developed countries. For instance, in the United States, FN episodes contribute to an annual hospitalization cost of $439 million, with an average stay of 8.5 days and a mean cost of $26,000 per stay for neutropenia secondary to cancer [8]. Similarly, a Canadian study reported an average total cost of $6,324 Canadian dollars per FN episode [9].

In the pediatric population, studies have demonstrated a wide range of costs per FN event, ranging from $511 to $16,341 [10–15]. In most cases, inpatient care costs were double that of outpatient treatment, with hospitalization being the primary cost driver, accounting for 62–83% of the total treatment cost per FN episode [10, 16].

Given the economic challenges faced by the Mexican public health care system, it is crucial to gather information regarding the costs associated with FN management strategies. Such data can assist decision-makers in promoting cost-effective health strategies. Therefore, the objective of this study was to perform a cost-minimization analysis (CMA) comparing two treatment options for children with FN: inpatient intravenous antibiotic management versus sequential intravenous-oral outpatient antimicrobial management.

Methods

Type of study

A piggy-back study was conducted during the execution of a non-inferiority clinical trial, carried out in three public pediatric hospitals in Mexico City. The methodology and results of this clinical trial were previously published in detail [17]. In the aforementioned study, it was concluded that in the studied population, step-down oral outpatient management of low-risk febrile neutropenia episodes in children with cancer was as safe and effective as inpatient intravenous management. Therefore, for the economic evaluation, a cost-minimization analysis was performed from a societal perspective, utilizing the information collected on the direct (medical and nonmedical) and indirect costs incurred during the participation of subjects in the clinical trial. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and clinical best practices. The study was approved by the local research committees. Informed consent was obtained from the parents or primary caregivers of the subjects before participation in the study, and the children were asked for assent if they were ≥8 years old. The protocol was approved by the local ethics committee. Clinical Trials Identifier: NCT04000711.

For the purpose of this report, we provide a concise summary of the key features of the noninferiority trial to facilitate the CMA. The study was conducted in three public hospitals in Mexico City that cater to the most socioeconomically disadvantaged segment of society, which lacks any form of social insurance. All patients from 1 to 18 years of age who presented with an FN episode (defined as a single oral temperature greater than or equal to 38.3 °C or a temperature greater than or equal to 38 °C for at least an hour, with an absolute neutrophilic

count (ANC) of less than 500 cells/microliter), were identified. The inclusion criteria were as follows: subjects who received 48–72 h of i.v. antibiotic treatment, were hemodynamically stable, remained afebrile for at least 24 h, and did not have a documented source of infection. The exclusion criteria were as follows: positive culture; an absolute neutrophil count (ANC) < 100/μL and thrombocytopenia < 30 000/μL; an FN episode within seven days from the start of the last chemotherapy session; leukemia on remission-induction therapy; relapsed acute leukemia; underwent hematopoietic stem cell transplantation; mucositis grade III or IV; allergy to cefixime, the need to receive any other medication intravenously; oxygen supplementation; and total parenteral nutrition. Subjects who met the inclusion criteria and lacked all exclusion criteria were considered low risk.

After 48–72 h of intravenous antibiotic treatment, subjects considered at low-risk of infection were recruited and randomly assigned to the outpatient group (experimental group), which continued their treatment for FN with oral antibiotic (Cefixime) at home or, to the inpatient group (control group) which continued intravenous Cefepime as standard of care management for FN. Subjects in both groups were daily monitored by a pediatrician exclusively hired for the research protocol, until resolution of FN episode (subject remains afebrile and an increase in the absolute neutrophils count > 500/mm^3 is documented, without signs or symptoms of infection), or until the occurrence of any unfavorable clinical outcome, which included any of the follows: (1) Therapeutic failure, defined as the resumption of fever in a patient with persistent neutropenia. For all patients with resumption of fever, the antibiotic regimen was switched, and if the patient was in the outpatient treatment group, he/she was readmitted to the hospital. (2) New focus of infection, as documented by physical examination or by laboratory and other diagnostic tests. (3) Hemodynamic instability, which was defined as a decrease in blood pressure below the 5th percentile for the patient's age that did not revert with the administration of crystalloid solutions. (4) Death.

