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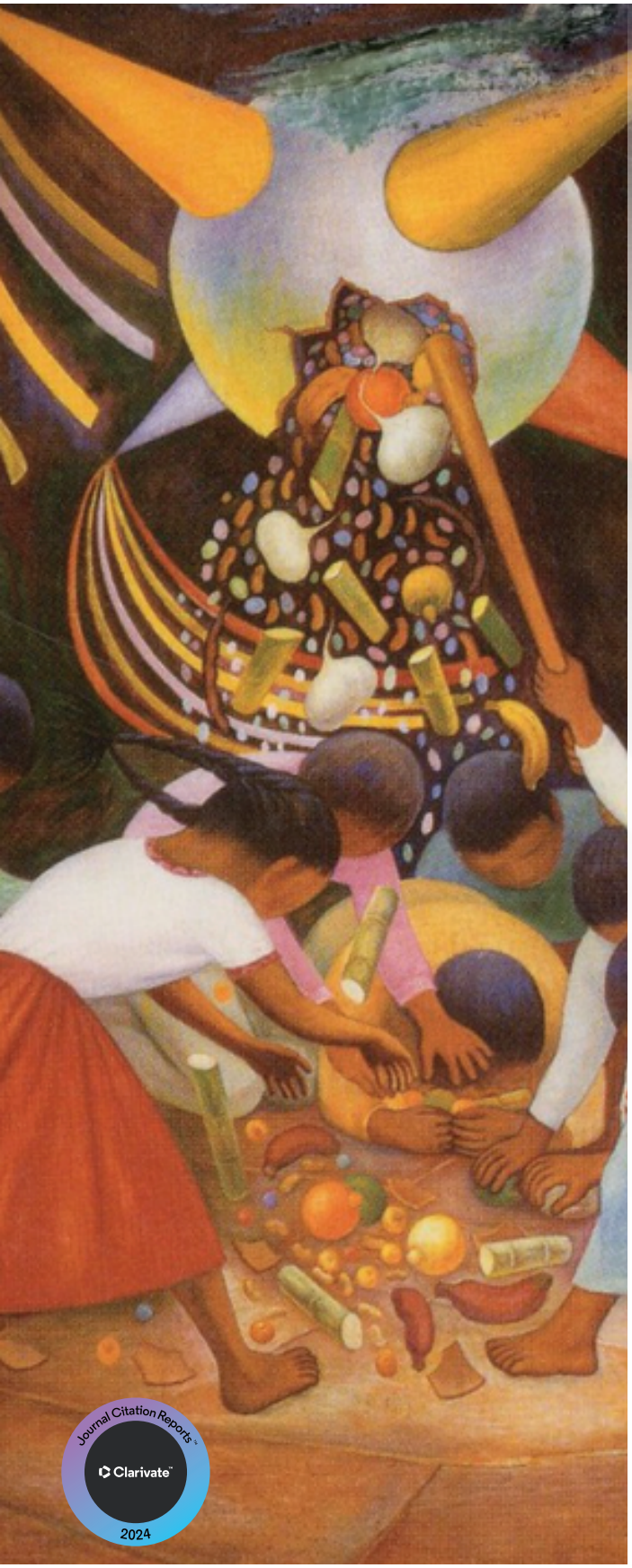

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REVIEW ARTICLE

Scientific evidence in the management of traumatic brain injury in pediatrics: ibero-American academy of pediatric neurology

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Abstract

Traumatic brain injury (TBI) is a common problem in Latin America and affects many children. Research has advanced, but international publications do not necessarily reflect our reality. For this reason, the Ibero-American Academy of Pediatric Neurology (AINP) formed a committee to review the available evidence, evaluate it, and decide how it could be applied in our region. Articles were searched in different databases and those corresponding to original works were selected, preferably those that received the best qualifications according to the 2011 version of Oxford Levels of Evidence. The main findings are the need to develop a trauma team available throughout the pediatric level III emergency, early monitoring of intracranial pressure, and multimodal monitoring as methods to improve outcomes. We concluded that much remains to be done and more evidence is needed, but more organization is required to provide specialized resources in the emergency care of these patients.

Keywords: *Cranial Trauma. Concussion. Management. Children. Adolescents. Treatment.*

Evidencia científica en manejo del traumatismo craneal en pediatria: Academia Iberoamericana de Neurología Pediátrica

Resumen

El traumatismo craneano (TC) es un problema frecuente en América Latina y afecta a muchos niños. La investigación ha avanzado pero las publicaciones internacionales no necesariamente toman en cuenta nuestra realidad. En tal virtud la Academia Iberoamericana de Neurologia Pediatrica (AINP) formo un comité para revisar la evidencia disponible, calificarla y decidir cómo se podía aplica en nuestra región. Se buscaron artículos en distintas bases de datos y se seleccionaron aquellos correspondientes a trabajos originales de preferencia los cuales recibieron calificación de acuerdo a los niveles de evidencia de Oxford versión 2011. Los resultados más importantes son la necesidad de desarrollar un equipo de trauma disponible en toda emergencia pediátrica de III nivel, la monitorización temprana de la presión intracraneana y el monitoreo multimodal como métodos para mejorar los pronósticos. Se concluye que falta mucho por hacer, y más evidencia es necesaria pero más organización es necesaria en proveer recursos especializados en la atención de emergencia de estos pacientes.

Palabras clave: *Trauma Craneano. Concusión. Manejo. Niños. Adolescentes. Tratamiento.*

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Introduction

Traumatic brain injury (TBI) is the leading cause of death or severe disability in children; according to its severity, it increases susceptibility to functional deficits, cognitive impairment, and mental health problems[1].

Epidemiology

TBI is the most frequent cause of death and disability in children over 1 year of age. The mortality rate is higher in children under 4 years old compared to those aged 5-14 years[2]. The most common causes of TBI are falls in children under 14 years, followed by abuse in children under 2 years, and traffic accidents[3]. Up to 61% of children with moderate or severe head trauma will experience some degree of disability[2,4,5].

Definition and Classification

TBI is defined as injury to the structures of the head due to an external mechanical force, with or without interruption of structural continuity[2,3]. The most accepted classification based on severity uses the Glasgow Coma Scale (GCS), defining mild TBI as a GCS score of 14-15, moderate TBI as a GCS score of 9-13, and severe TBI as a GCS score below 8[4].

Several international guidelines have been published in recent years, but they may not necessarily apply in Latin America. In this regard, AINP (for its Spanish acronym) recently approved guidelines for the treatment of head trauma in children in our region.

Materials and methods

A systematic review was conducted using the PRISMA protocol (Fig. 1). Studies written in English or Spanish were selected. Animal studies and articles that did not meet the objectives of our study were excluded. Only studies on mild, moderate, or severe pediatric head trauma that included an analysis of TBIs in pediatric patients were included. Topics with the most substantial evidence were chosen to seek the best available information, and management results were analyzed to produce valid conclusions.

For this systematic literature review, the PubMed database was used. The search was conducted between January 1 and March 30, 2023. We used an advanced search strategy with the following terms: ("trauma" [Title/Abstract] AND "pediatric" [Title/Abstract] AND "management" [Title/Abstract]) OR ("traumatic brain injury" [Title/Abstract] AND "pediatric" [Title/Abstract]) OR ("head" [Title/Abstract] AND "pediatric" [Title/Abstract] AND "guides" [Title/Abstract]) OR ("injuries" [Title/Abstract] AND "pediatric" [Title/Abstract] AND "Recommendations" [Title/Abstract]).

Data extraction and analysis

The following information was collected from each article: author/year, methods, number of participants, and study design. Main results were also extracted, including outcome measures and the main limitations of each study. The primary and secondary objectives of the studies were analyzed, and the main conclusions of each study were collected.

The ROBINS-I tool was used to assess bias in observational studies. The selected articles on the management of TBI in pediatrics were re-analyzed according to the latest available scientific evidence and selected according to the 2011 version of Oxford Levels of Evidence.

Results

Due to its accessibility, rapid acquisition, and diagnostic performance, computed tomography (CT) of the skull is the imaging modality of choice for moderate and severe pediatric TBI.

Magnetic resonance imaging (MRI) is indicated when the clinical scenario remains unclear, when there is a clinical-radiological dissociation, after performing a CT, and in clinically stable children. It allows better identification of contusions and diffuses axonal injury.

Specialized guidelines, such as the Pediatric Emergency Care Applied Research Network, are used in mild trauma to select the population requiring emergency imaging and reduce radiation exposure.

Two systematic reviews with a recommendation grade A and evidence level 1a[6,7] and then "feasibility and accuracy of rapid MRI versus CT for TBI in young children"[8] and two retrospective studies[9] and "risk factors associated with TBI and application of guidelines for requesting CT after TBI in children in France"[10] have evidence level 1b.

Routine follow-up CT scans are not recommended unless there is evidence of increased intracranial pressure (ICP) or neurological deterioration. We found two systematic reviews of cohort studies with homogeneity, with evidence level 2a and a recommendation grade B[11,12].

Treatment of severe TBI

The following describes some aspects of managing severe TBI (Fig. 2).

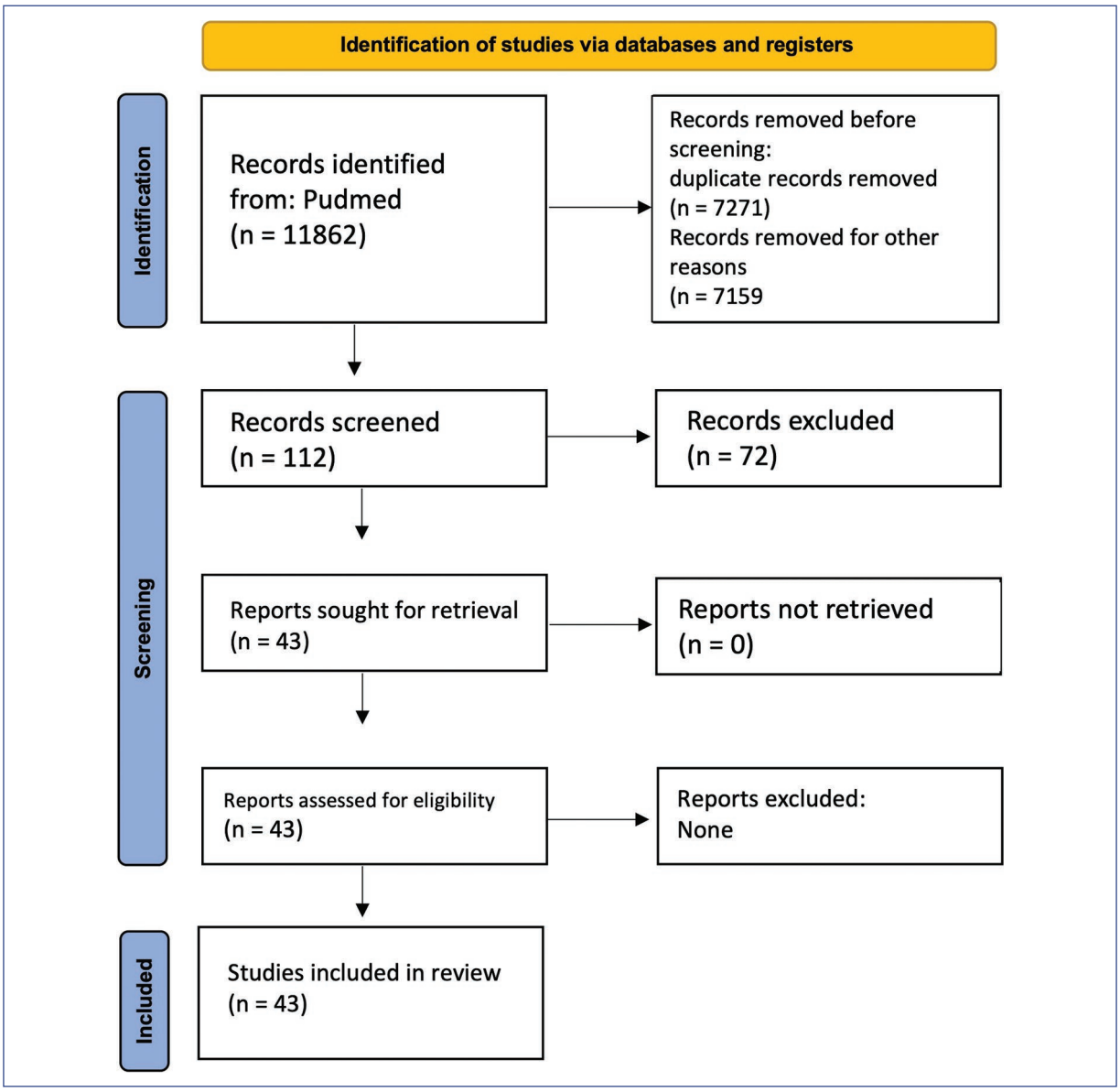

Figure 1. PRISMA flow diagram for a systematic review of pediatric traumatic brain injury management. Identification, screening, and inclusion process

Appropriate level of analgesia and sedation

The use of a combination of benzodiazepine and opioids is recommended for the initial management of TBI; the use of midazolam and morphine or fentanyl is suggested. We found a systematic review, "Management of severe pediatric TBI: 2019 consensus and guideline-based algorithm for the first and second tier therapies"[13] with evidence level 2a, and an article reflecting expert opinion, "Differences in medical therapy goals for children with severe TBI: an international study" with evidence level 5, but both with recommendation grade B.

Controlled mechanical ventilation

The suggested ventilatory goals are PaO2: 90-100 mmHg and PaCO2 between 35 and 40 mmHg. An article with evidence level 2a and recommendation grade B was found[13].

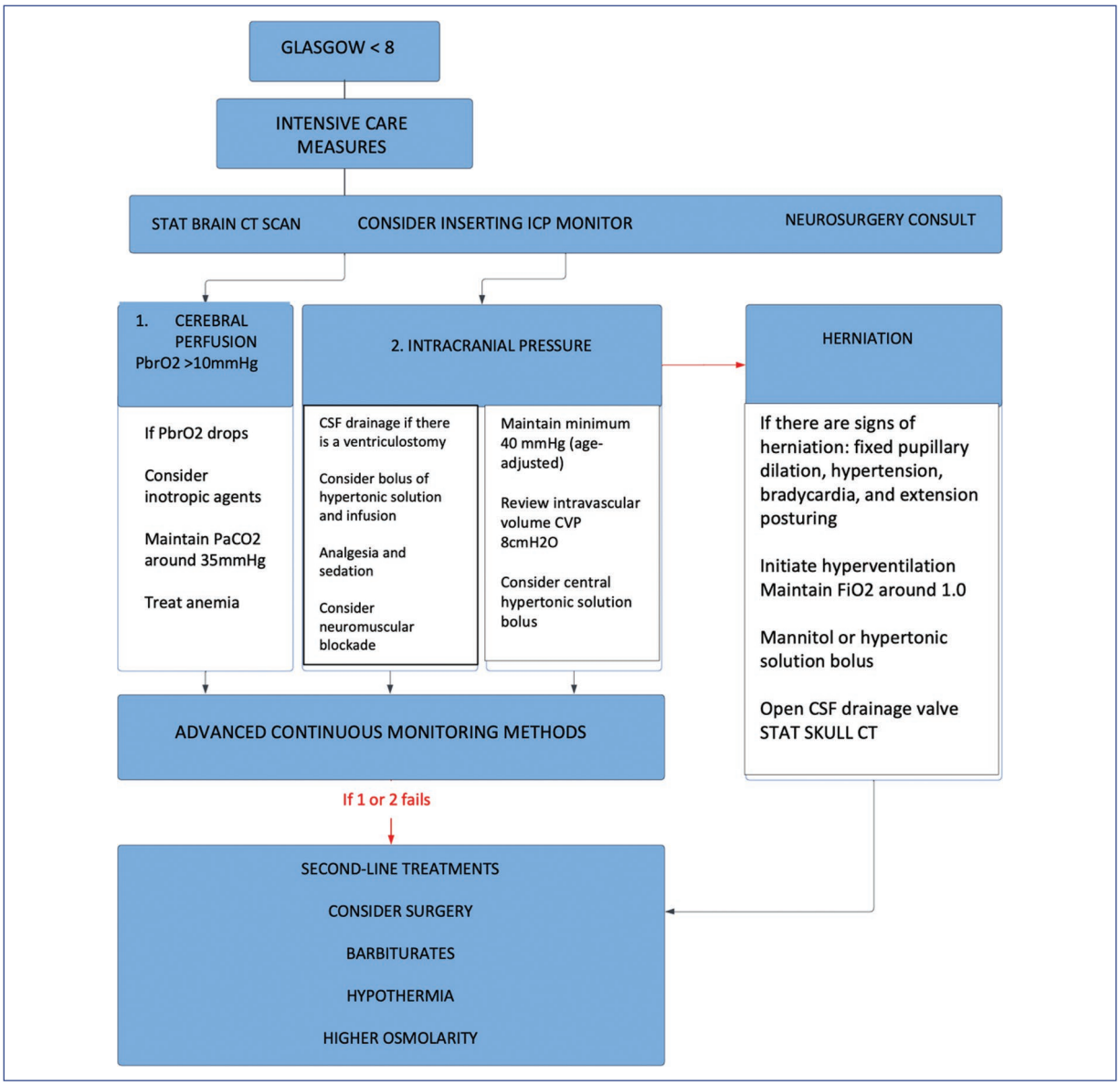

Figure 2. Treatment algorithm for pediatric traumatic brain injury.

Maintenance of normothermia and fever prevention

Post-traumatic temperature elevations have been shown to increase inflammatory processes, including elevation of pro-inflammatory cytokines and increased neutrophil accumulation in injured tissue. It is recommended to maintain normothermia with values above 35°C and below 38°C. We selected two systematic review studies of cohort studies with homogeneity, with evidence level 2a and recommendation grade B: severe TBI management: evidence-based medicine guideline[13-15].

Appropriate intravascular volume status

To address normovolemia, at least 75% of maintenance fluids and a neutral fluid balance are required, with a urine flow rate of more than 1 mL/kg/h. The use of 0.9% saline solution is recommended in the initial fluid prescription; to avoid the risk of hypoglycemia, the initial use of 5% dextrose in IV saline infusion is suggested in infant patients. Two systematic reviews of cohort studies with homogeneity represent the best evidence and have evidence level 2a and recommendation grade B[13,16].

Nutritional support

Early initiation of enteral nutritional support (within 72-h post-injury) is suggested to decrease mortality and improve outcomes. This recommendation is supported by a systematic review of homogeneous cohort studies: "Guidelines for the management of pediatric severe TBI, third edition: Update of the brain trauma foundation guidelines"[17] which have evidence level 2a and recommendation grade B.

Treatment with antiepileptic drugs and continuous EEG (cEEG) use

Prophylactic treatment is suggested to reduce the incidence of early post-traumatic seizures (within 7-day post-trauma), both clinical and subclinical. There is insufficient evidence to recommend levetiracetam over phenytoin based on efficacy for post-traumatic seizure prevention. The scientific basis comes from six systematic reviews of cohort studies with homogeneity: "Early use of antiseizure medication in mechanically ventilated TBI cases: A retrospective pediatric health information system database study"[18], "Antiepileptic prophylaxis for early or late post-traumatic seizures in children with TBI: A systematic review"[19], and "Severe TBI management: Evidence-based medicine guideline"[15] and three more by Kochanek mentioned above in the text. All have evidence level 2a and recommendation grade B[12,13,17].

cEEG use

Evidence supports its use throughout management, particularly when neuromuscular blockade is used. However, there is insufficient data to confirm that seizure treatment improves brain injury outcomes, as noted by the analysis of two systematic reviews of cohort studies with homogeneity with evidence level 2a and recommendation grade B, but also an expert opinion: "Consensus statement on cEEG in critically ill adults and children, part I: indications"[13,15,20].