Resources utilization and costs

To capture economic resource data, an electronic case report form (eCRF) was designed by a computer engineer. The eCRF allowed for automated cost calculations during the follow-up of both outpatient and inpatient subjects, capturing information on consumed medical resources. The form incorporated the prices and unit costs of resources obtained from hospital fees, human resources departments, and financial reports on drug and supply purchases. Given that in our country, cancer is considered a catastrophic disease, all expenses related to treatment and associated complications are cover by the government. Therefore, even though patients did not make any payments for the management of NF episodes, the costs of the most expensive subsidy category fee were used for calculation of direct hospital costs. This was done in order to reflect costs as accurately as possible, the actual expense of managing NF events. Data collection was performed by a physician from the research team.

Additionally, a separate questionnaire was designed to gather daily information from primary caregivers or parents, regarding nonmedical expenses incurred during patient care. This questionnaire included inquiries about the caregivers' employment status at the time of the survey, whether patient care activities resulted in the total or partial interruption of their work, and income loss attributable to these circumstances. These questions were answered at the end of the trial, and the costs were linked to the monetary values provided by the respondents.

Direct medical costs encompassed various input categories, such as bed days, laboratory and imaging tests, antibiotics, general medications, work hours of physicians, nurses, social assistants, and psychologists, as well as medical devices and supplies (e.g., gloves, face masks, gauzes, alcohol prep pads, syringes, needles, dressings, medication infusion equipment, catheters, flexible needles, three-way stopcocks). Due to prior to subjects randomization (after 48–72 h of hospitalization) all subjects, regardless of the randomly assigned groups, had been managed on an inpatient basis, the costs incurred during the initial days of hospitalization before randomization were not taken into account.

Direct nonmedical costs encompassed expenses incurred by the primary caregiver, including transportation, food, cell phone usage, toiletry supplies, payment to any other caregiver, and other minor expenses. The estimation of indirect costs revolved around the lost income of the primary caregiver.

The total costs were calculated by summing the cost values throughout the follow-up period until the resolution of the FN episode or patient discontinuation. Additionally, the resources utilized for the treatment of adverse events associated with FN were taken into account. Inflation adjustments were applied to the cost values obtained from the eCRF, as they were initially calculated using 2017 prices when the trial concluded. The national Consumer Price Index of Mexico was used for cost adjustment. All cost findings are presented in US dollars, and were calculated using the monthly average of official exchange rate for July 2022.

The statistical analysis primarily focused on evaluating the probability distribution of costs using measures of centrality and variability. However, since decision-makers are primarily interested in the arithmetic mean, we employed a nonparametric bootstrap procedure to draw statistical inferences regarding the differences in the

mean costs. This approach offers the advantage of avoiding parametric assumptions about the cost distribution while enabling inferences about the arithmetic means or its differences [18]. The nonparametric bootstrap procedure has been recommended for evaluating the robustness of standard parametric tests (such as Student's t-test) or as a primary statistical test for making inferences about the arithmetic means of costs when the sample size is small to moderate [18]. Before running each bootstrap procedure we specified the initial value of the random-number seed typing 1 in the syntax to be able to reproduce results, then we performed the t tests bootstrapped using 1000 replications each time which is recommended to estimations of confidence intervals using the percentile or bias-corrected methods. Postestimation methods were utilized to compute various confidence intervals for the differences in mean costs. All statistical analyses were conducted using StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

Results

As described in the aforementioned non-inferiority clinical trial, a total of 117 febrile neutropenia (FN) episodes were examined, with 60 episodes in the outpatient group and 57 episodes in the inpatient group (Table 1). However, complete cost data were available for only 115 FN episodes, leading to the exclusion of 2 episodes from the CMA. In the outpatient treatment group, all subjects (100%) achieved a favorable outcome, compared to 93.1% of subjects in the inpatient group. The noninferiority analysis yielded a z value of 5.9 ($p<0.001$), indicating that early discharge with oral outpatient antibiotic treatment is as safe and effective as in-hospital treatment for pediatric patients with low-risk FN episodes.