ICP monitoring during severe TBI

ICP measurement is recommended to determine if there is intracranial hypertension (ICH). Since much of current care is based on preventing and treating elevated ICP, early detection of elevated ICP with monitoring is considered to allow timely administration and precise treatment titration compared to management without an ICP monitor. Certain studies support the association of successful control of ICH based on ICP monitoring with better survival and neurological outcomes.

We selected four systematic reviews of cohort studies with homogeneity with evidence level 2a, a propensity-weighted effectiveness analysis study with evidence level 2b, and a retrospective observational study: "Functional outcome after ICP monitoring in children with severe TBI"[12,13,15,17,21,22].

Advanced neuromonitoring

If brain tissue oxygen partial pressure ($PbrO_2$) monitoring is used, it is suggested to maintain a level > 10 mmHg. However, we do not have sufficient evidence to support a recommendation for the use of a brain interstitial PO_2 ($PbrO_2$) monitor to improve outcomes.

The use of advanced neuromonitoring should only be for patients without contraindications for invasive neuromonitoring, such as coagulopathy, and for patients who do not have a diagnosis of brain death.

A systematic review of cohort studies with homogeneity by Kochanek *et al.* provides evidence level 2a and a recommendation grade B[17].

Treatment thresholds

An ICP goal of < 20 mmHg is suggested to improve overall outcomes. Preventing ICH is important to avoid cerebral herniation events, which can trigger a cascade of often fatal sequelae.

A systematic review of cohort studies with homogeneity: "Guidelines for the management of pediatric severe TBI, third edition: Update of the brain trauma foundation guidelines"[17], a prospective observational study with evidence level 2b, "ICH and cerebral hypoperfusion in children with severe TBI: Thresholds and burden in accidental and abusive insults"[23], and a retrospective observational study, "Relationship of ICP and cerebral perfusion pressure (CPP) with outcome in young children after severe TBI"[24], with evidence level 3b and a recommendation grade B for all three.

CPP thresholds

Treatment should aim to keep the CPP at a minimum of 40 mmHg. The strongest evidence comes from a prospective observational cohort study with evidence level 1b and recommendation grade A, a systematic review of cohort studies showing homogeneity with evidence level 2a and recommendation grade B, a

prospective observational study with evidence level 2b and recommendation grade B, and a retrospective observational study with evidence level 3b and recommendation grade B[17,23-25].

Treatment of elevated ICP

Intervention is recommended when ICP rises to more than 20 mmHg for at least 5 min, whereas a gradual progression of interventions is warranted for an ICP elevation between 20 and 25 mmHg.

Hyperosmolar therapy

For ICP control, it is recommended to administer boluses or continuous infusion of 3% hypertonic saline solution. The recommended effective doses for the acute use of 3% hypertonic solution boluses range between 2 and 5 mL/kg over 10-20 min. Similarly, the suggested effective doses for continuous infusion of 3% saline solution range between 0.1 and 1.0 mL/kg body weight per hour. Administering the minimum dose necessary to maintain ICP below 20 mmHg is important. In cases of refractory ICP, a bolus of 23.4% hypertonic saline solution is recommended, with a suggested dose of 0.5 mL/kg and a maximum of 30 mL[26].

In the context of multiple ICP-related therapies, sustained serum sodium levels (> 72 h) above 170 mEq/l are suggested to prevent complications of thrombocytopenia and anemia, whereas sustained serum sodium levels above 160 mEq/l are suggested to prevent deep vein thrombosis[26].

Although mannitol is commonly used to treat elevated ICP in pediatric TBI, no studies were identified that met the inclusion criteria for its use as evidence for this topic. If used, mannitol should be administered as a bolus (0.5-1 g/kg) over 10 min, and blood pressure should be monitored, as arterial hypotension should be avoided.

Three systematic reviews of cohort studies with homogeneity were published by Kochanek, one by Carney: "Guidelines for the Management of Severe TBI, Fourth Edition" and one by Birrer: "Severe TBI management: Evidence-based medicine guideline" provide evidence level 2a, and a systematic review: "Current Management of Pediatric TBI" had evidence level 2b[12,13,15,17,27].

Three retrospective observational studies: "Hyperosmolar Therapy in Pediatric Traumatic Brain Injury: A Retrospective Study," "Hypertonic Saline in Pediatric Traumatic Brain Injury: A 9-Year Review of Experience with 23.4% Hypertonic Saline as Standard Hyperosmolar Therapy," "Clinical Indicators of Intensive Care Associated with Discharge Outcomes in Children with Severe Traumatic Brain Injury," one standard, one cohort, and one multicenter, and a systematic review indicated evidence level 2b, but all have recommendation grade B[26,28-30].

Analgesics, sedatives, and neuromuscular blockade for ICP control

In the treatment of ICH, if therapy is ineffective, additional analgesia and sedation should be considered, along with the possible initiation of neuromuscular blockade. It is suggested to avoid bolus administration of midazolam and/or fentanyl during ICP crises due to the risks of cerebral hypoperfusion. According to FDA recommendations, prolonged continuous infusion of propofol is not indicated for sedation or treatment of refractory ICH. In the absence of evidence, specific indications, choice, and dosage of analgesics, sedatives, and neuromuscular blockers should be left to the treating physician.

Three systematic review articles of cohort studies with homogeneity, a systematic review with evidence level 2a, a retrospective cohort study with evidence level 2b, a systematic review with evidence level 2b, and a prospective observational study with evidence level 2c provide the evidence supporting this grade B recommendation[12,13,15,17,26,31,32].

CSF drainage

External ventricular drainage can be used to measure ICP in children after TBI and may provide additional therapeutic benefits from CSF drainage. CSF drainage through an external ventricular drain is suggested to control increased ICP and improve outcomes in children with severe TBI. Refractory elevated ICP contributes to mortality; therefore, controlling elevated ICP is an important factor in patient survival after severe TBI.

Four systematic review studies of cohort studies with homogeneity, evidence level 2a, and a prospective observational study, evidence level 2c, provide these grade B recommendations[12,13,15,17,33].

Ventilation therapies

Severe prophylactic hyperventilation to a $PaCO_2$ < 30 mmHg is not recommended in the first 48 h after injury. If hyperventilation is used in the treatment of

refractory ICH, advanced neuromonitoring is suggested for the evaluation of cerebral ischemia. Three systematic review studies of cohort studies with homogeneity with evidence level 2a and a retrospective cohort study with evidence level 2b provide these grade B recommendations[12,13,17,34].

Second-line therapies

Temperature control/hypothermia

Prophylactic moderate hypothermia (32-33°C) is not recommended over normothermia for improving overall outcomes. The late application of moderate hypothermia during the second-tier management stage is used as an option to control refractory ICH. The target temperature is 32-33°C or 34-35°C. If hypothermia is used and rewarming is initiated, it should be performed at a rate of 0.5-1.0°C every 12-24 h or more slowly to avoid complications.

If phenytoin is used during hypothermia, it is suggested to monitor and adjust the dose to minimize toxicity, especially during the rewarming period.

A multicenter prospective randomized controlled phase II trial provides level 1b evidence and grade A recommendation, whereas five systematic reviews of cohort studies with homogeneity and a meta-analysis with evidence level 2a provide grade B recommendations[12,13,15,17,35-37].

Barbiturates

High-dose barbiturate treatment is suggested in hemodynamically stable patients with refractory ICH despite maximum medical and surgical treatment. Continuous blood pressure monitoring and cardiovascular support are required to maintain adequate CPP. If barbiturate infusion fails to control ICP, decompressive craniectomy or other second-tier therapies should be considered.

Four systematic reviews of cohort studies with homogeneity providing evidence level 2a, one systematic review and one retrospective cohort study with evidence level 2b provide the scientific basis for these grade B recommendations[12,13,15,17,26,38].

Decompressive craniectomy

Decompressive craniectomy is suggested to treat neurological deterioration, herniation, or ICH refractory to medical treatment. An extensive fronto-temporoparietal craniectomy (12 × 15 cm or 15 cm in diameter) is recommended over a smaller one. It is suggested that secondary decompressive craniectomy, performed as a treatment for early or late refractory ICP elevation, reduces ICP and the duration of intensive care, although the relationship between these effects and favorable outcomes is uncertain. The evidence for the benefit of this procedure is not entirely clear, and risks versus benefits should always be weighed.

Two prospective cohort studies with evidence level 1b and grade A recommendation, four systematic reviews of cohort studies with homogeneity, and one systematic review with evidence level 2a and grade B recommendation, a systematic review of "Current management of pediatric traumatic brain injury" with evidence level 2b and grade B recommendation, a retrospective descriptive study and a literature review with evidence level 4 and grade C recommendation, and an article reflecting expert opinion: "Long-term outcome after decompressive craniectomy: an uncomfortable truth?" were analyzed for these recommendations[12,13,15,17,26,39,40].

Corticosteroids

The use of corticosteroids is not suggested to improve outcomes or reduce ICP. For these recommendations, three studies by Kochanek and one by Birrer were taken as scientific bases, as systematic reviews of cohort studies with homogeneity, with evidence level 2a and grade B recommendation, and a systematic review by Raikot et al., with evidence level 2b and grade B recommendation[12,13,15-17].

Conclusions

The increase in scientific evidence regarding the treatment, prognosis, and follow-up of patients with severe pediatric TBI contributes to developing evidence-based recommendations for implementing reliable protocols that can be adapted to multiple settings. Although evidence is still insufficient, guidelines for severe pediatric TBI have been updated to include better treatment options.

Further future research is still required to confirm the efficacy of current recommendations in the pediatric age group to improve the prognosis of children who suffer severe cranial injury.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

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REVIEW ARTICLE

Types of statistical analysis in prognostic studies

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Abstract

Prognostic studies may have a descriptive exploratory objective on an outcome or a comparative objective in the search for factors associated with it. A second objective is explanatory to determine the effect of a particular prognostic factor adjusted for its confounders, with or without the intention of establishing causality. The third objective is the construction of a predictive prognostic scale. For each of these objectives, there are recommended statistical methods for clarification and validity. In this article, the methods and application examples are presented. The proper selection of analytical methods allows for clear and valid communication of the results of a prognostic study.

Keywords: *Statistical analysis. Prognosis. Validity.*

Tipos de análisis estadísticos en los estudios de pronóstico

Resumen

Los estudios pronósticos pueden tener un objetivo exploratorio descriptivo sobre un desenlace o comparativo en la búsqueda de factores asociados al mismo. Un segundo objetivo es explicativo para determinar el impacto de un factor pronóstico en particular ajustado a sus confusores con o sin la intención de establecer rutas causales. El tercero es la construcción de una escala pronóstica predictiva. Para cada uno de estos objetivos existen métodos estadísticos recomendados para su clarificación y validez, los cuales fueron revisados en una publicación previa. En este artículo presentamos los métodos y ejemplos de aplicación. La adecuada selección de los métodos analíticos permite una comunicación clara y válida de los resultados de un estudio pronóstico.

Palabras clave: *Análisis estadístico. Pronóstico. Validez.*

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Introduction

Prognostic studies analyze the potential consequences of suffering from a disease and can be classified according to three general objectives: exploratory, explanatory, or predictive[1]. Exploratory studies aim to establish the probability of occurrence of relevant outcome(s) in the studied patients. For explanatory studies, the intention is to validate the independent effect of a particular factor of interest on the outcome(s), adjusted for known confounding factors. Studies with the third objective aim to construct a prognostic prediction scale, as precise as possible, based on patient data[1-4]. Each purpose requires a distinct methodology to obtain valid and useful data for reliable statistical analysis[1]. During the reading, review, or execution of a prognostic study, it is common to find readers with doubts about the recommended statistical procedures according to the objectives mentioned above. This review analyzes the recommended statistical strategies for data analysis for the different prognostic objectives.

Prognostic studies with exploratory purpose

In this type of study, the analysis can be conducted in a descriptive or comparative manner (Fig. 1). Descriptive analysis aims to report the frequency and proportion (or percentage) of patients who developed the outcome under study (e.g., mortality or a sequela). For this information, the patient follow-up method must be considered. If all patients had the same follow-up time (e.g., 24 h), it is only necessary to present the cumulative incidence of the outcome(s). For example, in a study on the prognosis of intubation in patients with severe asthma attacks, one can report that 20% of individuals admitted to the emergency room ended up receiving ventilation assistance within 24 h after admission. In this analysis, it is feasible to report on several outcomes (e.g., fatality or ventilator-associated pneumonia, among others). If, in addition, one wishes to consider the rate at which the outcome occurs, it can be reported as an incidence rate (events per person-time). For the first option, actuarial tables are used; for the second, survival tables and Kaplan–Meier curves are adequate (Table 1 and Fig. 2)[5].

If one also wishes to establish whether any factor present at the beginning of the clinical course follow-up (initial cohort) could explain the different outcome(s), the first approach is to observe the proportion of subjects with this factor among those who did or did not present the studied outcome(s). In the case that the follow-up time is the same for all patients, it is sufficient to compare their cumulative incidence rates using a test of difference in proportions (for example, the Chi-square test) or the 95% confidence intervals (CI) of the differences in proportions (if the interval includes the value "0", it is not statistically conclusive)[6].

Table 1. Actuarial and survival table of the need for orotracheal intubation in patients with asthmatic crisis (fictitious data of n=135 persons)

Actuarial analysis			
Timing	**Intubated (n)**	**% Events in the period**	**% Cumulative survival**
Admission	0	0	100
6 h	5	3.7 (5/135)	96.3
12 h	6	4.7 (6/130) 17.7	91.8
18 h	22	(22/124)	75.5
24 h	12	11.7 (12/102)	66.7
30 h	6	6.7 (6/90)	62.2
36 h	2	2.4 (2/84)	60.7
42 h	3	3.6 (3/82)	58.5
48 h	1	1.2 (1/81)	57.8
Person-time survival analysis			
Admission	0	0	100
2 h	1	0.7 (1/135)	93
3 h	5	3.7 (5/134)	89.6
6 h	(1 lost)	-	89.6
9 h	3	2.3 (3/133)	87.5
19 h	5 (1 lost)	3.1 (4/130)	84.8
22 h	10	8 (10/125)	78
25 h	2	1.7 (2/115)	76.7
30 h	(1 lost)	-	76.7
39 h	1	0.8 (1/114)	76.1
41 h	15	13.3 (15/113)	65.9
48 h	3	2.7 (3/110)	64.2

The percentage of events is the number of events presented in the period among patients not yet intubated. The probability of not being intubated is the product of the probability of remaining without intubation in the previous period and the probability of remaining without being intubated in the analysis period. In the actuarial table, the periods are fixed; in the survival table, it is recorded when at least one event occurs or if the follow-up of at least one patient is lost.

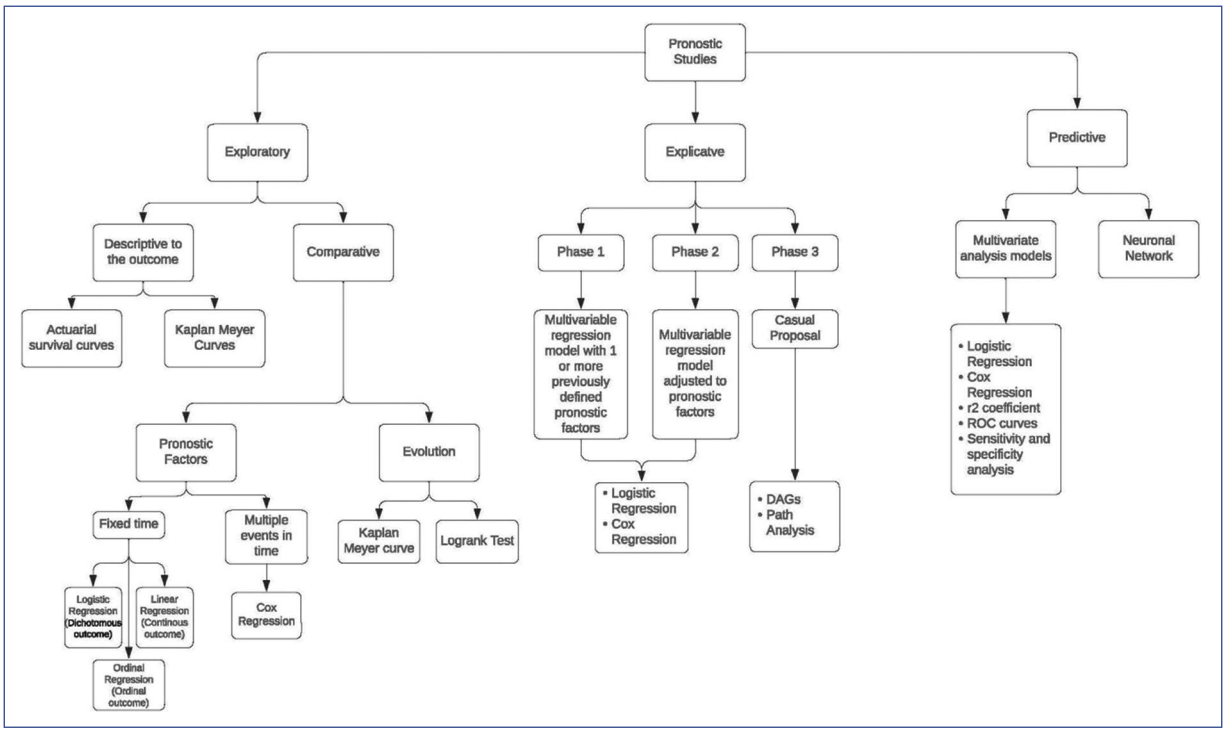

Figure 1. Diagram of recommended statistical methods according to the objective of the prognostic study.

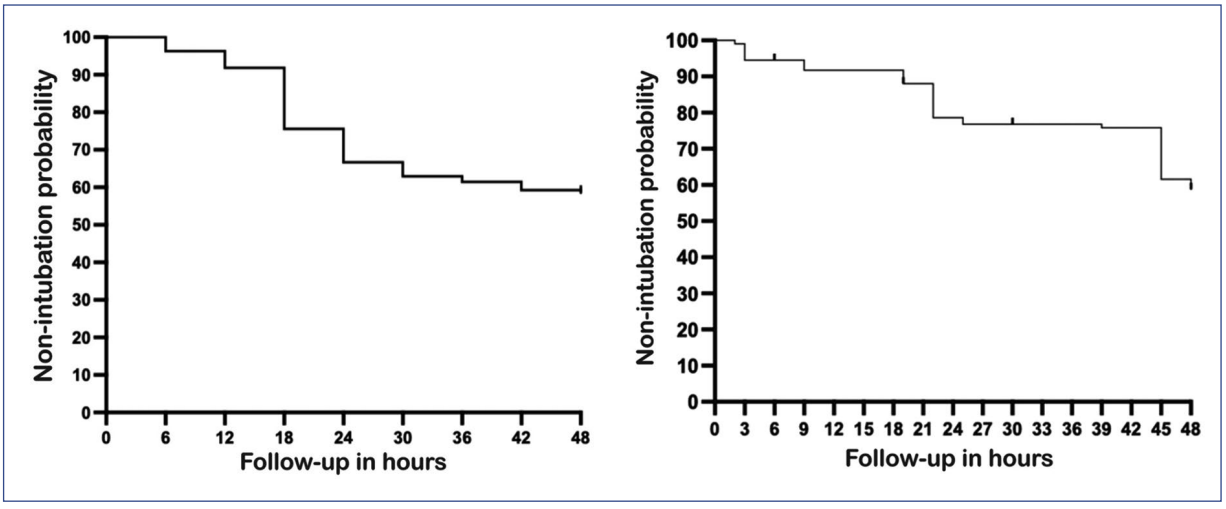

Figure 2. Actuarial curves with fixed analysis times (equal intervals) versus the Kaplan–Meier survival curve where it decreases in the presence of at least one event in the real follow-up time, the vertical mark indicates the censoring of at least one patient (loss to follow-up without presenting the event). The presented data are fictitious and obtained from table 2.

Another approach involves comparing the velocities of outcomes between patients with and without the factor. The test of choice is the "log-rank test"[5,7]. For example, the median intubation-free survival was 12 h for patients with atopy, compared to 20 h for those without atopy (mean difference of –8 h, 95% CI from –12 to –6 h, log-rank test p = 0.001, data calculated as an example).

A severe problem in bivariate comparisons (groups with and without the prognostic factors to be evaluated) is that, in some cases, statistically significant differences can be found due to multiple possible comparisons. This is due to the increased risk of committing a type I error (bias due to "multiple comparisons")[8]. These models assume the possibility of knowing how much a factor influences the outcome, considering the partial effect of others (adjustment), that is, how much the factor influences independently of another or others. The correct way to jointly analyze several factors to establish which one(s) are associated with the outcome and review which one(s) are more influential is through multivariable regression models[9,10]. The choice of model will depend on how the outcome variable was measured and the form of follow-up (at fixed or continuous times), as well as verifying compliance with a series of statistical assumptions necessary to establish its validity (Table 2)[9,10]. For outcomes with fixed times, the most used regression models are binary logistic (dichotomous outcome: presence or absence of the outcome), multiple linear (quantitative outcome: days of hospitalization), or ordinal (hierarchical qualitative outcome: mild, moderate, and severe damage)[10].

The interpretation is based on the beta coefficients of each model. In logistic and ordinal regression, the exponential of beta or odds ratio (OR) is used. They are from zero to infinity and the null value is "1", the further away from 1 the greater association. If the CI does not include it, it will be significant at the established level (90, 95, or 99%) (Table 2a). In multiple linear regression, the comparison is made with the values of the standardized beta coefficients, which eliminates the original unit of measurement and allows for comparability of the effect of each factor. In this model, the null hypothesis of no association is the existence of a standardized coefficient with a value of "0". The further it deviates ($-\infty$ or $+\infty$), the greater the impact it will have on the prognosis. If the X% CI includes the value of "0," the result will not be significant at the established level, or there will be no association[11,12] (Table 2b).

In these models, as for the multivariable linear model, the following assumptions are considered: linearity between predictors and outcome, homoscedasticity, normality and independence of residuals, and multicollinearity or high correlation among predictor factors. In logistic regression, it is mainly concerned with avoiding multicollinearity and independence in individual exposure to factors. When linearity does not exist, scale transformation options or stepwise analyses may be employed to facilitate the analysis, although it is recommended to consult with a statistical expert to avoid losing clinical significance. Multicollinearity is the second major problem in multivariable analysis; to avoid it, we recommend carefully reviewing the factors to be considered, and when there is a high correlation among some of them, consider including in the model only the factor with better measurement, greater validity, stronger association with the outcome, and less loss or absence in its capture.

When the outcome is a proportion adjusted for the time of presentation, the recommended model is Cox regression[13,14]. This model assumes that the risk(s) are always continuous and proportional (proportional hazards assumption), so the beta coefficient is presented as a hazard ratio (HR). It is also necessary to meet the assumptions of the absence of multicollinearity, linearity in the predictor variables with the logarithm of the outcome rate, and the absence of outliers. The interpretation of an HR is similar to that of an OR, that is, how many times more or less likely the presence of the complication is when exposed to a factor compared to not being exposed to it (Table 2c)[12-14]. In all the above models, researchers should report on statistically significant factors and highlight those with more extreme values concerning the null value. Other multivariable regression models are not mentioned here; interested readers are advised to consult statistical professionals.

Prognostic studies with explanatory purpose

As mentioned earlier, the objective is to validate the impact of a prognostic factor of interest controlled by its possible confounders. It should be remembered that a confounding factor is one known to be causal of the outcome of interest but associated with the prognostic factor under study without being part of the pathophysiological pathway by which the factor under study explains the outcome. In this analysis, it is also recommended to perform a multivariable regression with the same specifications mentioned previously. The main difference is that only the prognostic factor of interest and its confounders should be included in the model, not just any factor. It is important to select confounders adequately because as they increase, it will be necessary to expand the sample size[11,15,16].

Table 2. Prognostic factors associated with relapse of urticaria syndrome (fictitious data)

a) Example of logistic regression analysis, risk of relapse 1 month after resolution			
Factors	**OR (Exponent of beta)**	**(95% CI, lower-upper limit)**	**p-value***
History of allergy	3.5	(2.1 a 4.3)	0.001
Use of antihistamines	0.4	(0.35 a 0.6)	0.02
Female sex	1.2	(0.8 a 1.6)	0.83
Age under 18 years	2.1	(0.3 a 5.2)	0.45
Nutritional status Obesity Overweight Adequate weight	 1.9 1.4 reference	 (0.7 a 2.2) (0.9 a 3.1)	 0.55 0.67

Associated factors are a history of allergy and use of antihistamines, the former with a greater risk impact and the latter with a moderate protective or preventive effect. *Wald statistical test. Null value = 1.

b) Example of linear regression analysis, risk of lesion persistence, number of days			
Factors	**Standardized beta**	**(95% CI of standardized betas)**	**p-value***
History of allergy	1.2	(0.9 to 1.4)	0.002
Use of antihistamines	–0.6	(–0.3 to–0.8)	0.031
Female sex	0.03	(–0.8 to 1.8)	0.83
Age under 18 years	0.01	(–0.3 to 0.5)	0.51
BMI	0.03	(–0.02 to 0.02)	0.87

Associated factors are: history of allergy and use of antihistamines, the former with a greater positive association (having the history means more days of persistence), and the latter with a moderate reducing (inverse) effect on the days. *Student's t-test. Null value = 0.

c) Example of Cox regression analysis, continuous risk of relapse			
Factors	**Hazard ratio**	**(95% CI, lower-upper limit)**	**p-value***
History of allergy	3.3	(2 a 4.2)	0.002
Use of antihistamines	0.39	(0.31 a 0.6)	0.02
Female sex	1.02	(0.75 a 1.7)	0.83
Age under 18 years	2.2	(0.31 a 5.2)	0.46
Nutritional status Obesity Overweight Adequate weight	 1.8 1.3 reference	 (0.7 a 2.3) (0.8 a 3.2)	 0.57 0.69

Associated factors are a history of allergy and use of antihistamines, the former with a greater risk impact, and the latter with a moderate protective or preventive effect. *Wald statistical test. Null value = 1. CI: Confidence intervals; OR: Odds ratio; BMI: Body mass index.

We suggest including the most involved, prevalent, better-measured confounders, with the potential to be modifiable in the future and the easiest to obtain[4]. In the final analysis report, the association estimator between the studied prognostic factor (relative risk, OR, HR, or standardized beta) and the outcome (e.g., relapse rate) should be shown, indicating the confounding factors to which the association was adjusted. It does not make sense to report on the estimators of the confounders since these were not adjusted for their own confounders and, therefore, they do not have explanatory value. If the factor of interest is removed, the study loses its objective. An example of a report is presented in table 3.

A proposed phase for this purpose is the causal network[4]. In this model, the factor under study and its outcome are not only adjusted for confounders analyzed but also antecedent and modifying factors are

Table 3. Prognostic factors associated with relapse of urticaria syndrome (fictitious data)

a) Example of logistic regression analysis. History of allergy as a prognostic factor for relapse 1 month after resolution			
Factors	**OR (exponent of beta)**	**(95% CI, lower-upper limit)**	**p-value***
History of allergy	3.5	(2.1 a 4.3)	0.001

Adjusted for use of antihistamines, sex, age, and nutritional status

b) Example of linear regression analysis. Effect of history of allergy as a prognostic factor for the duration of lesion persistence in number of days			
Factors	**Standardized beta**	**(95% CI of standardized betas)**	**p-value****
History of allergy	1.2	(0.9 a 1.4)	0.002

Adjusted for use of antihistamines, sex, age, and nutritional status.

c) Example of Cox regression analysis. History of allergy as a prognostic factor for continuous risk of relapse			
Factors	**Hazard ratio**	**(95% CI, lower-upper limit)**	**p-value***
History of allergy	3.3	(2 a 4.2)	0.002

Adjusted for use of antihistamines, sex, age, and nutritional status.
*Wald statistical test, p-value.
**T statistical test, p-value.
CI: Confidence intervals; OR: odds ratio

also added. Directed acyclic graphs models and path analysis have been proposed for its presentation[3,4]. Given their limited use in clinical medicine, readers are invited to consult specific sources[4].

Prognostic studies with predictive purpose

These models are created to generate diagnostic and prognostic scales. In general, it is recommended to analyze these models in three phases: construction, internal validation, and external validation. In this review, we will only refer to their internal validation. For validation, two main types of analysis are primarily used: multivariable regression models and neural network models. In the former, modeling with regression analysis again depends on the type of dependent variable. The difference lies in the construction of the model. The objective of the selected model is based on one that is (1) more predictive, (2) parsimonious, (3) simple to apply, and (4) universal[9,11,16,17].

To validate a predictive model based on multivariate regression, it is necessary to consider a large sample size, generally ten patients for each factor to be considered. Once the sample is available, the analysis is executed with a statistical computer program. Regardless of the program used, it will request a dependent variable (the outcome of interest) and the introduction of independent variables or covariates. The objective of the analysis is to find an equation that allows obtaining (predicted) values as close as possible to those observed in patients (real). If this approximation is excellent, it will generally be excellent for patients with similar conditions who did not participate in the equation validation study (external validity). The prediction can be in terms of the probability of an outcome, time to an event, time to an outcome, and level of severity, among others. The method of selecting the most predictive variables of the outcome is based on the amount of variation explained by the equation. The most used estimator to address this situation is the coefficient of determination or R^2 (pseudo R^2 for logistic regression). The R^2 coefficient ranges from zero, which predicts nothing, to one, which implies a perfect prediction. To find the variables that will generate the most predictive equation, computers use three methods: forward, backward, or stepwise (Fig. 3 and Table 4). In the first method, all proposed variables are reviewed, and the most significant in its association with the outcome is selected (for example, the smallest "p" value). Next, the second most significant is sought, and if a significant change in R^2 is found, a third most associated factor is added. This process is repeated until no significant improvement in R^2 is observed, indicating a lack of predictive gain with more factors (Table 4a). The second method performs the procedure in the opposite way. It begins by introducing all the factors considered and calculating R^2. Then, it eliminates non-significant (associated) factors one by one and reviews the R^2 coefficient, which does not reduce the prediction. When removing a factor causes R^2 to decrease, the program stops subtracting factors, and the remaining ones are those that

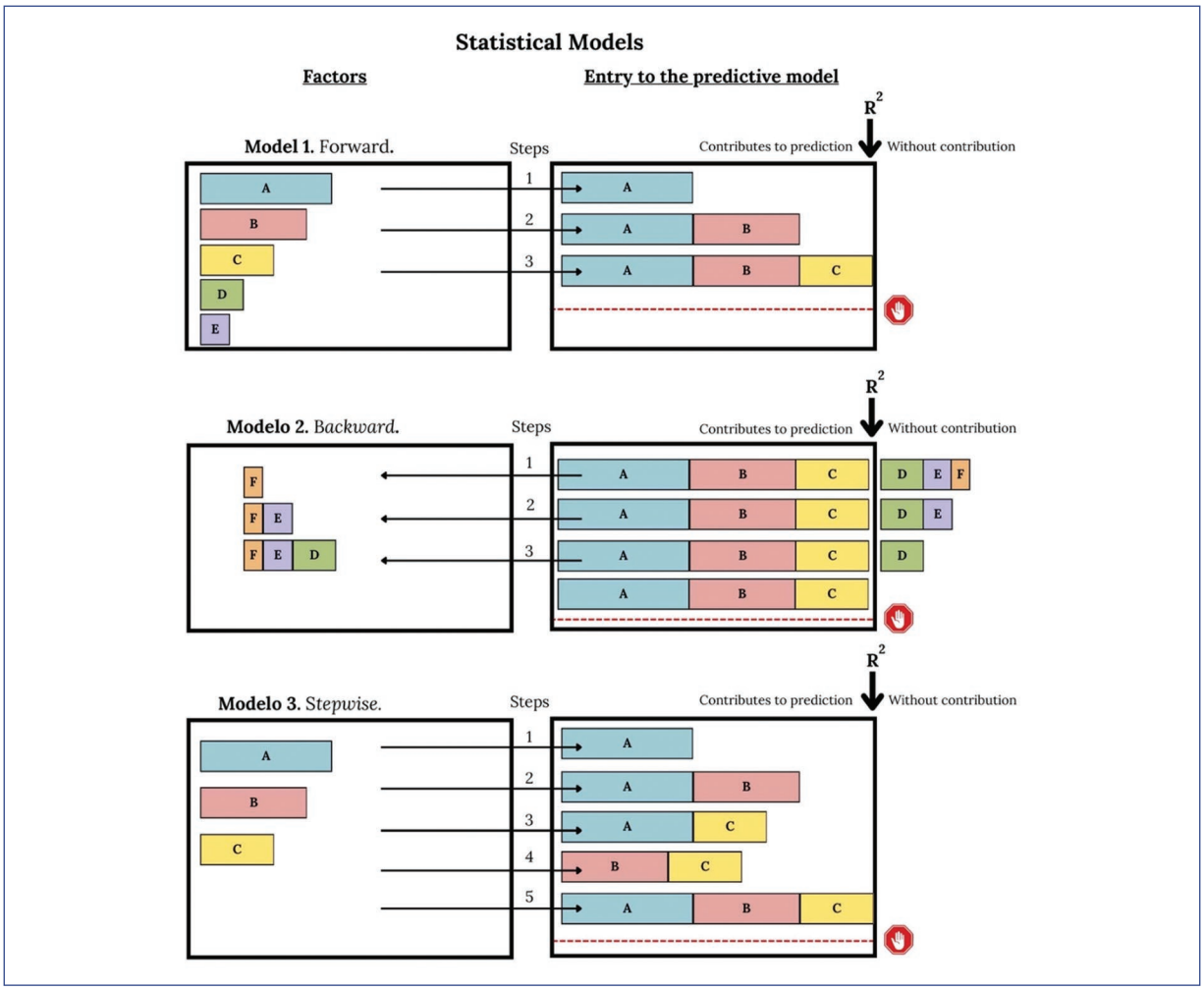

Figure 3. Statistical modeling options to obtain the most precise prediction model. The squares represent prognostic variables and their size indicates the level of association with the prognostic variable. The R^2 value informs about the maximum prediction range.

provide the greatest prediction (Table 4b). The third method (stepwise) is the most recommended. The selection is based on conducting trials of incorporating and removing factors in search of the combination with the highest coefficient of determination, that is, the most predictive (Table 4c).

In prognostic scales where the outcome is quantitative (for example, days of hospital stay or years of survival), it is only necessary to establish the best prediction equation. However, if the outcome variable is qualitative (for example, cure), the programs determine the probability of the event as present if the constructed equation gives a score of 0.5 or more (50% or more). It is possible to improve the interpretation of diagnostic and prognostic validity by estimating its highest sensitivity and specificity by constructing a receiver operating characteristic curve and its area under the curve (Fig. 4). It is also feasible to determine the degree of discrimination of the prediction equation through specific analyses[18]. Alongside the validation of the most predictive model, it is necessary to consider other criteria. Parsimony refers to the model that has fewer included factors. In general, a model with more factors considered allows for better prediction. However, its use can become complicated if more than ten are included, given the difficulty in memorizing them or the lack of availability of information on some occasions. If a model with fewer factors does not significantly reduce the prediction by more than 10%, it will be more recommendable. Simplicity refers to having factors that can be determined or measured with unsophisticated methods in terms of cost, time, and execution. Universality implies that the factors can be determined or measured with unsophisticated

Table 4. Predictive models of allergic dermatitis at 1 year of life in neonates with intolerance to breast milk according to model types (fictitious data n = 416)

a) Example of logistic regression analysis. Forward model			
Factors	**beta**	**p-value***	**Pseudo-R^{2}****
Model 1			
Birth weight (g)	0.004	< 0.001	0.57
Constant	10.8	< 0.001	
Model 2			0.59
Family atopy	2.01	0.002	
Birth weight (g)	–0.004	< 0.001	
Constant	10.8	< 0.001	
Model 3			
Vaccination reaction	1.67	0.016	0.61
Family atopy	2.1	0.001	
Birth weight (g)	–0.004	< 0.001	
Constant	10.7	< 0.001	
b) Example of logistic regression analysis. Backward model			
Factors	**Beta**	**p-value***	**Pseudo-R^{2}****
Model 1			
Birth weight (g)	–0.004	< 0.001	0.609
Family atopy	1.9	0.004	
Vaccination reaction	1.56	0.027	
Iron intake	0.024	0.51	
Calcium intake	0.01	0.53	
Constant	10.8	< 0.001	
Model 2			
Birth weight (g)	1.2	< 0.001	0.608
Family atopy	2.01	0.003	
Vaccination reaction	1.57	0.025	
Iron intake	0.25	0.61	
Constant	9.8	< 0.001	
Model 3			0.83
Birth weight (g)	–0.004	< 0.001	
Family atopy	2.11	0.001	
Vaccination reaction	1.7	0.16	
Constant	10.8	< 0.001	
c) Example of logistic regression analysis. Stepwise model			
Factors	**beta**	**p-value***	**Pseudo-R^{2}****
Final model (3 steps)			
Birth weight (g)	–0.004	< 0.001	0.607
Family atopy	2.12	0.001	
Vaccination reaction	1.7	0.016	
Constant	10.8	< 0.001	

Prognostic factors considered were birth weight, family atopy, vaccination reaction, iron intake, and calcium intake.
*Wald statistical test, *p-value. **Pseudo-R^{2} of Nagelkerke.

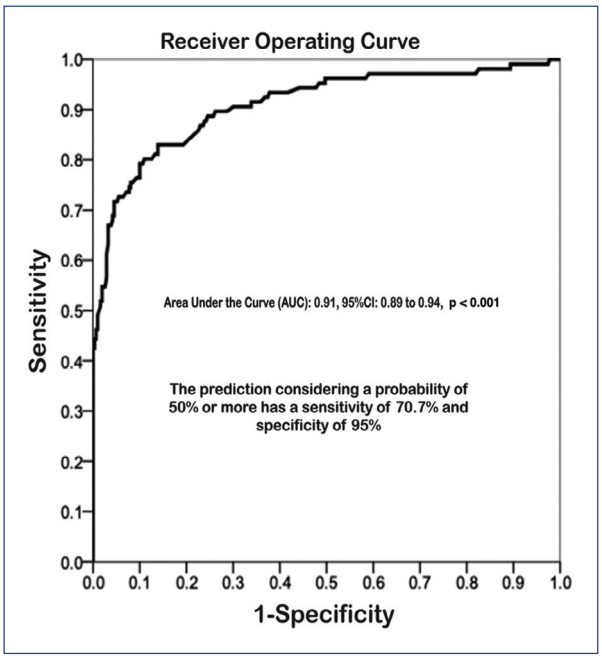

Figure 4. Receiver operating characteristic curve of predictive validity of equation obtained in the analysis of table 4c.

methods in terms of cost, time, and execution, which will allow their application in different settings.

Finally, neural network models are based on learning algorithms to obtain the best predictions. Computer systems functions such as the human mind, receiving information continuously, and determining the pathways that facilitate the approach to a result or "output" with layers or connection capacity. These models are gaining much acceptability due to their high level of prediction[19-20]. However, they work as "black boxes," where the connections and functions related to this prediction are unknown, and they are not exempt from methodological biases[21]. To develop them, it is necessary to have the support of specialists in the field, and their validation never ends, given that the more information, the better the prediction. On the other hand, they are not exempt from the criteria mentioned above for simplicity and availability of information.