Direct medical costs

Direct medical costs encompass resources directly utilized for patient care. The mean cost in the inpatient group was nearly 13 times higher than that in the

Table 1 General and laboratory characteristics of 117 FN episodes by management group at randomization

	Outpatient management ($n=60$)	Inpatient management ($n=57$)	p *
Age in years, mean (95% CI)	6.8 (5.7–7.9)	7.2 (6.2–8.3)	0.55
Sex			0.01
Female	29 (48%)	40 (70%)	
Cancer type			0.33
Blood	37 (62%)	40 (70%)	
Solid tumor	23 (38%)	17 (30%)	
Hospital			0.77
HIMFG	49 (82%)	45 (79%)	
INP	8 (13%)	10 (17%)	
HJM	3 (5%)	2 (4%)	
Maximum temperature (°C)	38.4	38.5	0.26
Leukocytes in/mm^3,			0.95
Mean	1 737	1 749	
95% CI	1 492–1 983	1 470–2 027	
ANC, x10^3/mcL			0.13
Mean	280	248	
95% CI	250–309	218–278	
AMC, x10^3/mcL			0.85
Mean	433	420	
95% CI	321–546	326–513	
Hemoglobin, mg/dl			0.30
Mean	12.4	10.7	
95% CI	9.3–15.4	10.3–11.2	
Platelets, x10^3/mcL			0.64
Mean	208	196	
95% CI	169–248	159–232	
Use of GCSF			0.94
Yes	14 (23%)	13 (23%)	

HIMFG = Federico Gómez Children's Hospital, NIP = National Institute of Pediatrics, HJM = Hospital Juárez de México, ANC = absolute neutrophil count, AMC = absolute monocyte count, GCSF = granulocyte colony stimulating factor, CI = confidence interval

* The chi-square test was performed for categorical variables, and Student's t test was performed for numerical variables

Table 2 Direct medical cost comparison between both options for management of 115 FN episodes in children

Resources	Outpatient management (*n* = 59)	Inpatient management (*n* = 56)	Mean difference	*p* value	CI (95%)
Length of stay, mean (SD) median	$0 ($0) $0	$443 ($216) $405	-$443	< 0.001	[$-499, $-387]
Inpatient consultations, mean (SD) median	$0 ($0) $0	$498 ($265) $416	-$498	< 0.001	[$-566, $-430]
Specialty visits, mean (SD) median	$21 ($21) $13	$0 ($0) $0	$21	< 0.001	[$15, $27]
Drugs, mean (SD) median	$38 ($7) $37	$204 ($241) $130	-$167	< 0.001	[$-230, $-103]
Lab tests, mean (SD) median	$34 ($13) $32	$38 ($26) $32	-$4	0.353	[$-11, $4]
Other medical supplies and devices, mean (SD) median	$0 ($0) $0	$16 ($13) $12	-$16	< 0.001	[$-20, $-13]
Total, mean (SD) median	$92 ($31) $81	$1,200 ($670) $967	-$1,108	< 0.001	[$-1,282, $-934]

Costs are per FN episode. All monetary values are US dollars. A detailed description of other medical supplies and devices is provided in Table 3

Table 3 Amount of resources consumed in the management of 115 FN episode, by management group

Resources	Outpatient management (*n* = 59)	Inpatient management (*n* = 56)
Days of hospital stay, mean (SD) median	0 (0) 0	4.3 (2.5) 4
Inpatient consultations, mean (SD) median	0 (0) 0	24.1 (13.1) 20
Specialty visits, mean (SD) median	4.2 (2.6) 3	0 (0) 0
Days of pharmacotherapy, mean (SD) median	5.1 (3.1) 5	4.8 (2.3) 5
Lab tests		
Blood count tests, mean (SD) median	2.7 (0.9) 2	2.5 (0.8) 2
C-reactive protein test, mean (SD) median	0.5 (0.7) 0	0.5 (0.7) 0
Other medical supplies and devices		
Intravenous solutions[ml], mean (SD) median	0 (0) 0	769 (749.6) 620
Gauzes, mean (SD) median	0 (0) 0	11.9 (19.9) 3
Alcohol Prep Pads, mean (SD) median	0 (0) 0	6.3 (5.6) 5
Syringes, mean (SD) median	0 (0) 0	22.4 (15.8) 18
IV set, mean (SD) median	0 (0) 0	0.7 (1.5) 0
Dressings, mean (SD) median	0 (0) 0	1.5 (1.3) 1
Transparent film roll, mean (SD) median	0 (0) 0	1.1 (1.4) 1
Surgical gloves, mean (SD) median	0 (0) 0	25.5 (28.6) 17
IV measure volume set, mean (SD) median	0 (0) 0	1.7 (5.1) 0
IV catheter, mean (SD) median	0 (0) 0	0.6 (0.9) 0
Three way stop cock, mean (SD) median	0 (0) 0	1.4 (2.9) 1
Urine dipstick test, mean (SD) median	0 (0) 0	4.5 (6.5) 3
Swabstick applicator with 2%chlorhexidine gluconate and 70% isopropyl alcohol, mean (SD) median	0 (0) 0	1.4 (2.1) 1