Conclusion

The recommended statistical analyses in prognostic studies vary according to their objective. These analyses can be merely descriptive, comparative, exploratory, explanatory, or prediction models. The most used methods are multivariable regressions, which are executed and reported according to the objective of the prognostic study. We always recommend seeking advice from a professional in the corresponding area and a statistician to achieve the proposed objective and communicate the results more efficiently.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

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RESEARCH ARTICLE

Overall manifestations and survival of pediatric patients with Langerhans cell histiocytosis. A middle-income country (mic) national multicenter study

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Abstract

Background: *Langerhans cell histiocytosis (LCH) is a rare neoplastic disease characterized by clonal proliferation of dendritic cells. It is Mexico's ninth most frequent malignancy in patients under 18 years of age. The aim of the study was to determine the clinical characteristics, treatment, and survival of Mexican pediatric patients diagnosed with LCH treated from January 2010 to December 2018.* **Methods:** *We conducted a retrospective study of LCH using data from 19 accredited hospitals throughout the Mexican Republic. Patients < 18 years who were diagnosed with LCH between January 2010 and December 2018 were included (253 patients) in the study.* **Results:** *All patients had a histopathological diagnosis, and extension studies were performed at their treatment centers. The median age at diagnosis was 19 months. The most frequently*

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affected sites included the bone (178 cases; 70%) and the skin (131 cases; 51.7%). Of the patients in Group 1, 48 (42%) had bone marrow involvement, 62 (53%) had splenomegaly, and 39 (34.8%) had liver involvement. Of the patients who underwent chemotherapy treatment, 61.2% exhibited a complete response, and 36 patients (14.2%) relapsed after complete remission. The most frequent sites of relapse were the skin, bone, lymph nodes, and liver. The overall survival rate was 91.3% and was lower for patients in Group 1 (77%) compared with those in Groups 2 (97%) and 3 (100%), p = 0.001. **Conclusion:** *The current report aims to demonstrate the findings of a multicenter study conducted on Mexican children with LCH; consequently, these treatment results for a relatively infrequent disease merit further research.*

Keywords: *Langerhans cell histiocytosis. Mexico. Children.*

Manifestaciones clínicas generales y supervivencia de pacientes pediátricos con histiocitosis de células de Langerhans. Un estudio nacional multicéntrico en un país de medianos ingresos (mic)

Resumen

Introducción: *La histiocitosis de células de Langerhans (HCL) es una enfermedad neoplásica rara, caracterizada por una proliferación clonal de células dendríticas. Constituye la novena neoplasia maligna más frecuente en México en menores de 18 años. El objetivo de este estudio fue conocer las características clínicas, tratamiento y supervivencia de pacientes pediátricos con diagnóstico de HCL atendidos desde enero de 2010 a diciembre de 2018.* **Métodos:** *Se realizó un estudio retrospectivo de HCL en 19 hospitales acreditados en toda la República Mexicana. Se incluyeron pacientes menores de 18 años diagnosticados de HCL entre enero de 2010 y diciembre de 2018.* **Resultados***: Todos los pacientes tuvieron diagnóstico histopatológico y se les realizaron estudios de extensión en sus centros de tratamiento. Se incluyeron en el estudio 253 pacientes con HCL. La mediana de edad en el momento del diagnóstico fue de 19 meses. Los sitios de afectación más frecuentes fueron hueso en 178 (70%) y piel en 131 (51,7%). De los pacientes del grupo 1,48 (42%) tenían afectación a médula ósea, 62 (53%) esplenomegalia y 39 (34,8%) afectación hepática. De los pacientes que recibieron tratamiento de quimioterapia, 61.2% tuvo respuesta completa y 36 pacientes (14,2%) tuvieron recaída de la enfermedad después de haber entrado en remisión completa. Los sitios de recaída más frecuentes fueron la piel, huesos, ganglios linfáticos e hígado. La supervivencia global fue del 91,3% y fue menor para los pacientes del grupo de riesgo 1 (77%) en comparación con los de grupos de riesgo 2 (97%) y 3 (100%) con p = 0.001.* **Conclusión:** *El fin del presente informe es demostrar los hallazgos de un estudio multicéntrico realizado en niños mexicanos con HCL; en consecuencia, los resultados del tratamiento de una enfermedad relativamente infrecuente merecen más investigación, especialmente en términos de tratamiento.*

Palabras clave: *Histiocitosis de células de Langerhans. México. Niños.*

Introduction

Histiocytic disorders (HDs) are diverse diseases derived from myeloid progenitors of monocytic, histiocytic, and dendritic lines. According to the current classification, these disorders can be divided into C, H, L, M, and R groups. Langerhans cell histiocytosis (LCH) belongs to the L group, which also includes Erdheim-Chester disease (ECD), indeterminate cell histiocytosis, and mixed HDs (ECD-LCH)[1,2]. In Mexico, the incidence of HDs is 4.3 cases per million children under 18 years of age[3].

The clinical presentation of LCH is heterogeneous, ranging from single lesions to the involvement of multiple organs, including the liver, spleen, and bone marrow. Similar findings have been noted in different countries[4-6].

The Histiocyte Society has observed in its studies that the administration of vinblastine and prednisone confers a survival rate of up to 99% in patients without at-risk organs; the survival rate falls to 84% in patients with liver, spleen, and/or bone marrow involvement[7]. Other studies have demonstrated the usefulness of other drugs, such as cytarabine, and the importance of prolonged treatments of up to 12 months[8,9].

The $BRAF^{V600]E}$ somatic mutation was recently described in up to 57% of patients with LCH[10,11]. This mutation has been linked to greater involvement in organs at risk (88%), more significant reactivation at 5 years (43% vs. 28%), and increased resistance to chemotherapy (22% vs. 3%)[12,13]. The disease relapses frequently, so new treatment strategies are constantly being explored based on drugs such as cladribine, clofarabine, bisphosphonates, vemurafenib, and dabrafenib[14-21].

Since 2010, treatment for children with LCH in Mexico has been based on the provisions of the LCH III protocol of the Histiocyte Society and the National Technical Protocols of the National Council for the Prevention and Treatment of Cancer in Childhood and Adolescence[22].

This study evaluated pediatric patients' clinical characteristics, treatment, and survival across 19 hospitals accredited for caring for children with cancer in Mexico. This investigation focused on diagnoses between January 2010 and December 2018.

Table 1. Treatment protocol in children with LCH in Mexico

Induction If there is a complete response at the end of the first induction, maintenance is performed; if there is not, another 6 weeks are given.	Vinblastine 6 mg/m^2 IV weekly for 6 or 12 weeks Prednisone 40 mg/m^2 oral for 6-12 weeks
Maintenance Low risk - 25 weeks High risk - 52 weeks	Vinblastine 6 mg/m^2 IV every 3 weeks Prednisone 40 mg/m^2 oral for 5 days, every 3 weeks

Methods

An observational retrospective study was conducted in hospitals accredited for treating children with cancer. All centers throughout Mexico were invited to participate, of which nineteen hospitals accepted this invitation. All patients included were newly diagnosed with LCH, under 18 years of age, and diagnosed between 2010 and 2018. The patients' diagnoses were based on histopathology and immunohistochemistry and, in some cases, electron microscopy (6.3%). Extension studies were performed at the patients' treatment centers. All participants were classified according to a clinical group: (1) Group 1 presented involvement of at-risk organs (liver, spleen, and bone marrow); (2) Group 2 did not exhibit at-risk organ involvement; and (3) Group 3 exhibited involvement of the central nervous system and spinal cord. We collected information regarding initial clinical manifestations, affected sites, laboratory studies at diagnosis, histopathology studies, relapse or progression, survival, and mortality. Since 2010, most institutions in Mexico have followed the national protocol based on the Histiocyte Society's LCH III described in table 1: Patients in Group 1 are given a 12-month course of chemotherapy, and patients in Groups 2 and 3 receive 6 months of chemotherapy. The patients were followed up at the discretion of each center.

Relapse was defined as disease reactivation after a documented complete response, defined as the disappearance of all metabolic activity in the evaluation after treatment through imaging studies.

Since this study was retrospective, our sample was determined by convenience; patients registered at each center during the study period were included.

Patients whose records contained at least 80% of the required information were included in the study.

Statistical analysis

We performed univariate analysis using central-tendency tests to better understand the characteristics of the patient sample and to establish how each variable was distributed. We calculated means and standard deviations for continuous numerical variables with normal distributions. We calculated the median and either the minimum or maximum value for variables that were not normally distributed. In the case of qualitative variables, we calculated frequencies and proportions.

The frequencies among the risk groups were determined using X^2, Fisher's exact, and Kruskal–Wallis tests according to the type of variable and its distribution. We presumed that $p < 0.05$ indicated statistical significance. We also used a Cox proportional hazard model with mortality as the event. Overall and event-free survival was analyzed using the Kaplan–Meier method, and a log-rank test was used to assess whether there were significant differences between the groups.

Results

Clinical features

From January 2010 through December 2018, 253 patients with LCH were diagnosed at the 19 participating institutions (Table 2). The median age at diagnosis was 19 months. Patients in Group 1 had a mean age at diagnosis of 15 months (range 0.75-120 months), patients in Group 2 had a mean age at diagnosis of 25.5 months (range 0.62-192 months), and patients in Group 3 had a mean age at diagnosis of 28 months (range 0.2-180 months) ($p = 0.0001$). The male-female ratio of the total cohort was 1.3:1. The most frequently affected sites were the bone (178 cases; 70%) and the

Table 2. Age and reference hospital

Variable	Group 1 (n = 112)	Group 2 (n = 71)	Group 3 (n = 70)
Age (years)	Median (min-max) 1.2 (0.06-10)	Median (min-max) 2.12 (0.05-16)	Median (min-max) 2.3 (0.01-15)
Reference hospital	**n (%)**	**n (%)**	**n (%)**
Instituto Nacional de Pediatría	23 (20.5)	21 (29.5)	6 (8.57)
Hospital Infantil Teletón de oncología	1 (0.89)	4 (5.6)	2 (2.85)
Centro Médico Nacional 20 de noviembre	2 (1.78)	6 (8.4)	4 (5.71)
Hospital Ángeles del Pedregal	1 (0.89)	1 (1.40)	0 (0)
Centro Estatal de Oncología de Campeche	2 (1.78)	3 (4.22)	1 (1.42)
CECAN, Veracruz	7 (6.25)	2 (2.81)	3 (4.28)
Hospital General de Celaya	1 (0.89)	2 (2.81)	1 (1.42)
Hospital para el niño del IMIEM	24 (21.4)	2 (2.81)	4 (5.71)
Hospital Materno Infantil del ISSEMyM	2 (1.78)	2 (2.81)	3 (4.28)
Hospital General de México	2 (1.78)	2 (2.81)	0 (0)
Hospital General de León	5 (4.46)	1 (1.40)	2 (2.85)
Hospital General "Dr. Agustín O'Horán"	8 (7.14)	9 (12.6)	7 (10)
Hospital para el Niño Poblano	2 (1.78)	2 (2.81)	0 (0)
Hospital del Niño "Federico Gómez Santos," Saltillo	2 (1.78)	0 (0)	0 (0)
HNRNP Tabasco	3 (2.67)	0 (0)	2 (2.85)
Hospital Infantil de Morelia	2 (1.78)	1 (1.40)	3 (4.28)
Hospital Infantil de México	22 (19.6)	9 (12.6)	26 (37.14)
Hospital Juárez de México	0 (0)	1 (1.40)	3 (4.28)
Hospital Universitario UANL	3 (2.67)	3 (4.22)	3 (4.28)

skin (131; 51.7%). Table 3 lists the primary clinical manifestations at diagnosis.

The most frequent sites of bone involvement were the skull (127; 50.1%), spine (32; 12.6%), femur (28; 11%), pelvis (14; 5.5%), and humerus (11; 4.3%).

The most frequently positive immunohistochemistry markers for diagnosis included CD1a (199; 78.6%), S100 (166; 65.6%), CD207 (71; 28%), CD68 (41; 16.2%), and Birbeck granules, determined by electron microscopy (16; 6.3%).

Pulmonary involvement was observed in 13 patients (11.6%) in Group 1 and 5 patients (7%) in Group 2, mainly presenting as alveolar infiltrate in 16 cases (8.7%), bullae in one case (0.54%), and bronchiectasis in one case (0.54%).

Forty-eight patients (42%) in Group 1 had bone marrow involvement, 62 (53%) had splenomegaly, and 39 (34.8%) had liver involvement. The values of hemoglobin, leukocytes, and platelets at diagnosis were statistically significantly different among the patient groups. Platelet levels (median 204,000 cells/μL) and hemoglobin (median 7.6 g/dL) were lower in patients in Group 1 ($p = 0.0001$).

Treatment

Two hundred and thirty-five patients (92.5%) received treatment according to the national protocol based on the LCH III protocol with 6 mg/m² vinblastine and 40 mg/m² prednisone for 6 or 12 months, depending on the risk group. Ten patients (3.9%) received first-line treatment with vincristine (1.5 mg/m²), cytarabine (100 mg/m²), and prednisone (20 mg/m²). Six patients (2.3%) received the LCH II protocol, three patients

Table 3. Clinical characteristics by group in patients with LCH according to the risk group at diagnosis

Variable	Group 1 Frequency (%) (n = 112)	Group 2 Frequency (%) (n = 71)	Group 3 Frequency (%) (n = 70)	p-value
Gender				
Male	58 (0.51)	47 (0.66)	40 (0.57)	0.15
Female	54 (0.48)	24 (0.33)	30 (0.42)	
Clinical manifestations				
Skin lesions	69 (0.61)	42 (0.59)	19 (0.27)	0.000
Adenopathy	76 (0.67)	33 (0.46)	18 (0.25)	0.000
Diabetes Insipidus	14 (0.12)	10 (0.14)	12 (0.17)	0.68
Lung involvement	16 (0.14)	5 (0.07)	0 (-)	0.003
Bone lesions	66 (0.58)	56 (0.8)	55 (0.78)	0.002
Otitis	15 (0.13)	10 (0.14)	1 (0.01)	0.016
Weight loss	24 (0.21)	6 (0.08)	3 (0.04)	0.002
Proptosis	7 (0.06)	12 (0.17)	7 (0.10)	0.07
General symptoms	65 (0.58)	20 (0.28)	15 (0.21)	0.000
Tumor	1 (0.009)	2 (0.02)	0 (-)	0.28
Retinal gliosis	0 (-)	1 (0.01)	0 (-)	0.27
Medullary Syndrome	0 (-)	0 (-)	1 (0.01)	0.26
Pain	0 (-)	2 (0.02)	1 (0.01)	0.22
Vasculitis	1 (0.008)	0 (-)	0 (-)	0.53
Diarrhea	0 (-)	1 (0.01)	0 (-)	0.27
Gingival hyperplasia	1 (0.008)	0 (-)	0 (-)	0.53
Hematopoietic condition	89 (0.79)	0 (-)	0 (-)	0.000

Test statistic = X^2.

(1.1%) received treatment with etoposide 100 mg/m² as a single drug, and five patients (1.9%) underwent surgical treatment only. Three patients (1.1%) received no treatment.

Of the patients who underwent chemotherapy, 61.2% had a complete response with the first induction; this rate increased to 87% after the second induction treatment. Nineteen patients (7.9%) had no response or experienced disease progression after the second induction; they switched to a second-line of treatment. That treatment included cytarabine (100 mg/m²), prednisone (40 mg/m²) or cladribine (5 mg/m²), and cytarabine 100 mg/m² (Table 4).

Relapse

Thirty-six patients (14.2%) experienced disease relapse after presenting complete remission. The most frequent sites of relapse included the skin, bone, lymph nodes, and liver (Table 5). The second-line treatments consisted of several combinations: (1) cytarabine, vincristine, and steroids in 14 cases (38.8%); (2) vinblastine and prednisone in 11 cases (30.5%); (3) clofarabine in one case (2.7%); (4) cladribine in four cases (11.1%); (5) etoposide and cytarabine in five cases (13.8%); and (6) no treatment in one case (2.7%).

Twenty-two patients (8.6%) died. The causes of death included refractory disease in six patients (27.2%), septic shock in 10 patients (45.4%), infection in two patients (9%), hematological alteration in one patient (4.5%), pneumonia in one patient (4.5%), and intracranial hemorrhage in one patient (4.5%).

The overall survival rate was 91.3%, and it was lower for patients in Group 1 (77%) compared with patients in Groups 2 (97%) and 3 (100%) (p = 0.001; Fig. 1). Event-free survival was 66% for patients in Group 1, 74% for patients in Group 2, and 93% for patients in Group 3 (p = 0.0012; Fig. 2).

The mortality risk of each independent variable was analyzed by calculating the hazard ratios (HR) with a 95% confidence interval (CI); statistically significant differences were incorporated into a broad multivariate Cox proportional hazard model. We then used the stepwise backward method to reduce those differences until the best-fit model was obtained (log-likelihood = –25.94, X^2 (3) = 33.83, p = 0.000). Finally, the reduced model was verified using tests and diagnostics for a proportional hazard model with p = 0.10. In this model, variables associated with mortality included an age under 1 year (HR 5.037, p = 0.001), splenomegaly (HR 6.494, p = 0.000), and refractory disease (HR = 2.80, p = 0.005) tables 6 and 7.

Table 4. Treatment response, relapse and deaths by groups

Variable	Group 1 Frequency (%) (n = 112)	Group 2 Frequency (%) (n = 71)	Group 3 Frequency (%) (n = 70)	p-value
1st induction	109	65	66	
Complete response	40 (0.35)	41 (0.57)	53 (0.75)	0.000
Very Good partial	36 (0.32)	14 (0.19)	10 (0.14)	0.016
Partial	11 (0.09)	12 (0.16)	6 (0.08)	0.25
No response	12 (0.10)	4 (0.05)	1 (0.01)	0.03
Progression	12 (0.10)	0 (-)	0 (-)	0.00
2nd induction				
Complete response	84 (0.75)	61 (0.86)	64 (0.91)	0.012
Very good partial	13 (0.11)	4 (0.05)	2 (0.028)	0.092
Partial	2 (0.017)	1 (0.014)	0 (-)	0.791
No response	6 (0.05)	1 (0.014)	3 (0.02)	0.391
Progression	4 (0.035)	3 (0.042)	2 (0.028)	1.0
Relapse	23 (20.5)	10 (14.1)	3 (4.28)	0.009
Death	19 (16.9)	2 (2.81)	1 (1.42)	0.000

Test statistics: Fisher×s exact test.

Table 5. Relapse sites in patients with LCH according to the group

Variable	Group 1 Frequency (%) (n = 112)	Group 2 Frequency (%) (n = 71)	Group 3 Frequency (%) (n = 70)	p-value
Skin	3 (0.02)	2 (0.02)	3 (0.04)	0.900
Bone	10 (0.08)	8 (0.11)	0 (-)	0.007
Lymph nodes	5 (0.04)	0 (-)	1 (0.01)	0.14
Liver	3 (0.02)	1 (0.01)	4 (0.05)	0.38
Spleen	2 (0.01)	1 (0.01)	2 (0.02)	0.73
Lung	1 (0.008)	0 (-)	1 (0.01)	0.75
Middle ear	1 (0.008)	0 (-)	0 (-)	1.0
Orbit	1 (0.008)	0 (-)	1 (0.01)	0.75
Pituitary gland	0 (-)	1 (0.01)	0 (-)	1.0
Bone marrow	0 (-)	1 (0.01)	0 (-)	1.0

Test statistic: Fisher×s exact test; LCH: langerhans cell histiocytosis.

The primary factors associated with mortality included belonging to Group 1 (HR 8.23; 95% CI 2.4-27.9; p = 0.001) and the involvement of the skin, bone, liver, spleen, or bone marrow.

Discussion

LCH is a rare disease; its incidence in Mexico is similar to that reported in other countries. The aberrant differentiation of mononuclear cells through the mitogen-activated protein kinase pathway characterizes LCH and conditions its activation[23].