Costs are per FN episode

outpatient group ($1,200.12 vs. $92.45). The main cost drivers in the inpatient care group were the length of stay and inpatient consultations. Consequently, the outpatient management of FN in pediatric patients has the potential to yield cost savings of $1,108 per FN episode, with this difference being statistically significant (as indicated in Table 2). A comprehensive list of resource quantities consumed by the treatment groups is presented in Table 3, providing insights into the cost factors contributing to the between-group differences. It is worth noting that length of stay and related issues were specific to hospitalized patients, which explains why the outpatient group had numerous zeros in certain resource categories (Table 3).

Direct nonmedical costs

Inpatient care for FN episodes also led to higher nonmedical costs for parents or primary caregivers, primarily due to payments made to different caregivers during hospitalization. However, the anticipated savings associated with outpatient treatment were not as substantial as those observed in direct medical costs (Table 4). The mean cost in the inpatient group was nearly double that of the outpatient group ($96.17 vs. $52.76). Among the expenses borne by parents or caregivers, the cost of hiring an additional caregiver to support patient care emerged as the most significant out-of-pocket cost in both treatment groups ($26 outpatient group VS $48 inpatient group) ($p < 0.001$).

Table 4 Direct nonmedical cost comparison between both options for the management of 115 FN episodes in children

Resources	Outpatient management (*n* = 59)	Inpatient management (*n* = 56)	Mean difference	*p* value	CI (95%)
Transportation, mean (SD) median	$3 ($8) $0	$13 ($15) $10	-$10	< 0.001	[$-14, $-6]
Feeding, mean (SD) median	$13 ($14) $7	$23 ($16) $19	-$10	< 0.001	[$-15, $-5]
Mobile phone, mean (SD) median	$4 ($5) $3	$5 ($5) $5	-$1	0.182	[$-3, $1]
Personal hygiene supplies, mean (SD) median	$2 ($3) $0	$3 ($4) $3	-$1	0.098	[$-2, $0]
Another caregiver, mean (SD) median	$26 ($29) $18	$48 ($32) $37	-$22	< 0.001	[$-33, $-11]
Other minor items, mean (SD) median	$4 ($11) $0	$3 ($7) $0	$0.5	0.772	[$-3, $4]
Total, mean (SD) median	$53 ($57) $35	$96 ($65) $74	-$43	< 0.001	[$-65, $-21]

Costs are per FN episode. All monetary values are in US dollars

Table 5 Indirect cost comparison between both options for the management of 115 FN episodes in children

	Outpatient management (*n* = 59)	Inpatient management (*n* = 56)	Difference	*p* value	CI (95%)
Quit of job activities by caregivers					
Definitely, n (%)	29 (49.15)	37 (66.07)	-16.92	0.067	[-35.06, 1.22]
Temporarily, n (%)	12 (20.34)	7 (12.50)	7.84	0.259	[-5.86, 21.54]
Income loss due to quit of job activities by caregivers					
Definitely, n (%)	24 (40.68)	26 (46.43)	-5.75	0.538	[-24.21, 12.71]
Temporarily, n (%)	4 (6.78)	3 (5.36)	1.42	0.752	[-7.46, 10.31]
Income lost, mean (SD)	$41 ($67)	$38 ($60)	$3	0.778	[-$20, $27]

Costs are per FN episode. All monetary values are US dollars. Percentages showed in the last rows refer specifically to those caregivers who had income loss due to quitting job

Table 6 Comparisons of total costs between groups by cost category of 115 FN episodes in children

Cost category	Outpatient management (*n* = 59)	Inpatient management (*n* = 56)	Mean difference	*p* value	CI (95%)
Direct medical costs, mean (SD) median	$92 ($31) $81	$1,200 ($670) $967	$-1,108	< 0.001	[$-1,282, $-934]
Direct nonmedical costs, mean (SD) median	$53 ($57) $35	$96 ($65) $74	$-43	< 0.001	[$-65, $-21]
Indirect costs, mean (SD) median	$41 ($67) $7	$38 ($60) $3	$3	0.778	[$-20, $27]
Sum of costs, mean (SD) median	$187 ($108) $153	$1,352 ($722) $1,085	$-1,165	< 0.001	[$-1,361, $-968]

Costs are per FN episode. All monetary values are US dollars

Indirect costs

Surprisingly, no statistically significant differences were observed between the groups regarding the proportions of parents or primary caregivers who had to suspend their job activities or experience income loss due to caring for patients during FN treatment (Table 5). In the outpatient group, 49% (29) of parents or caregivers reported quitting their jobs, and 20% [12] temporarily suspended their employment. In the inpatient group, 66% (37) of parents or caregivers quit their jobs, and 12.5% [7] temporarily quit. The questionnaire used included additional questions to assess the impact of job cessation on income loss, which is presented in Table 5, albeit without statistically significant differences between the groups.

Sum of costs

The data presented in Table 6 underscores the substantial contribution of direct medical costs (accounting for slightly over 95% of total costs) in the context of febrile neutropenia (FN) management among pediatric cancer patients. The mean difference observed between the treatment groups provides valuable support for decision-making within the public health care system, as outpatient management of FN demonstrates the potential for significant cost savings without compromising patient health.

In relation to direct nonmedical costs, Fig. 1 illustrates that the arithmetic mean is an unbiased estimator. Consequently, the percentile and bias-corrected methods yield comparable results. However, for cost categories where the arithmetic mean is biased, the bias-corrected method generates confidence intervals with improved coverage probability (closer to the nominal value of 95%) compared to the percentile method.

Discussion

This CMA aimed to evaluate the economic outcomes associated with sequential outpatient treatment versus inpatient treatment for pediatric patients experiencing febrile neutropenia (FN) episodes. The analysis took a