We have reported the results of the largest Mexican cohort to date (253 patients) diagnosed with LCH over 8 years at 19 institutions. Roughly half of the patients (44%) had high-risk organ disease. Patients in this group exhibited a survival rate of 77%, similar to that

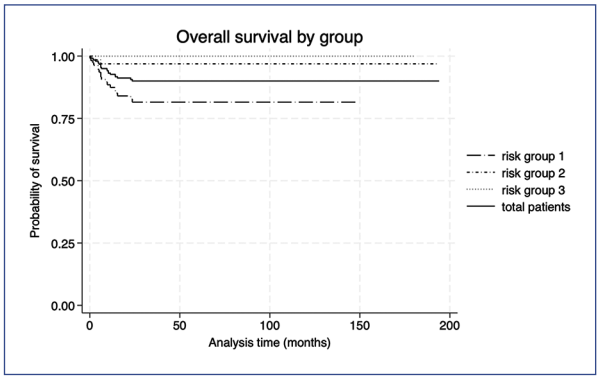

Figure 1. Global overall survival and by risk group. (2010-2018) n = 253.

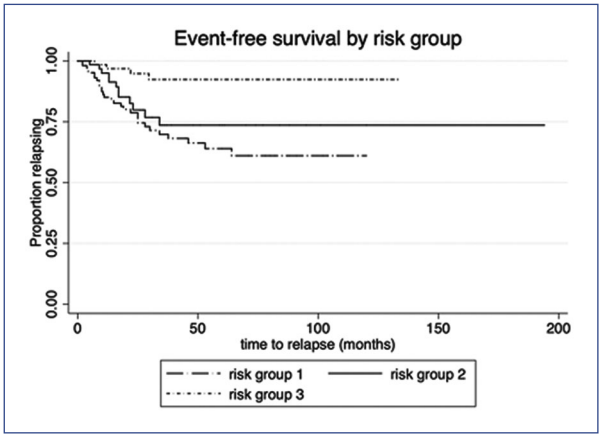

Figure 2. Event-free survival by risk group (2010-2018) n = 253.

Table 6. Cox proportional hazards model for mortality in pediatric patients with LCH in Mexico (2010-2018) n = 253

Variable	HR (IC95%)	p-value
Sex (female)	1.041 (0.43-2.47)	0.92
Risk Group		
Risk group 1	11.985 (2.78-51.66)	0.001
Risk group 2	0.292 (0.06-1.25)	0.09
Relapse	2.119 (0.85-5.25)	0.10
Clinical manifestations		
General symptoms	1.709 (0.72-4.02)	0.22
Dermatitis	4.160 (1.39-12.36)	0.010
Lymphadenopathy	2.088 (0.84-5.17)	0.11
Diabetes insipidus	1.382 (0.46-4.10)	0.56
Lung disorders	2.584 (0.86-7.67)	0.08
Otitis	1.586 (0.46-5.39)	0.46
Proptosis	1.066 (0.24-4.58)	0.93
Splenomegaly	6.821 (2.75-16.9)	0.000
Bone marrow infiltration	4.669 (1.98-10.99)	0.000
Bone lesions	0.246 (0.10-59.4)	0.002
Laboratory studies		
Hyperbilirubinemia	6.780 (2.73-16.83)	0.000
Hypoproteinemia	6.712 (2.59-17.37)	0.000
Hypoalbuminemia	4.466 (1.80-11.07)	0.001
Hemoglobin (mg/dL)	0.734 (0.62-0.86)	0.000
Leukocytes	0.983 (0.91-1.06)	0.66
Platelets	0.993 (0.990-0.996)	0.000

HR: hazard ratios.

Table 7. Reduced COX model

Variable	HR (IC95%)	p-value
Age < 1 year	5.037 (1.90 a 13.31)	0.001*
Splenomegaly	6.494 (2.48 a 16.96)	0.000*
Refractory disease	2.802 (1.00 a 7.84)	0.050*

Log likelihood: –90.17; X^2 (3): 33.87; p = 0.000*; HR: hazard ratios.

reported internationally (1 year of overall survival up to 99%)[7-24].

Validated risk-stratification criteria for children include disease sites and responses to initial therapy. Patients with lesions in "risk organs," including the bone marrow, spleen, or liver (Group 1), have a significantly higher risk of mortality than patients with lesions limited to "non-risk" sites (7). Risk stratification for LCH is based on the analysis of outcomes of prospective pediatric trials. Patients with high-risk LCH exhibit a survival rate of almost 90%. Still, outcomes are significantly worse if the disease progresses during the 1st 12 weeks of therapy[8].

In patients without risk organ involvement, the survival rate has been reported to be 98.2%, with a relapse rate of 26% for patients in Group 2[25]. We noted similar results in our population.

Gene alterations, such as the $BRAF^{V600E}$ mutation, have been shown in recent years to be a factor associated with high-risk characteristics, in addition to relapses and disease refractoriness[26]. However, it is not possible to routinely test for gene alterations in our population; this fact is a limitation of our study.

In general, the treatment received by our patients is recommended by the Histiocyte Society based on vinblastine and prednisone, which has been the standard treatment used internationally[27]. The treatment duration is 12 months for patients with risk organ disease and 6 months for those without organ disease. The primary second-line treatments used in patients with relapsed or refractory disease include cytarabine, etoposide,

steroids, and other drugs[28,29]. The LCH-IV study is one of the largest LCH trials to date; the Histiocyte Society is currently carrying it out. This prospective multi-arm study will evaluate first- and second-line treatments and include patient follow-up[30]. There is no question that multisystem/multifocal bone involvement constitutes a recurring problem[31]. Our patients could access drugs, such as cladribine, which is currently recognized as yielding adequate outcomes.

Single bone lesions are effectively treated with limited curettage or corticosteroid injections[32]. Large pelvic or vertebral lesions not amenable to curettage may be treated with radiation therapy. Our patients were offered a similar chemotherapy regimen as children in Group 1 who relapsed. Recently, indomethacin has been considered an alternative for bone LCH[33].

Besides our inability to detect BRAF V600E, another limitation of this retrospective study was that the histopathological study and follow-ups were performed according to the protocols of each center.

Conclusion

This study represents the first effort in Mexico to conduct a national analysis of LCH. We observed that LCH is a pathology characterized by relatively homogeneous patient care across Mexico. It has been reported that survival is acceptable; however, the frequency of recurrence is still high. Therefore, increased access to second-line drugs with limited toxicity is necessary. The challenge now is to access BRAF V600E testing so that patients can benefit from effective targeted therapies and form a cooperative group that involves most institutions.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

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ARTÍCULO DE INVESTIGACIÓN

Calidad de vida y agotamiento: niños y adolescentes en tratamiento oncológico

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Resumen

Introducción: *El cáncer infantil es una enfermedad compleja que requiere intervenciones interdisciplinarias. Este estudio busca describir la calidad de vida y el agotamiento en niños diagnosticados con cáncer, utilizando instrumentos validados que reflejan las peculiaridades de esta enfermedad.* **Método:** *Se llevó a cabo un estudio observacional analítico en niños y adolescentes de 2 a 18 años con cáncer. Se emplearon el PedsQL Cancer Module y el FACIT-F para evaluar calidad de vida y fatiga, respectivamente, analizando estadísticamente para identificar correlaciones y desarrollar un modelo explicativo.* **Resultados:** *Se identificaron síntomas físicos y psicológicos notables como náuseas, fatiga, hiporexia, irritabilidad y tristeza. Los instrumentos PedsQL Cancer Module y FACIT-F indicaron una calidad de vida disminuida. Hubo una alta concordancia entre las percepciones de niños y padres, excepto en la ansiedad por procedimientos, donde los niños reportaron mayores niveles. Estos síntomas reflejan el impacto del tratamiento oncológico, en el bienestar de los niños. La concordancia en las evaluaciones sugiere que los padres comprenden bien estas experiencias, destacando la pertinencia de intervenciones psicosociales que mejoren la calidad de vida a partir de una adecuada red de apoyo.* **Conclusiones:** *Es crucial que el tratamiento del cáncer pediátrico aborde no solo aspectos médicos, sino también el apoyo integral al bienestar emocional y psicosocial de los pacientes y sus familias.*

Palabras clave: *Calidad de vida. Fatiga. Pediátrico. Cáncer.*

Quality of life and burnout: children and adolescents in cancer treatment

Abstract

Background: *Pediatric cancer is a complex disease that requires interdisciplinary interventions. This study aims to describe the quality of life and exhaustion levels in children diagnosed with cancer, using validated instruments that reflect the peculiarities of this disease.* **Method:** *An observational analytical study was conducted on children and adolescents aged 2 to 18 years with cancer. The PedsQL Cancer Module and FACIT-F instruments were used to assess quality of life and fatigue, respectively, with statistical analysis performed to identify correlations and develop an explanatory model.* **Results:** *Notable physical and psychological symptoms such as nausea, fatigue, hyporexia, irritability, and sadness were identified. The PedsQL and FACIT-F indicated a diminished quality of life. There was high concordance between the perceptions of children and*

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their parents, except in the anxiety related to procedures, where children reported higher levels. These symptoms reflect the impact of cancer treatment on children's well-being. The concordance in evaluations suggests that parents have a good understanding of these experiences, highlighting the relevance of psychosocial interventions to improve quality of life through an adequate support network. **Conclusions:** *It is crucial that pediatric cancer treatment addresses not only medical aspects but also the comprehensive support for the emotional and psychosocial well-being of the patients and their families.*

Keywords: *Quality of life. Fatigue. Pediatrics. Cancer.*

Introducción

El mundo identifica el cáncer infantil como una de las principales causas de mortalidad en niños y adolescentes. Para países desarrollados se reporta que más del 80% de los niños afectados por la patología se recuperan; sin embargo, para aquellos países en vía de desarrollo la tasa de curación se acerca al 20%[1]. Los países en vía de desarrollo registran bajas tasas de supervivencia, que se asocian con las limitaciones para obtener un diagnóstico preciso y la baja accesibilidad a los tratamientos. De hecho, estar en dicho contexto aumenta la probabilidad de abandono al tratamiento, muerte por toxicidad y recidivas, relacionándose con las restricciones para acceder a los medicamentos y tecnologías[1].

En Colombia, la Cuenta de Alto Costo (CAC) del año 2021 reportó a 7,801 menores de 18 años con algún tipo de cáncer, con mayor incidencia de leucemia linfoide aguda, tumores del sistema nervioso central y los linfomas no Hodgkin. Las regiones de Colombia con mayor mortalidad fueron Bogotá 50.4, Amazonía 34.1, Central 28.22, Pacífico 24.85, Oriental 22.92 y Caribe 20.7 (cifras del 2021) por cada millón de habitantes menores de 18 años; encontrándose un aumento de 1,583 casos nuevos de cáncer comparado con las cifras del año 2018[2], donde se reportó una incidencia de 6,218 menores diagnosticados con cáncer, representando un incremento del 20.3% de diagnósticos con esta enfermedad.

Un diagnóstico correcto es vital para tratar a los niños, porque cada cáncer requiere un régimen terapéutico concreto que puede incluir cirugía, radioterapia o quimioterapia[3]. Cuando el cáncer es detectado en la fase inicial y de forma temprana, la probabilidad de responder favorablemente al tratamiento es más alta, y secundario a esto, también se aumenta la tasa de supervivencia que si se identifica en fases tardías. Al ser instaurada la terapia de manera temprana, los esquemas pueden ser de baja intensidad y por ello se logra mitigar algunos efectos y manifestaciones clínicas.

El diagnóstico de cáncer en un niño es una situación que impacta y modifica la estructura y dinámica familiar, debido a las implicaciones que reviste la gravedad de la patología, los efectos del tratamiento y la probabilidad latente de morir[4]. Los cambios físicos y las molestias en niños con cáncer son ampliamente descritas, entre las que se encuentra el dolor, el miedo, la angustia y la desesperanza, entre otras muchas.

Los niños que se enfrentan a un tratamiento contra el cáncer deben experimentar síntomas y molestias que alteran sus actividades diarias y la vida misma, situación que impacta a los padres y hermanos. Es necesario que el equipo de salud tenga la capacidad de evaluar la presencia de síntomas y molestias, para poderlas controlar y de esa manera desplegar intervenciones que favorezcan la resiliencia, calidad de vida y el afrontamiento de la enfermedad[5].

La calidad de vida relacionada con la salud (CVRS) y la fatiga se aceptan como mediciones desde la perspectiva del sujeto que experimenta la enfermedad, como indicadores esenciales en la evaluación de resultados que supera medidas tradicionales como la morbimortalidad y la expectativa de vida. Es muy importante tener datos del desenlace de la enfermedad en cada fase de esta que contemplen la percepción del paciente y permitan develar los deseos y motivaciones en el proceso de la toma de decisiones y la percepción del sujeto en la calidad de la asistencia sanitaria.

Teniendo presentes las implicaciones del cáncer tanto para el niño como para la familia es necesario hablar de la CVRS, medida que permite a los cuidadores valorar el impacto que genera la enfermedad y los tratamientos derivados de esta sobre el ámbito físico, psicológico y social[6]. La medición del impacto de las intervenciones sobre la salud de los sujetos ya no requiere únicamente la elaboración de indicadores tradicionales, por lo que se hace necesario medir variables asociadas que permitan establecer de forma integral el impacto de la enfermedad y el tratamiento, así como la orientación de los esfuerzos terapéuticos.

Desde esta perspectiva, para los programas hospitalarios que ofrecen tratamiento y seguimiento a los niños con cáncer es primordial comprender cómo la CVRS se comporta en cada fase de la enfermedad y en cada circunstancia que se desprende de esta. Por esta razón, la implementación de escalas validadas para el seguimiento de indicadores complejos como la calidad de vida y de evaluaciones funcionales de enfermedades crónicas es esencial en los escenarios de cuidado directo y programas de seguimiento. En la región se cuenta con resultados de investigación en los que se ha empleado la escala PedsQL Cancer Module™ (Inventario Pediátrico de Calidad de Vida Módulo Cáncer)[7] y FACIT-F Peds (*Functional Assessment of Chronic Illness Therapy,* Evaluación funcional de la terapia de enfermedades crónicas o agotamiento)[8], que han orientado la toma de decisiones en entornos clínicos y de seguimiento de pacientes en el campo de la consulta externa. Por ello, este trabajo se enfocó en describir cómo se comporta la calidad de vida en los niños con cáncer y cómo la perciben los padres de estos, de igual manera se exploró el nivel de fatiga percibido por los niños, lo que permitió un análisis respecto al cansancio y niveles de energía percibidos.

Método

Se desarrolló un estudio observacional analítico de una cohorte de niños y adolescentes con edades de 2 a 18 años durante el periodo de estudio con un muestreo por conveniencia, que tuvieran diagnóstico de algún tipo de cáncer y que se encontraran en alguna fase del tratamiento de dicha patología. Se definió desde el protocolo que serían excluidos aquellos pacientes con diagnóstico de cáncer que no tuvieran instaurado tratamiento o que se encontrarán en estado crítico, o que los padres no contarán con habilidades de lectoescritura.

La recolección de datos se realizó mediante el registro de variables sociodemográficas y variables clínicas individuales. Además, se aplicaron los instrumentos PedsQL Cancer Module™[7] y FACIT-F Peds tanto en los pacientes incluidos como en sus padres o cuidadores.

El primer instrumento es un producto derivado del PedsQL Versión 3.0 - español (Colombia), diseñado para la evaluación genérica de la calidad de vida autorreportada por niños que enfrentan la enfermedad, así como la calidad de vida informada por los padres en el contexto colombiano[7]. Esta escala abarca 27 ítems distribuidos en ocho dominios que evalúan diversas dimensiones vinculadas con la calidad de vida, presentando adaptaciones en su diseño según la edad de los pacientes. Para este estudio se contó con la firma de un acuerdo de utilización y se recibieron instrucciones de uso y gestión de los datos según el manual de los autores. Los dominios que contempla PedsQL Cancer Module™ son los siguientes:

- Dolor y molestia (2 ítems).
- Náuseas (5 ítems).
- Ansiedad frente a los procedimientos (3 ítems).
- Ansiedad frente a los tratamientos (3 ítems).
- Preocupaciones (3 ítems).
- Problemas cognitivos (5 ítems).
- Apariencia física percibida (3 ítems).
- Comunicación (3 ítems).

Cada uno de los ocho dominios, integra diferentes preguntas que pretenden indagar por la presencia de dichas manifestaciones en los últimos 30 días y en la última semana. El rango de posibles respuestas varía desde 0 «nunca ha sido un problema» hasta 4 «casi siempre ha sido un problema». Se emplea una escala Likert de 5 puntos, que varía desde 0 (nunca) hasta 4 (casi siempre), a excepción de los informes de niños de 5 a 7 años, quienes utilizan una escala Likert de 3 puntos (0 = nunca, 2 = a veces, 4 = casi siempre), la cual se combina con un apoyo visual representado por expresiones faciales (0 = cara feliz, 2 = cara neutral, 4 = cara triste). Cada puntuación individual en los ítems se invierte y luego se transforma de manera lineal en una escala de 0 a 100 (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Las puntuaciones superiores reflejan una mayor calidad de vida en relación con la salud[7].

Adicionalmente, se aplicó el cuestionario FACIT-F Peds, el cual evalúa otras enfermedades y afecciones crónicas. Este es un instrumento diseñado para evaluar la sensación de fatiga en niños y adolescentes de 8 a 18 años durante los últimos siete días. Incluye 13 ítems de tipo Likert que evalúan dos dimensiones. La puntuación para la dimensión de cansancio varía de 0 a 44, mientras que la dimensión de energía se evalúa en una escala de 0 a 8. También esta escala permite generar un *score* global, donde unas puntuaciones más elevadas señalan una menor sensación de fatiga diaria[8,9]. La aplicación de los cuestionarios se realizó en las habitaciones de los pacientes, en las casas de los pacientes o en la consulta externa de los pacientes, siempre garantizando un ambiente libre de ruidos y de factores distractores.

El estudio contó con aval ético del comité de Colsubsidio con acta y aval 300-1 que verificó la idoneidad del consentimiento y asentimiento informado.

Análisis estadístico

Se realizó un análisis estadístico descriptivo y se calcularon medidas de tendencia central y de dispersión, como la media, la mediana, la moda, la desviación estándar y el rango intercuartílico (RIC), para obtener información sobre el comportamiento de las variables.

Se realizó el cálculo de los puntajes acorde a la guía de PedsQL módulo de cáncer para niños y padres y posteriormente se realizó pruebas de hipótesis con un alfa de 0.05 para determinar si existieron diferencias en las medianas de las diferentes dimensiones del PedsQL entre los niños y los padres con el test de U de Mann-Whitney.

Para estimar la confiabilidad se aplicaron las pruebas de reproducibilidad test-retest evaluada mediante el coeficiente de correlación intraclase (CCI) y el coeficiente alfa de Cronbach. Un CCI menor de 0.40 indica una concordancia pobre, valores entre 0.41 y 0.60 una concordancia moderada, valores entre 0.61 y 0.80 una buena concordancia y > 0.80 una concordancia excelente[10]. Por su parte, el coeficiente alfa de Cronbach varía de 0 a 1, considerándose aceptables valores superiores a 0.7[11].

Por último, se realizó un análisis multivariante con un modelo de regresión de Poisson con variable dependiente el puntaje total de FACIT-F y con variables independientes la sintomatología reportada por la población de estudio y variables relacionadas con la patología. Se seleccionó el modelo más parsimonioso con el menor valor del criterio de Akaike (AIC), la bondad de ajuste del modelo se examinó por medio el pseudo R cuadrado de Nagelkerke y la prueba de la devianza y la sobredispersión del modelo Poisson fue valorada para la confirmación del modelo. La información fue procesada y analizada con el *software* estadístico R versión 4.3.