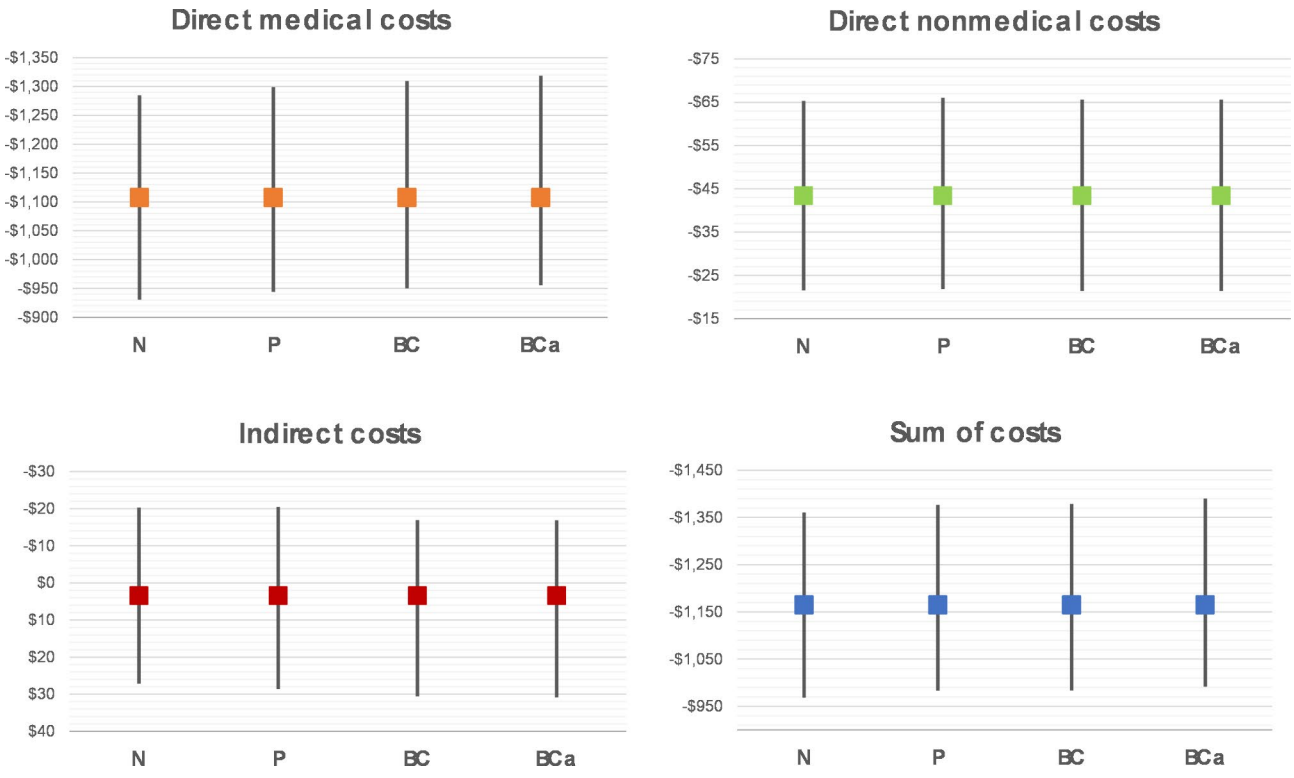

Fig. 1 Confidence intervals for mean costs from bootstrap analysis. N: normal; P: percentile; BC: bias-corrected; BCa: bias-corrected and accelerated

societal perspective, considering both direct and indirect medical costs associated with each treatment strategy. Notably, unlike other cost studies, our research utilized real-world data prospectively collected from patients enrolled in a clinical trial across three hospitals.

Our findings revealed that outpatient treatment of FN in children with cancer resulted in an average cost savings of $1,108 compared to inpatient treatment. The significantly lower cost of outpatient management primarily stemmed from reductions in hospitalization expenses and human resource costs, which accounted for 36% and 41% of direct medical costs, respectively. We meticulously documented the number of healthcare professionals involved in patient care on a daily basis, enabling us to identify healthcare professional fees as the most substantial cost driver. This category encompassed fees for medical staff, consulting specialists, nursing personnel, and other supportive care professionals such as psychologists and social workers.

Previous economic studies on FN have commonly focused on bed days as the most cost-intensive aspect [11, 12, 15]. For instance, Hendricks et al. reported that bed day costs constituted 58.2% of total hospital costs for adults with cancer [15], while Costa et al. found that bed day costs accounted for 62% of total treatment costs in the pediatric population [10].

Other economic analyses in this domain have either exclusively examined patients at lower risk of complications, such as those with solid tumors [13], or have solely reported hospitalization costs of FN episodes without comparing them to an outpatient group [9]. Furthermore, some studies have solely considered the perspective of healthcare payers [11]. In contrast, our CMA stands out by prospectively capturing information and adopting a societal economic perspective. This approach not only provides decision-makers with valuable insights into the costs of FN treatment but also sheds light on the financial burden faced by parents or caregivers when caring for children with FN in a hospital setting.

Among the expenses borne by parents or caregivers, the cost of hiring additional caregivers to support patient care emerged as the most significant out-of-pocket cost in both treatment groups. Primary caregivers reported the need to hire additional assistance to care for their children so that they could continue working. Despite this, 69% of primary caregivers in the outpatient group and 47% in the inpatient group reported partial or complete cessation of work, with similar average income loss in both groups.

Most cost studies on FN in oncology patients have utilized data from over a decade ago, with the most recent study analyzing data from 2012 but published in 2017 [8]. Consequently, there is a knowledge gap concerning the current costs of treating these patients, given the rise in healthcare costs in recent years and the increasing number of adult patients receiving outpatient treatment.

Outpatient management of FN episodes in children remains less common. Nonetheless, our clinical trial-based economic analysis demonstrates the safety and effectiveness of outpatient treatment for FN episodes in children and underscores the substantial cost reduction potential [17]. This evidence can further support the case for early discharge and continued treatment at home.

Current information regarding the costs of treating children with FN in Latin America is outdated and limited [2, 9]. A study conducted 19 years ago in Brazil examined a small sample of 22 hospitalized patients with FN episodes, reporting a median cost of $2,660 per episode, with bed days accounting for 62% of total costs [9].

Another study conducted in Chile 18 years ago reported average costs of $638 for outpatient treatment and $903 for inpatient treatment of FN episodes [2]. In this study, patients participated in a trial where, during the first 24 to 36 h of hospitalization, they were randomly assigned to receive antibiotics either on an outpatient or inpatient basis. However, both groups continued to receive intravenous antibiotics (ceftriaxone and teicoplanin). After at least 72 h of intravenous treatment, it was determined individually whether patients could switch to oral antibiotics or continue with intravenous antibiotics. In the outpatient group, patients had to visit the clinic daily for laboratory sampling and intravenous antibiotic infusion, followed by a one-hour observation period. It is possible that the costs associated with clinic visits, daily laboratory studies, and intravenous medication administration increased the costs of outpatient treatment. As a result, the cost difference between the treatment groups in the study was not substantial. Previous reports indicate that oral administration of medications, as opposed to intravenous administration, can reduce costs by approximately 80% [16]. In our study, we observed a remarkable 92% decrease in average costs.

The adoption of this outpatient treatment approach in Mexico has the potential to yield cost savings estimated between 1.5 and 2.5 million dollars for the public healthcare system. This approximation is derived from epidemiological data on cancer in Mexico. Referring to the cancer fact sheet for Mexico from Globocan 2020, there were 530,602 prevalent cases of cancer in the general population over a 5-year period. Among these cases, pediatric cancer constitutes only 5% of the total, accounting for 26,530 cases, with Acute Lymphoblastic Leukemia (ALL) representing 50% of pediatric cancer cases, thus resulting in an estimated 13,265 cases of pediatric ALL. The incidence of febrile neutropenia (FN) in children with ALL varies from 50 to 80%, with 20% categorized as low-risk FN. This leads to an estimated number of cases ranging from 1,327 to 2,122 for ALL with low-risk FN. Consequently, by multiplying our per-capita savings estimate of $1,165 by the number of cases eligible for outpatient treatment, we arrive at the aforementioned magnitude of potential savings.

Our study has several limitations. Firstly, direct medical costs were underestimated because the public hospitals where the study was conducted subsidize all services. Consequently, the actual savings may be even greater than what is reported. Secondly, although transfusion therapy is an important support for cancer patients, the costs associated with the blood bank were not quantified in this study nevertheless, it is likely that the need for blood transfusions occurred upon the patient's admission to the hospital, before they were included in the study. Additionally, it is probable that this need occurred in both inpatient and outpatient patients. Thirdly, the costs for patients in both treatment strategy groups were collected prospectively from the moment they met the inclusion criteria and signed the informed consent form. Therefore, the costs of the initial 48–72 h of treatment were not quantified for either group. This indicates that both outpatient and inpatient treatments incur higher costs during this initial period. However, it is likely that the cost difference between the groups maintained a similar proportion since all patients received the same treatment during the first 48 to 72 h. Fourth, another challenge may be the generalization of our findings to regions in Mexico or other countries with similar characteristics, as there is inherent variability in healthcare infrastructure, treatment protocols, and some demographic characteristics of patients. While this could limit the extrapolation of our results beyond the specific context of the studied population, we are beginning to generate evidence of the cost-saving potential of step-down outpatient treatment compared to inpatient treatment for FN episodes in children with cancer.

This CMA is the first in Mexico to demonstrate the cost-saving potential of step-down outpatient treatment compared to inpatient treatment for FN episodes in children with cancer, resulting in an average 92% reduction in direct costs.

Abbreviations

FN	Febrile neutropenia
CMA	Cost-minimization analysis
eCRF	electronic case report form

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Author contributions

ARL and MJAR: Conception and design, MJAR: Data collection and collation, ARL and MJAR: Data analysis and interpretation, MJAR and ARL: Manuscript writing: ARL and MJAR: Final approval of the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This research received ethical approval from the ethics committee of Hospital Infantil de México Federico Gómez (HIM-2014-026). We declare that all methods were performed in accordance with relevant guidelines and regulations. Informed consent was obtained in writing from all subjects participating in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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