Resultados

Se incluyeron 46 pacientes pediátricos con diagnóstico hematooncológico. Se obtuvieron diferentes variables sociodemográficas, antropométricas, clínicas y de calidad de vida en cada uno de los pacientes y sus familias. En la tabla 1 se resumen las características de los pacientes incluyendo edad, sexo, diagnóstico y otras variables relevantes de su entorno.

Entre los pacientes incluidos, la edad mediana entre ambos sexos fue de 11 años (8-14). Treinta (65.2%) pacientes fueron de sexo femenino, encontrándose una razón femenino: masculino de 1:1,8. El 71.7% (n = 33) de los pacientes y sus familias provenían de la capital del país, el resto procedían de ciudades secundarias o zonas rurales. En 41 pacientes se tenía información disponible relacionada con el diagnóstico principal. El cáncer más frecuente fue la leucemia (n = 23/41, 56.1%), seguido de los tumores óseos (n = 6/41, 14.6%) y los linfomas (n = 4/41, 9.7%). En relación con los estadios de la enfermedad, el 22.6% (n = 7/31) se encontraba en estadio 1 y el 12.9% (n = 4/31) en estadio 4. En relación con el tratamiento, el 69.2% (n = 27/39) recibió quimioterapia, el 12.8% (n = 5/39) fue llevado a cirugía y 3 pacientes (7.7%) recibieron quimioterapia y radioterapia concomitante. El tiempo mediano de tratamiento fue de 4 meses (3-10) (Tabla 2).

Dentro de los síntomas físicos más frecuentes reportados por los pacientes se encuentran las náuseas (n = 15/46, 32.6%), la fatiga/adinamia (n = 15/46, 32.6%), la hiporexia (n = 12/46, 26.1%) y la pérdida de pelo (n = 11/46, 23.9%), entre otros. Los síntomas psicológicos más frecuentes fueron la irritabilidad (n = 14/46, 30.4%), la tristeza (n = 12/46, 26.1%) y el miedo (n = 11/46, 23.9%), entre otras cosas.

En relación con los resultados del PedsQL se observó que el puntaje total global para los niños fue de Q2 (cuartil 2 o mediana) de 69.4 y un rango intercuartílico (RIC) 53.5-83.1 y en los padres un puntaje similar, Q2 de 68.5 (RIC: 55.6-83.5). Al analizar cada una de las dimensiones se evidenció que los puntajes más altos en Q2 fue de 80 para náuseas tanto para los padres como para los niños (RIC: 72.5-92.5) y (RIC: 70-91.3), seguido de apariencia física percibida en niños (Q2: 79.2; RIC: 52.1-91.7) y en padres (Q2: 83.3; RIC: 66.7-100) (Fig. 1). Se exploró si existían diferencias en el puntaje global y por dimensión entre los padres y los niños. La única diferencia estadísticamente significativa fue la dimensión de ansiedad en los procedimientos (p = 0.036) siendo el puntaje de la mediana más alta en el grupo de niños (Q2: 75; RIC: 52.1-100) y en padres menor (Q2: 50; RIC: 20.8-83.3) (Fig. 1). En las dimensiones restantes se observan puntajes similares para ambos grupos.

En relación con la confiabilidad entre las mediciones de los pacientes y sus padres, se realizó un CCI para cada uno de los dominios y para el total. Se encontró una concordancia excelente en los dominios de dolor y molestia (CCI: 0.85; intervalo de confianza del 95% [IC95%]: 0.69-0.93), ansiedad hacia los procedimientos

Tabla 1. Características sociodemográficas de los niños con cáncer que se encontraban en tratamiento en una institución de alta complejidad

Información demográfica	n (%)
Edad (años)	
Mediana (RIC)	11 (8-14)
Sexo	
Masculino	30 (65.2)
Estrato socioeconómico	
Bajo (1-2)	34 (73.9)
Medio (3)	11 (23.9)
Alto (4)	1 (2.2)
Tipo de afiliación	
Contributivo	34 (73.9)
Subsidiado	12 (26.1)
Procedencia	
Bogotá D.C.	33 (71.7)
Otras ciudades	13 (28.3)
Estructura parental	
Nuclear	27 (58.7)
Monoparental	12 (26.1)
Extensiva	4 (8.7)
Reconstruida	3 (6.5)
Asistencia escolar	
Sí	34 (73.9)
Virtual	17 (50)
Presencial	17 (50)
Inasistencias regulares desde el diagnóstico (n = 35)	
Sí	19 (54.3)
Reducción de rendimiento escolar (n = 35)	
Sí	13 (37.1)
Reducción de actividades de entretenimiento (n = 45)	
Sí	25 (55.6)
Apoyo familiar	
Excelente	16 (34.8)
Bueno	12 (26.1)
Regular	8 (17.4)
Deficiente	10 (21.7)
Calidad de relaciones sociales (n = 32)	
Buena	22 (68.8)
Regular	7 (21.9)
Mala	3 (9.4)

RIC: intervalo intercuartílico.

Tabla 2. Características clínicas de diagnóstico y tratamiento de pacientes que se encontraban en tratamiento en una institución de alta complejidad

Información clínica	n (%)
Diagnóstico (n = 41)	
Neoplasias hemato-linfoides	
Leucemia	23 (56.1)
Linfoma de Hodgkin	3 (7.3)
Otros linfomas	1 (2.4)
Neoplasias sólidas	
Osteosarcoma	6 (14.6)
Otros sarcomas	3 (7.3)
Cáncer de SNC	1 (2.4)
Tumor de Willms	1 (2.4)
Otros	3 (7.3)
Edad de diagnóstico (años)	
Mediana (RIC)	6 (4-12)
Tratamiento (n = 39)	
Cirugía	5 (12.8)
Quimioterapia	27 (69.2)
Radioterapia	2 (5.1)
Quimio-radioterapia	3 (7.7)
Trasplante de células progenitoras	2 (5.1)
Tiempo de tratamiento (meses)	
Mediana (RIC)	4 (3-10)
Ingresos a UCI (n = 21)	
> 1 ingreso	7 (33.3)

RIC: intervalo intercuartílico; SNC: sistema nervioso central; UCI: unidad de cuidados intensivos.

(CCI: 0.95; IC95%: 0.88-0.98), problemas cognitivos (CCI: 0.83; IC95%: 0.65-0.92) y apariencia física (CCI: 0.94; IC95%: 0.86-0.97). La concordancia para el dominio de náuseas fue perfecta, y la concordancia de la valoración total de los dominios fue también excelente (CCI: 0.96; IC95%: 0.90-0.98). En la tabla 3 se detallan los CCI de todos los dominios.

Para la valoración de la sensación de fatiga se usó la escala FACIT-F aplicada en la población de estudio, donde se obtuvo una mediana de energía de 5 (RIC: 4- 5), cansancio (Q2: 11; RIC: 9-13) y un puntaje global de 15 (RIC: 13-18).

Por último, se realizó un modelo de regresión Poisson para determinar las variables de síntomas reportados por niños, así como las de características de su tratamiento. El modelo evidenció significancia estadística en la relación entre tener dispositivos médicos, náuseas y ansiedad con un menor puntaje en la escala FACIT-F. A su vez, se encontró una relación inversa entre meses de diagnóstico y el puntaje de FACIT-F (Tabla 4).

Discusión

Adentrarse en la complejidad del cáncer infantil brinda información relevante para optimizar la atención en salud de esta población. Al comprender mejor este fenómeno, se puede fortalecer el seguimiento clínico, tomar decisiones interdisciplinarias que sean precisas y enfocarse en las soluciones de los problemas específicos que enfrentan los niños y adolescentes con cáncer[12], lo cual

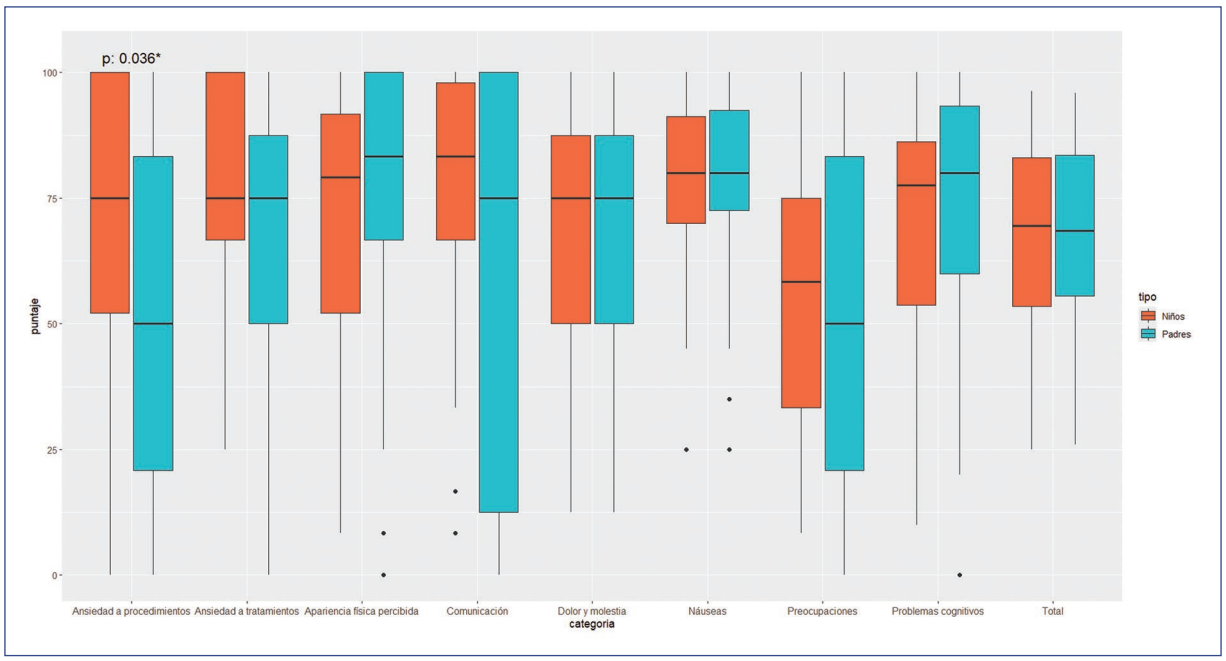

Figura 1. Puntaje total y por dimensiones del intrumento PedsQL Cancer Module™ (Inventario Pediátrico de Calidad de Vida Módulo Cáncer) niños y padres.

Tabla 3. Coeficiente de correlación intraclase (CCI)

Dominio PedsQL Cancer Module	CCI	IC95%
Dolor y molestia	0.85	0.69-0.93
Náuseas	1.00	
Ansiedad frente a los procedimientos	0.95	0.88-0.98
Ansiedad frente a los tratamientos	0.68	0.39-0.84
Preocupaciones	0.78	0.54-0.89
Problemas cognitivos	0.83	0.65-0.92
Apariencia física percibida	0.94	0.86-0.97
Comunicación	0.37	–0.02 a 0.66
Total	0.96	0.90-0.98

IC95%: intervalo de confianza del 95%.

se alinea con el enfoque de esta investigación, en la que se logró recopilar información sobre diversos aspectos de la vida de los niños con cáncer y sus familias.

La muestra refleja las condiciones sociodemográficas y clínicas. La edad mediana de 11 años y la predominancia del sexo femenino (65.2%) son consistentes con reportes previamente realizados en estudios pediátricos de oncología[13].

La conformación de los datos sociodemográficos, clínicos y relacionados con la calidad de vida permiten tener una aproximación a las necesidades, y conceptos que subyacen del hecho de experimentar una enfermedad y tratamiento complejo. Detallar el espectro de impacto de la enfermedad y del tratamiento en aquellos menores que experimentan cáncer es esencial para enfocar intervenciones y estrategias de seguimiento y control de necesidades de cuidado. En este sentido, en Colombia se han realizado pocos estudios sobre niños y adolescentes con enfermedades crónicas en cuanto a lo que sienten antes, durante y después del diagnóstico y del tratamiento. La mayoría de los estudios realizados en Colombia se centran en evaluar la calidad de vida de los adultos, pero no hay muchos estudios sobre los niños y adolescentes con cáncer[14-16], lo que impulsa el fortalecimiento de estas áreas de conocimiento y la adopción de nuevas maneras de cuidar según emerge la nueva evidencia.

El predominio de leucemia está en línea con las tendencias globales de incidencia de cáncer en niños, donde la leucemia representa la mayoría de los casos[17], sin embargo para nuestro estudio este tipo de cáncer está seguido por tumores óseos y linfomas lo cual es diferente a las cifras globales reportadas.

En cuanto al tratamiento, el tiempo promedio de tratamiento fue de cuatro meses y la mayoría de los niños

Tabla 4. Modelo de regresión de Poisson para puntaje FACIT-F en la población de estudio

Variable	Error estándar	p valor	Exp (B)	IC 95%
Número previo de cirugías	0.02194	0.4004	1.01	0.97-1.06
Tener dispositivos médicos	0.10681	< 0.001	0.74	0.60-0.92
Náuseas	0.11393	< 0.001	0.69	0.55-0.87
Ansiedad	0.12620	< 0.001	0.67	0.52-0.86
Horas de sueño	0.04434	0.8755	1.00	0.92-1.1
Meses de diagnóstico	0.00532	0.0258	0.98	0.97-0.99
Pseudo R cuadrado de Nagelkerke 0.70 Criterio de Akaike (AIC) 201.67 Test de sobredispersión p valor 0.07 Prueba de *deviance* < 0.001				

FACIT: *Functional Assessment of Chronic Illness Therapy,* IC95%: intervalo de confianza del 95%.

recibieron quimioterapia; a algunos también se les realizó cirugía y en algunos casos se combinó la quimioterapia con radioterapia. Desde este punto de vista se contrasta con los resultados de un estudio realizado en Pakistán, donde se reportó que los pacientes en su mayoría estaban bajo quimioterapia durante la recolección de la información[18], lo que refuerza la necesidad de que los proveedores de cuidado promuevan un enfoque multidisciplinario que aborde tanto los aspectos clínicos como los psicológicos, físicos y sociales que se pueden ver afectados por presencia de la enfermedad y el tratamiento mismo.

Los resultados del estudio muestran que los síntomas más comunes experimentados por niños en tratamiento oncológico incluyen náuseas, fatiga, pérdida del pelo e hiporexia. Estos síntomas son característicos de los efectos secundarios asociados con los tratamientos de cáncer, como la quimioterapia, que tiene impacto significativo en la calidad de vida. La presencia de náuseas y hiporexia sugiere desafíos en términos del control de síntomas molestos e indeseables, que adicionalmente se configuran como factores de riesgo para impactar el estado nutricional del paciente, ya que comprometen la ingesta adecuada y suficiente de alimentos y por ello marcan pautas sobre la necesidad de planear cuidados enfocados en estrategias nutricionales y de uso de fármacos para controlar dichos síntomas[19]. La fatiga, reportada en un tercio de los pacientes, compromete el rendimiento escolar y disminuye la interacción con pares, aspectos todos fundamentales para el desarrollo emocional y social del niño[20]. Por lo tanto, se debe entender y abordar la fatiga por medio de intervenciones multidisciplinarias que pueden incluir ajustes en el régimen de tratamiento, terapia física y apoyo psicosocial[21].

Además, los síntomas psicológicos como irritabilidad, tristeza y miedo destacan la carga emocional que el tratamiento del cáncer impone a los niños. Estos efectos no solo afectan al paciente sino también a su familia, lo que subraya la necesidad de apoyo psicológico integral, como se ha reportado en otros estudios[20,22]. El manejo de estos síntomas debe ser una prioridad dentro de los programas de tratamiento, incorporando el asesoramiento y las terapias de apoyo para ayudar a los niños y sus familias a manejar mejor el estrés emocional asociado con la enfermedad y su tratamiento. Los datos del presente estudio confirman que existe una conexión significativa entre el agotamiento y todas las dimensiones de la CVRS en niños y adolescentes con un diagnóstico hematooncológico durante su tratamiento.

El análisis del PedsQL mostró que tanto niños como padres reportan impactos similares en términos de calidad de vida, aunque los niños reportaron mayor ansiedad relacionada con los procedimientos médicos. Este hallazgo sugiere que mientras los padres pueden estar al tanto de la disminución de la CVRS física, podrían no percibir completamente la ansiedad que sus hijos experimentan durante los tratamientos, como se refuerza en otros estudios[23] y que hacen resaltar la importancia de comunicar efectivamente las experiencias y preocupaciones de los niños a sus cuidadores y proveedores de salud. Sin embargo, hay estudios que muestran que las mediciones reportadas por los padres pueden ser una herramienta útil para evaluar el estado de salud de los pacientes pediátricos

con cáncer, especialmente en aquellos casos donde la comunicación directa con el paciente puede ser limitada[16].

Por otra parte, cuando se realizó el análisis multivariante, este estudio evidenció cómo el cansancio en los pacientes pediátricos se asocia de manera estadística con el uso de dispositivos médicos, las náuseas y ansiedad. Sin embargo, es importante considerar que este análisis no abarca todos los posibles factores que podrían influir en el cansancio, como el apoyo psicológico y factores familiares, entre otros, que pueda haber recibido el grupo de pacientes durante este periodo o el impacto de su entorno social. Por lo tanto, estos resultados deben interpretarse dentro del contexto de las limitaciones de este estudio, se reconoce la importancia de generar más estudios que tengan en cuenta la experiencia de cansancio en los pacientes como factor multifactorial y que cuenten con un tamaño de muestra suficiente para mayor precisión de los estimadores, control de error tipo I y validez de los resultados[16].

Agradecimientos

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Este estudio se considera de bajo riesgo de acuerdo con la Resolución 8430 de 1993. Se llevó a cabo un registro anónimo de datos y no se realizaron intervenciones que afectan variables biológicas, psicológicas o sociales en los participantes del estudio. Además, se garantizó el respeto a los principios éticos fundamentales, como la autonomía, la justicia, la beneficencia y la no maleficencia. Cabe destacar que se obtuvo el consentimiento informado de los participantes, el cual fue previamente evaluado y aprobado por el Comité de Ética de la Clínica Infantil Colsubsidio con aval 300-1, asegurando así el cumplimiento riguroso de las normas éticas establecidas.

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido la aprobación del Comité de Ética para el análisis y publicación de datos clínicos obtenidos de forma rutinaria. El consentimiento informado de los pacientes no fue requerido por tratarse de un estudio observacional retrospectivo.

Uso de inteligencia artificial para generar textos. Los autores declaran que no han utilizado ningún tipo de inteligencia artificial generativa en la redacción de este manuscrito ni para la creación de figuras, gráficos, tablas o sus correspondientes pies o leyendas.

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RESEARCH ARTICLE

Prevalence of bacteriuria and bacterial resistance in adolescents from the center of the state of Tlaxcala, Mexico

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Abstract

Urinary tract infections and bacteriuria are common in the pediatric population, and antibiotic resistance is increasing significantly. Recurrent urinary infections, symptomatic or asymptomatic, are a risk factor for developing chronic kidney disease in adolescents and young adults. This study aimed to assess the prevalence of bacteriuria diagnosed by culture to identify the main causal agents and sensitivity to antibiotics in adolescents from the central region of the state of Tlaxcala. A cross-sectional study was carried out among 905 adolescents from 11 to 18 years old who lived in the central region of the state of Tlaxcala, Mexico. Bacteriuria was evaluated by positive nitrites and leukocyte esterase, and urine culture with antibiogram. Multivariate logistic regression models were executed to evaluate the risk of presenting bacteriuria, with a confidence level of 95%. A total of 31 participants had a positive urine culture, with a bacteriuria prevalence of 3.4%, of which 29 cases were asymptomatic. The most frequent agent was Escherichia coli) in both sexes (28.6% in men and 29.7% in women) and regarding bacterial resistance: E. coli presented greater resistance to ampicillin, trimethoprim/sulfametoxazol and ceftriaxone. The risk factors associated with bacteriuria were female sex, sexual activity, use of contraceptives, and greater consumption of sweetened beverages. Bacteriuria is common in this adolescent population, so its early identification is necessary to treat it, and to prevent its complications.

Keywords: *Bacteriuria. Urinary tract infection. Adolescents. Bacterial resistance. Tlaxcala. Mexico.*

Prevalencia de bacteriuria y resistencia bacteriana en adolescentes del centro del estado de Tlaxcala, México

Resumen

Las infecciones del tracto urinario y bacteriuria son comunes en la población pediátrica, y la resistencia a los antibióticos está aumentando significativamente. Las infecciones urinarias recurrentes, sintomáticas o asintomáticas, son un factor de riesgo para desarrollar Enfermedad Renal Crónica en adolescentes y adultos jóvenes. El objetivo de este estudio fue evaluar

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la prevalencia de bacteriuria diagnosticada por cultivo, identificar los principales agentes causales y la sensibilidad a antibióticos, en adolescentes de la región centro del estado de Tlaxcala. Se realizó un estudio transversal en 905 adolescentes de 11 a 18 años de edad que vivían en la región centro del estado de Tlaxcala, México. La bacteriuria se evaluó mediante nitritos y esterasa leucocitaria positivas, y urocultivo con antibiograma. Se ejecutaron modelos de regresión logística multivariados para evaluar el riesgo de presentar bacteriuria, con un nivel de confianza del 95%. Un total de 31 participantes presentaron urocultivo positivo, siendo la prevalencia de bacteriuria del 3.4%, de los cuales 29 casos fueron asintomáticos. El agente que se presentó con mayor frecuencia fue Escherichia coli en ambos sexos (28.6% en hombres y 29.7% en mujeres), y respecto a la resistencia bacteriana: E. coli presentó mayor resistencia a Ampicilina, Trimetoprim/Sulfametoxazol y Ceftriaxona. Los factores de riesgo asociados a la bacteriuria fueron el sexo femenino, actividad sexual, uso de anticonceptivos y un mayor consumo de bebidas azucaras. La bacteriuria es frecuente en esta población adolescente, por lo que es necesaria su identificación temprana para tratarlas y prevenir sus complicaciones.

Palabras clave: *Bacteriuria. Infección urinaria. Adolescentes. Resistencia bacteriana. Tlaxcala. México.*

Introduction

Urinary tract infection (UTI) is a significant public health problem worldwide, representing the second most common cause of infection in the general population[1]. In Mexico, it is the third leading cause of morbidity in adolescents and adults[2]. In addition, it is associated with high healthcare costs due to the misuse of antibiotics and antimicrobial resistance, which leads to the use of broader-spectrum and more expensive drugs[3].

UTI has been considered a risk factor associated with renal malformations, chronic kidney disease (CKD), and hypertension. As a result, urine cultures have been routinely performed, often yielding positive results in apparently healthy and asymptomatic individuals, a characteristic termed asymptomatic bacteriuria (AB)[4]. Other studies have shown that AB has been associated with urinary symptoms such as nocturnal enuresis, urinary urgency, and foul-smelling urine in up to 70% of cases, which has been termed covert bacteriuria rather than asymptomatic[5]. AB has also been linked to urological abnormalities in 47% of cases, including vesicoureteral reflux (21-33%), renal scarring (10-26%), and bladder trabeculation (7-16%). However, other studies have reported a lower prevalence of urological abnormalities (renal malformations in 3-14% and reflux in 7-13% of cases), while some have found no differences between patients with AB and the general population[4].

The AB prevalence is estimated at 3% in school-age children, 1% in preadolescent children[5], and between 1.1 and 1.8% in adolescent females, while it is almost non-existent in males. Some studies report that AB is not associated with significant genitourinary tract malformations[6]. The bacteria isolated in patients with AB are primarily enterobacteria originating from the digestive system. *Escherichia coli* is the most frequent cause of symptomatic UTIs and AB. However, other bacteria such as *Enterobacteriaceae, Pseudomonas aeruginosa*, *Enterococcus* species, and Group B *Streptococcus* can also be found. In males, *Enterococcus* species and Gram-negative bacilli are more common[4].

UTIs, symptomatic and asymptomatic, are very common in the pediatric population. Over the past two decades, antibiotic resistance has been increasing significantly due to extended-spectrum beta-lactamase (ESBL) producing microorganisms[7]. *E. coli* is the microorganism with the highest antibiotic resistance in children and adolescents under 18-years-old: a meta-analysis in Organization for Economic Co-operation and Development (OECD) member countries showed a resistance prevalence of 53.4% for ampicillin, 23.6% for trimethoprim, 8.2% for amoxiclav, 2.1% for ciprofloxacin, and 1.3% for nitrofurantoin. Meanwhile, resistance in non-OECD countries was significantly higher: 79.8% for ampicillin, 60.3% for co-amoxiclav, 26.8% for ciprofloxacin, and 17% for nitrofurantoin[8]. In Mexico, it has also been shown that the susceptibility of many Gram-positive and Gram-negative uropathogens to widely used antibiotics has decreased, mainly due to prolonged and inappropriate use of these drugs[9]. Due to its frequency, *E. coli* has shown resistance to third-generation cephalosporins and quinolones, mainly due to the presence of ESBLs[10]. Likewise, *Enterococcus faecium* presents increasing resistance to vancomycin, *P. aeruginosa* to quinolones and third-generation cephalosporins, and *Enterobacter cloacae* and *Klebsiella pneumoniae* have shown multi-drug resistance[11].

Recurrent UTIs are one of the main risk factors for developing CKD in adolescents and young adults. It has been estimated that between 10 and 25% of children and adolescents with CKD have a history of chronic pyelonephritis[12]. Furthermore, it has been reported that 10% of adolescents with recurrent UTIs developed CKD

after 25 years of follow-up[13]. This study aimed to evaluate the prevalence of bacteriuria, the main causative agents, and antibiotic sensitivity in adolescents from the central region of the state of Tlaxcala.

Materials and methods

A cross-sectional analytical study was conducted from September 2019 to March 2022 among students aged 11-18 years from public and private secondary and upper secondary schools in the municipalities of Tlaxcala, Chiautempan, and Apetatitlán in the state of Tlaxcala, Mexico. The sample size was calculated for cross-sectional studies, considering a 95% confidence level, 5% precision, an expected prevalence of 4.3%, a design effect of 2.0, and using the correction for diseases with prevalences below 10%: multiplying the precision by the expected prevalence[14]. A multistage sampling strategy was employed, stratified by education level (secondary or upper secondary) and proportional to the size of the strata (number of schools per municipality). Simple random sampling was used at each stage and in each selected school. Students who were taking antibiotics or non-steroidal anti-inflammatory drugs and female students who were menstruating or whose period had ended three or fewer days before the study were excluded from the study. This study was conducted following the Declaration of Helsinki, considering the ethical principles for medical research involving human subjects[15]. The study was approved by the research Ethics Committees of the Hospital Infantil de México and the Tlaxcala Health Ministry. Invited participants signed an assent form, and their parents provided informed consent.

Evaluation of bacteriuria and bacterial sensitivity to antibiotics

Bacteriuria was assessed using a first-morning urine sample (midstream), with the Clinitek Status Plus equipment using Multistix 10sg reagent strips, considering the parameters of bacteriuria, leukocyte esterase, and nitrites as suggestive of bacteriuria or UTI[16,17]. In case of a positive parameter, a urine culture was performed. Uncentrifuged urine was inoculated using a calibrated loop on Blood Agar, MacConkey Agar, Biggy Agar, and Mannitol Salt Agar culture media. The inoculated plates were incubated at 37 ± 0.5°C for 72 h with daily review based on the literature[18]. After observing bacterial growth, differential staining and biochemical tests were performed to identify genus and species. Finally, an antibiogram was conducted using the Kirby-Bauer method[19]. The diagnosis of AB was based on the Mexican Clinical Practice Guideline on "Diagnosis and treatment of uncomplicated UTI in individuals under 18 years of age in primary and secondary care levels". The criteria for a clean midstream urine sample in patients without permanent catheters were the presence of significant bacteriuria without clinical manifestations and two positive cultures. Significant bacteriuria refers to the isolation of a recognized urinary pathogen in a urine culture, collected aseptically, with a colony-forming unit (CFU) count that varies according to the urine collection method: spontaneous micturition, transurethral catheterization, or suprapubic puncture[20]. In this study, the isolation of at least 100,000 CFU per mL of the same bacterial species was considered significant. In addition, since some authors recommend that in the case of males, the diagnosis of AB can be made with a single culture[21,22], and due to logistical difficulties in collecting a second sample in different schools, this study only cultured one urine sample for both males and females.

Evaluation of urinary symptoms

The assessment of urinary symptoms was conducted using the following questions: in the past year, have you experienced burning or pain while urinating? While urinating, do you feel the need to urinate more but cannot? Do you frequently feel an urgency to urinate more than usual? Has a doctor ever diagnosed you with an UTI?

Evaluation of family socioeconomic characteristics and sugary drink consumption in participants

A self-administered questionnaire was used for parents or guardians, consisting of 154 questions divided into sections: personal and pathological history, family environmental exposure, and occupational data. In addition, the following aspects were evaluated in the participants: pathological history, family medical history, medical care, hygienic-dietary habits, urinary history and symptoms, sexuality, substance use, quality of life, and physical examination.

The socioeconomic level was assessed according to the Mexican Association of Market Intelligence and Public Opinion Agencies (AMAI, for its Spanish acronym)[23], which classifies into seven social strata. However,

Table 1. Sociodemographic, anthropometric, and clinical characteristics of participants, by sex

Variables	Sex		p value
	Male (n = 415) (45.9%)	Female (n = 490) (54.1%)	
Age, years (mean ± SD)	13.8 ± 1.7	13.8 ± 1.6	0.641
Secondary school			
Public (%)	57.5	63.7	0.078
Private (%)	42.5	36.3	
Upper secondary (high school)			
Public (%)	45.4	68.1	0.001
Private (%)	54.6	31.9	
Socioeconomic level*			
Very low (%)	1.7	1.4	0.756
Low (%)	53.6	57.4	0.258
Medium (%)	44.7	41.2	0.290
Frequency of potable water supply to house*			
Daily (%)	51.8	54.1	0.477
Every third day (%)	37.3	35.8	0.649
Twice a week (%)	8.8	8.5	0.866
Once a week (%)	0.9	0.7	0.771
Occasionally (%)	0.6	0.6	0.801
Never (%)	0.6	0.3	0.447
Body mass index†			
Numerical, kg/m^2 (mean ± SD)	21.4 ± 0.2	22.1 ± 0.1	0.013
Underweight (%)	1.7	0.6	0.110
Normal (%)	56.2	58.6	0.439
Overweight (%)	23.2	28.5	0.068
Obesity (%)	18.9	12.3	0.004
Waist circumference, cm (mean ± SD)	79 ± 1.5	74 ± 1.3	0.012
Abdominal obesity‡			
Normal	71.4	75.8	0.134
Risk of abdominal obesity	18.7	15.6	0.224
Abdominal obesity	9.9	8.6	0.486

*Information was provided by parents and/or guardians.
The socioeconomic level was assessed using items on maternal education, paternal education, electricity supply (public service, private plant, solar panel, no electrical service), type of flooring in the house (cement, tile, wood, dirt, other material), number of people living in the household, and type of drainage or sewage connection (public network, septic tank, pipe leading to a ravine, pipe leading to a river, no drainage); according to the Mexican Association of Market Intelligence and Public Opinion Agencies (AMAI, for its Spanish acronym)[23], socioeconomic level is classified into seven social strata, however, for this analysis only four categories are considered: very low (score 0-89), low (score 135-190), medium (score 191-204), and high (score > 205).
†BMI was calculated using the formula weight (kg)/height^2 (m), and depending on the child's sex, BMI, and age, it was categorized as underweight (< 3rd percentile), normal (3rd-84.9th percentile), overweight (85th-97th percentile), and obesity (> 97th percentile)[25].
‡The Abdominal Obesity Index was calculated based on waist circumference values and classified as normal (< 75th percentile), risk of abdominal obesity (75th-90th percentile), and abdominal obesity (> 90th percentile)[26].
SD: standard deviation.

in this study, they were condensed into four categories: very low (score 0-89), low (score 135-190), medium (score 191-204), and high (score > 205).

The intake of sugary drinks was quantified by the number of portions consumed per day, and the following beverages were included in the study: cola, flavored soft drinks, diet soft drinks, powdered flavored water, natural fruit juice, industrialized juice, industrialized tea, coffee with milk, coffee without milk, atole (a traditional hot corn-based beverage) with milk, atole without milk, hot chocolate with milk, and hot chocolate without milk[24].

Evaluation of body mass index (BMI) and abdominal obesity

Body mass index (BMI) was calculated using the formula weight (kg)/height^2 (m), adjusted for age and sex. Participants were categorized into underweight (< 3rd percentile), normal (3rd-84.9th percentile), overweight (85th-97th percentile), and obese (> 97th percentile)[25]. Abdominal obesity was determined based on waist circumference values and classified as normal (< 75th percentile), at risk of abdominal obesity (75th-90th percentile), and abdominal obesity (> 90th percentile)[26].

Table 2. Results of urine cultures and etiological agents, by sex (n = 71)

Urine culture results and etiologic agents	Sex	
	Male* (n = 7) (9.9%)	Female* (n = 64) (90.1%)
Negative cultures	n = 4 (57.1%)	n = 36 (56.3%)
Positive cultures	n = 3 (57.2%)	n = 28 (43.8%)
Etiological agent (%)		
Escherichia coli	28.6%	29.7%
Staphylococcus epidermidis	14.3%	17.2%
Enterococcus faecalis	14.3%	12.5%
Lactobacillus	-	9.3%

*Algunos participantes mostraron cultivos con más de un agente etiológico: 2 hombres y 16 mujeres. Negative culture: considered when bacterial growth was < 100,000 CFU/mL over a 72-h period; Positive culture: considered when AB when bacterial growth was greater than 100,000 CFU/mL[20-22].
In the case of females, cultures with more than one etiological agent were observed.

Statistical analysis

In order to compare the sociodemographic, anthropometric and clinical characteristics by sex, comparisons of means were performed for numerical variables, using linear regression; and comparisons of percentages for nominal variables, using logistic regression. A comparison of bacterial resistance percentages of pathogens to each antibiotic was carried out. The presence of bacteriuria was compared against its absence across sociodemographic, anthropometric, and clinical characteristics. Furthermore, this study hypothesized that there was a higher risk of presenting AB in females compared to males. To test this, multivariate logistic regression models were executed with a 95% confidence level and adjusted for age, sex, sexual activity, contraceptive use, and sugary drink intake. Statistical tests were performed using STATA Version 15.0 software.

Results

Table 1 shows the sociodemographic, anthropometric, and clinical characteristics of the 905 participants. The average age was 13 years, 54.1% were female, about 60% were enrolled in public schools, and 55% were categorized as low socioeconomic status. Regarding nutritional status, 23.2% of males and 28.5% of females were overweight, while 18.9% of males and 12.3% of females were obese. In addition, 9.9% of males and 8.6% of females showed abdominal obesity.

Table 2 presents the results of the cultures and etiological agents by sex. Seventy-one urine cultures were performed on participants who showed suspicion of bacteriuria, that is, positive nitrite test, positive leukocyte esterase test, or moderate presence of bacteria in urine, resulting in 31 positive cultures (43.7%). The most frequent agent in both sexes was *E. coli* (28.6% in males and 29.7% in females), while *Staphylococcus epidermidis* was detected in 14.3% of males and 17.2% of females, and *Enterococcus faecalis* was isolated in 14.3% of males and 12.5% of females. Finally, *Lactobacilli* was found in 9.3% of the cultures from females, and 2 males and 16 females presented two etiological agents.

Table 3 shows the bacterial resistance of the etiological agents found in positive urine cultures. *E. coli* showed higher resistance to ampicillin, trimethoprim/SMX, and ceftriaxone; *S. epidermidis* demonstrated resistance to clindamycin and penicillin; and *E. faecalis* showed resistance to tetracycline and nitrofurantoin.

Table 4 presents the prevalence of bacteriuria and its associated risk factors. Thirty-one cases with positive urine cultures were identified, the prevalence of symptomatic or AB was 3.4%, AB was 3.5%, anf the prevalence of AB was. The most common symptom was urinary urgency (3.2% in cases with bacteriuria and 1.5% without bacteriuria). Furthermore, females showed a significantly higher prevalence of bacteriuria compared to males (3.1% vs. 0.3%, respectively; p = 0.0001).

Regarding risk factors related to bacteriuria, a higher percentage of adolescents with sexual activity and contraceptive use showed a higher prevalence of bacteriuria (3.2%) compared to those who did not report these activities (0.1%; p = 0.043 in both cases). In addition, those who reported consuming an average of more portions of sugary drinks per day (3.4 portions) showed a higher prevalence of bacteriuria compared to those without bacteriuria (2.1 portions) (p = 0.036).

Table 5 shows the probability of presenting bacteriuria (symptomatic or asymptomatic) concerning female sex and other risk factors. In a bivariate analysis, females were 8.3 times more likely to present bacteriuria than males (95% confidence interval [CI] 2.5-27.7; p = 0.001). In the multivariate analysis, the probability of presenting bacteriuria in females increased to 9 times higher than in males (95% CI 2.6-31.2; p = 0.000).

Discussion

This study demonstrated that bacteriuria is common in this adolescent population from central Tlaxcala

Table 3. Bacterial resistance to antibiotics of etiological agents found in positive urine cultures (n = 31)

Antibiotic	Etiological agent found in positive urine cultures*			p value
	Escherichia coli (Gram-negative) (n = 17) (55%)	*Staphylococcus epidermidis* (Gram-positive) (n = 8) (26%)	*Enterococcus faecalis* (Gram-positive) (n = 6) (19%)	
Ampicillin (%)	58.8	0	11.1	0.0001
Amoxicillin/Clavulanic acid (%)	29.4	N/A†	11.1	0.319
Nitrofurantoin (%)	23.5	20	16.6	0.932
Trimethoprim/SMX (%)	52.9	N/A†	N/A†	0.003
Clindamycin (%)	N/A†	60	0	0.012
Tetracycline (%)	N/A†	30	55.5	0.228
Penicillin (%)	N/A†	60	11.1	0.021
Ceftriaxone (%)	50	0	0	0.0001

*Positive urine culture was considered as bacterial growth greater than 100,000 CFU/mL[20-22].
†For the selection of the antibiotic used for each etiological agent, the characteristics of the bacteria (whether they were Gram-positive or Gram-negative) were taken into account.

state, with enterobacterium *E. coli* being the most frequent causative agent, isolated in nearly half of the cultures. In addition, bacterial resistance to ampicillin, trimethoprim/sulfamethoxazole, and ceftriaxone was observed. Furthermore, the main risk factors identified were female sex, sexual activity, use of contraceptive methods, and higher consumption of sugar-sweetened beverages.

The prevalence of symptomatic (3.4%) or AB (3.2%) found in our study is higher than the prevalence reported in a meta-analysis and systematic review of 40 studies from various countries, which considered a population of 49,806 children and adolescents under 19 years of age, showing a bacteriuria prevalence of 0.37% in males and 0.47% in females. The highest prevalences were found in uncircumcised males under 1 year of age and in females over 2 years old; however, the prevalence of AB decreased in adolescent males to 0.08%[27]. Another study evaluated the prevalence of asymptomatic urinary abnormalities in 2,500 adolescents using reagent strips and optical microscopy: adolescents with abnormal results were re-examined after 2 weeks, and those who had abnormal results twice underwent systemic clinical examinations and additional clinical and laboratory studies, detecting 23 cases of AB (0.9%), all of which were in females[28].

Asymptomatic urinary infections are generally caused by Gram-negative bacteria such as *E. coli*; however, bacterial strains associated with AB express fewer virulence factors than bacterial strains involved in febrile UTIs. It has been discovered that these strains have different genes for the production of fimbriae, which are important for *E. coli*'s ability to ascend the urinary tract[29]. The host response to AB is also altered, as interleukins (IL) 6 and 8 were found to be elevated in 63% and 76% of children under 6 years old with febrile UTIs, respectively; while no child with AB had elevated levels of IL-6, and only 30% had elevated levels of IL-8[30].

On the other hand, toll-like receptor 4 (TLR-4), an important transmembrane protein in cell signaling and activation of the innate immune system, has been observed to be reduced by almost 50% in children with AB. This could contribute to the weak mucosal immune response to bacteria in AB[31]. Analysis of the TLR-4 promoter sequence has shown that patients with AB have fewer genotype variants and reduced expression compared to patients with UTI symptoms, further supporting TLR-4 alterations at the genomic level in AB[32]. The combination of altered bacterial characteristics and host response in AB suggests that the phenomenon could represent a form of commensalism, a symbiotic relationship in which bacteria benefit while the human host normally neither gains benefit nor suffers harm[33]. In fact, intravesical inoculations with a modified *E. coli* strain isolated from patients with AB have been successfully used to treat recurrent UTIs in the adult population[5,34-36].

Regarding the uropathogens isolated in our study, *E. coli* was the most frequent (55%), a finding that is

Table 4. Risk factors associated with the presence of asymptomatic bacteriuria in the participant population

Variables	Bacteriuria‡		p value
	Absent (n = 874) (96.6%)	Present (n = 31) (3.4%)	
Age, years (mean ± SD)	13.7 ± 0.05	14.1 ± 0.31	0.305
Sex			
Male (%)	47.2	12.9	0.0001
Female (%)	52.8	87.1	
BMI*			
Underweight (%)	1.1	-	0.399
Normal (%)	57.4	54.8	0.781
Overweight (%)	26.3	19.4	0.371
Obese (%)	15.2	25.8	0.134
Socioeconomic level†			
Very low (%)	1.5	3.2	0.500
Low (%)	55.4	61.3	0.514
Medium (%)	43.1	35.5	0.307
Frequency of water supply to the house			
Daily (%)	53.6	43.3	0.266
Every third day (%)	36.1	46.7	0.242
Twice a week (%)	8.7	6.7	0.690
Once a week (%)	0.8	-	0.488
Occasionally (%)	0.6	-	0.558
Never (%)	0.2	3.3	0.076
Sexual activity			
Yes (%)	0.1	3.2	0.043
Use of contraceptives			
Yes (%)	0.1	3.2	0.043
Urinary symptoms in the last year§			
Asymptomatic	95.5	96.8	0.726
One or more symptoms (%)	4.5	3.2	0.726
Tenesmus (%)	2.3	0.0	0.236
Burning or pain when urinating (%)	1.2	0.0	0.401
Urinary urgency (%)	1.5	3.2	0.515
Water intake, number of glasses per day (mean ± SD)	5.2 ± 0.47	4.6 ± 0.08	0.247
Intake of sugary drinks, number of portions per day¶ (mean ± SD)	2.1 ± 0.11	3.4 ± 0.62	0.036

*Body mass index was calculated using the formula weight (kg)/height^2 (m), and depending on the child's sex, BMI, and age, it was categorized as underweight (< 3rd percentile), normal (3rd - 84.9th percentile), overweight (85th - 97th percentile), and obesity (> 97th percentile)[25].
†The socioeconomic level was assessed using items on maternal education, paternal education, electricity supply (public service, private plant, solar panel, no electrical service), type of flooring in the home (cement, tile, wood, dirt, other material), number of people living in the household, and type of drainage or sewage connection (public network, septic tank, pipe leading to a ravine, pipe leading to a river, no drainage); according to the Mexican Association of Market Intelligence and Public Opinion Agencies (AMAI, for its Spanish acronym)[23], socioeconomic level is classified into 7 social strata, however, for this analysis only 4 categories are considered: very low (score 0-89), low (score 135-190), medium (score 191-204), and high (score > 205).
‡Positive Bacteriuria was considered in those participants whose urine cultures showed bacterial growth greater than 100,000 CFU/mL[20-22]
§Urinary symptoms in the last year. Participants were asked: In the last year, have you had burning or pain when urinating? Have you felt an urgency to urinate? Have you felt the need to urinate more, but you couldn't? Possible responses were: Always, Almost always, Almost never, and Never.
¶Sugary drink intake was quantified by the number of portions consumed per day and included the following beverages: cola, flavored soda, diet soda, powdered flavor water, natural fruit juice, industrialized juice, industrialized tea, coffee with milk, coffee without milk, atole with milk, atole without milk, chocolate with milk, chocolate without milk[24].
SD: standard deviation.

below what was found in a Mexican study in adults, where *E. coli* was reported in 93.7% of cases[35] and in 60.3% of 1,045 cultures performed in Spanish children under 2-years-old[37]. Our finding is similar to that of a study conducted in adults from Monterrey and Colombia, which reported *E. coli* in 47.1%[38] and 62.6%[39] cultures, respectively.

Regarding bacterial resistance of etiological agents to antibiotics, in this study, *E. coli* showed 58% resistance to trimethoprim-sulfamethoxazole and 52% to ampicillin, while in a Colombian study, *E. coli* showed 43% resistance to trimethoprim-sulfamethoxazole and 51% to ampicillin[39]. Other studies in adults have reported that *E. coli* is the microorganism that presents the highest

Table 5. Risk of presenting asymptomatic bacteriuria in adolescent females in central Tlaxcala

Variables	Risk of UTI* (Odds ratio)	Confidence interval 95%	p value
Bivariate analysis			
Males (reference category)	1.0		
Females	8.3	(2.5-27.7)	0.001
Multivariate analyze			
Females	8.3	(2.5-27.6)	0.001
Adjusted for age			
Females	8.8	(2.6-30.2)	0.000
Adjusted for age, sexual activity, and contraceptive use			
Females	9.0	(2.6-31.2)	0.000
Adjusted for age, sexual activity, contraceptive use, and sugary drink intake			

*UTI: urinary tract infection.
The p-value was calculated using multivariate logistic regression models, with a 95% confidence level, and adjusted for age, sex, sexual activity, contraceptive use, and sugary drink intake.

resistance to ampicillin, trimethoprim-sulfamethoxazole, and ceftriaxone[36,39]. In the pediatric population of Ecuador, resistance to ampicillin was observed in 92% of cases, trimethoprim in 61%, and nalidixic acid in 68%; in Colombia, in 2007, resistance to ampicillin was shown in 79.7% and to trimethoprim in 52.8% of participants[40,41]. In the Spanish pediatric population, it was reported that *E. coli* showed resistance in 61% of cases treated with ampicillin and in 48% of cases treated with trimethoprim-sulfamethoxazole[37].

Scientific literature has reported that the main risk factors associated with the prevalence of UTIs and AB in adolescents are female sex, urinary tract malformations, history of kidney disease, poor hygiene, sexual activity, menstruation, and circumcision, among others[4]. In our study, as in others, the prevalence of AB in females was found to be significantly higher than in males (5.7% and 0.7% respectively). These differences may be due to anatomical characteristics, estrogen concentration, pH variations, and inadequate hygiene, as indicated in other investigations[21]. Similarly, sexual activity and the use of contraceptives are related to the prevalence of UTIs due to chemical alterations and loss of vaginal microbiota[42].

Some studies have shown that the most frequent UTI symptoms are dysuria, tenesmus, suprapubic pain, fever, and urinary urgency, although its asymptomatic form is very common[24,43]. In our study, almost a third of the participants with AB diagnosed by culture also reported having experienced burning or pain while urinating in the last year, and almost a fifth reported tenesmus. The Newcastle AB Research Group reported that, out of 13,464 girls between 4 and 18 years of age, the prevalence of AB was 1.9%, while among 1,595 boys from 5 to 18 years, the prevalence was 0.2%. Of the participants with AB, 21.4% had vesicoureteral reflux, and 15.4% had renal scars[44].

Our study identified that another risk factor related to AB is the higher intake of sugar-sweetened beverages. A 5-year longitudinal study conducted in the United States of America showed that participants who drank a greater quantity of soft drinks or who increased their consumption during the time period were 1.29-1.75 times more likely to report progression or onset of UTI symptoms[45]. Another study conducted on British women under 40 years of age found that drinking at least one serving of soft drinks per day was associated with the presence of UTIs, overactive bladder, and urinary incontinence[45,46].

The main limitation of this study is its cross-sectional design, as it cannot establish temporality in the cause-effect relationship. Moreover, this study only represents adolescents in high schools and secondary schools, both private and public, in three municipalities of the central region of Tlaxcala state. In addition, there could be a memory bias regarding urinary symptomatology, measured over the last year.

Conclusions

AB is common in adolescents and represents an important risk factor for the development of long-term complications, such as CKD. In this study, the prevalence of bacteriuria was higher than the national average and more than double that reported in Latin America. The uropathogens and bacterial resistance found are similar to those reported in the scientific literature. Furthermore, to avoid complications, it would

be appropriate to identify the causes of bacteriuria in young populations, as these may be associated with genitourinary tract malformations and inappropriate use of antibiotics.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

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RESEARCH ARTICLE

Direct medical costs of polyarthritis in a pediatric hospital in Mexico

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Abstract

Background: *Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. The polyarticular course (polyarthritis) represents 63-66% of patients with JIA. The aim was to determine the direct medical costs (DMC) of JIA of the polyarthritis type in pediatric patients of a tertiary hospital in Mexico.* **Methods:** *An analysis of the disease costs was developed from the perspective of the Instituto de Seguridad Social del Estado de México y Municipios Maternal and Child Hospital (HMI). The time horizon was 12 years. All patients diagnosed with JIA with polyarticular course treated by the pediatric rheumatology service of the HMI from January to September 2022 and with an active clinical record were included. Different costing techniques were used. The cost components were consultations, medications, hospitalization, and office and laboratory studies. The costs are reported in USD 2021.* **Results:** *Twenty-six records of patients with polyarticular arthritis from the HMI were analyzed, with a mean of 4,555.2 USD (standard deviation [SD] = 1,456.7) and a median of 3,828 USD (SD = 1,492) in the first 10 years of treatment. The components of DMC were medications (82.7%), office and laboratory studies (8.4%), hospitalization (8.0%), and consultations (1.8%). Biological disease-modifying drugs (bDMARDs) accounted for 95.3% of the drug component cost.* **Conclusion:** *The cost of bDMARDs represented the most critical cost of polyarticular JIA, reflected in the 2nd year of treatment. Including generic bDMARDs and reviewing purchase prices by health institutions in Mexico is necessary.*

Keywords: *Direct medical costs. Polyarthritis. Mexico. Juvenile idiopathic arthritis.*

Costos médicos directos de la poliartritis en un hospital pediátrico en México

Resumen

Introducción: *La Artritis Idiopática Juvenil (AIJ) constituye la enfermedad reumática más común en la edad pediátrica. El curso poliarticular (poliartritis) representa entre el 63-66% de los pacientes con AIJ. El objetivo fue determinar los costos médicos directos (CMD) de la AIJ del tipo poliatritis en pacientes pediátricos de un hospital de tercer nivel en México.* **Métodos:** *Se desarrolló un análisis de costos de la enfermedad desde la perspectiva del Hospital Materno Infantil del ISSEMyM (HMI). El horizonte temporal fue de 12 años. Se incluyeron a todos los pacientes con diagnóstico de AIJ con curso*

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poliarticular atendidos por el servicio de Reumatología Pediátrica del HMI de enero a septiembre de 2022 que contaban con expediente clínico activo. Se emplearon diferentes técnicas de costeo. Los componentes de costos fueron: consultas, medicamentos, hospitalización, estudio de gabinete y laboratorio. Los costos están reportados en USD 2021. **Resultados:** *Se analizaron 26 expedientes de pacientes con artritis poliarticular del HMI los cuales presentaron una media de 4,555.2 USD (D.E. = 1,456.7) y una mediana de 3,828 USD (D.E. = 1,492) en los primeros diez años de tratamiento. Los componentes de CMD fueron: medicamentos (82.7%), estudios de gabinete y laboratorio (8.4%), hospitalización (8.0%) y consultas (1.8%). Los medicamentos biológicos modificadores de la enfermedad (MBME) representaron el 95.3% del costo del componente de medicamentos.* **Conclusión:** *El costo de los MBME representó el costo más importante de la AJI poliarticular, este se reflejó a partir del segundo año de tratamiento. Resulta necesaria la inclusión de MBME enfermedad genéricos y la revisión de los precios de compra por parte de las instituciones de salud en México.*

Palabras clave: *Costos médicos directos. Poliartritis. México. Artritis idiopática juvenil.*

Introduction

Arthritis is a chronic degenerative disease characterized by joint inflammation that limits the range of joint motion with pain or joint tenderness. Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in the pediatric age group and is one of the leading causes of acquired disability in this age group[1]. The age of onset is typically between 1 and 16 years, with peak incidence around 5 years of age, and it frequently extends into adulthood. The disease is twice as common in females. The annual incidence of JIA worldwide is 8-23 cases/100,000 children under 16 years of age[2]. In Mexico, an annual incidence of 80-90 cases/100,000 children is reported[3]. The International League of Associations for Rheumatology proposes that JIA be classified into seven clinical subtypes: Oligoarticular, Rheumatoid-factor-positive polyarthritis and Rheumatoid-factor-negative polyarthritis systemic, enthesitis-related, psoriatic, and undifferentiated. These are mutually exclusive and have different clinical management approaches. In Mexico, it has been reported that the polyarticular course represents between 50% and 66% of patients with JIA[3-6] and that females account for 63% of JIA cases[4].

Treatment promotes better control of the disease's inflammatory activity, prevents disease progression and complications such as chronic damage, functional disability, and negative impact on growth and development, and achieves disease remission with a good quality of life. However, the costs of treatment can limit its adequate application in the population.

Treatment intends to achieve greater control of the inflammatory activity of the disease, avoiding consequences such as chronic damage and functional disability. The first line of treatment is non-steroidal anti-inflammatory drugs; these medications are used as adjuvants for the disease until the administration of disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX). The objective of MTX is to inhibit cell replication and block the production of cytokines such as interleukin 1 and tumor necrosis factor-α, preventing the replication of synovial cells and the production of collagenases (cartilage-destroying enzymes). When MTX fails to achieve the objective (due to intolerance or refractoriness), the following can be administered: leflunomide, sulfasalazine, cyclosporine, or methylprednisolone. In cases where there is no improvement because the arthritis is refractory to MTX, treatment continues with biological agent therapies such as etanercept, abatacept, tocilizumab, and anakinra[7,8].

Direct medical costs (DMC) are those incurred during the process of medical care. JIA's mean annual DMC internationally ranges from 193 USD in India[9] to 49,429 USD in the United Kingdom[10]. Costs have not been reported for other Latin American countries, specifically Mexico. Significant differences exist in the components of DMC across various studies. In some cases, the main cost corresponds to the pharmacological treatment component[9-15]; however, in other studies, the main cost component corresponds to health-care personnel[11,16-18]. The JIA subtype with the highest DMC is polyarthritis[19], followed by polyarthritis and systemic arthritis, although the differences between the latter two are minimal[19,20]. The management costs of JIA show significant variations between countries due to the specific characteristics of the health-care system (human, technological, and economic resources) and treatment protocols.

There is a clear absence in the scientific literature of cost evaluation studies for JIA in Latin America, particularly in Mexico. This situation confers the need to obtain estimates of the DMC of JIA in Mexico, especially for the polyarthritis type. The study aimed to determine the DMC of polyarthritis[21].

Methods

A partial economic evaluation of the cost-of-illness type was developed from the perspective of the Hospital Materno Infantil (HMI). The time horizon was 12 years, covering from the diagnosis of the disease to the last available measurement. All patients diagnosed with polyarticular JIA treated by the pediatric rheumatology service of the HMI who had an active clinical record and had not been referred to another Instituto de Seguridad Social del Estado de México y Municipios (ISSEMYM) medical unit for follow-up were included. Resource identification was carried out through the review of clinical records.

Medications were classified into seven groups according to the therapeutic objective established by the HMI's pediatric rheumatology service: (a) biological disease-modifying drugs, (b) synthetic disease-modifying drugs, (c) concomitant medications, (d) prophylactics, (e) treatments for adverse effects of other medications, (f) inflammation and pain, and (g) those to address complications from the disease.

Each patient contributes information depending on their chronological follow-up time within the institution, from their diagnosis to record review in 2022. Patients were classified according to their management status as (a) patient at the time of record review (in treatment [TX]), (b) in clinical remission with medication (CRMM), and (c) in clinical remission without medication (CRWM). Information on the patient's age, sex, and rheumatoid factor (+ or –) was also included.

Costs were estimated for each patient, including diagnostic, treatment, and follow-up costs. Cost components were divided into consultation costs, medications, hospitalization, imaging studies, and laboratory tests. The micro-costing technique (unit price × quantity) was used for medication and medical supply components. The average cost technique (institutional cost/recovery fees × quantity) was also used for imaging and laboratory studies, bed day/hospitalization costs, procedures, and consultations.

Costs primarily come from two sources of information: 1. The unit acquisition costs of medications and medical supplies from the HMI in 2021, and 2. The average costs/recovery fees reported by ISSEMyM, both published in the electronic version of the Official Gazette "*Gaceta del Gobierno*"[21]. In addition, costs from the recovery fee schedules of the *Hospital Infantil de México Federico Gómez* were used[22].

Two estimates of DMC were made. The first DMC estimate corresponds to an administrative-type approach, which provides information on the total average cost and per component for each patient with JIA per year for the entire patient population and projects the institution's budget according to its future service offerings. This estimate includes the report of central tendency measures, mean and standard deviation (SD), as well as the percentage contribution of each component to the total cost for each year. In addition, the average percentage contribution of each component over the 12 years of follow-up for this population is reported.

The second estimate includes a more analytical approach, with information corresponding to the specific DMCs for the population that did incur expenses in a given component in a specific year of the disease. This is considered valuable information for decision-making regarding its management. Since the costs obtained do not present a normal distribution, the distributions were evaluated using the Kernel density graphical method and the skewness/kurtosis statistics method. In this second analysis, non-parametric measures are reported (median and 25^{th}-75^{th} percentiles). Finally, a cost analysis of the resource structure of the medication component was performed according to the previously proposed classification.

All costs are reported in US dollars, using the exchange rate of December 31, 2021 (1 USD = 20.5157 MXN)[23]. This study was approved by the HMI research committee, registration 01-2022.

Results

Twenty-six medical records of patients with polyarticular arthritis were analyzed. Twenty-two records corresponded to female patients (84.6%), the frequency of positive rheumatoid factor was 43%, the mean age of patients was 16.1 years (SD = 1.8), the age of disease onset was 9.6 years (SD = 3.5) with an average disease treatment time of 6.5 years (SD = 2.9), with a minimum of 2 years and a maximum of 12 years. The results of the clinical evaluation indicate that 18 patients were in treatment (TX) (69.2%), six were in CRMM (23.1%), and two were in CRWM (7.7%).

Table 1 reports the total DMCs and by component for each of the 12 years, finding a mean of USD 4,555.2 (SD = 1,456.7) in the first 10 years, and the relative weight of the components of consultation, hospitalization, imaging, and laboratory studies, and finally medications of 1.8%, 8.0%, 8.4%, and 82.7%, respectively.

Table 2 presents the median estimate and interquartile range (IQR) of patients who required medical attention from the institution for each component, total DMC, and

Table 1. Annual direct medical costs by component and percentage

Year	Cost component	n	Mean	Standard deviation	%
1	Hospitalization	26	$305.3	$1,019.1	17.8
	Consultation	26	$124.3	$257.9	7.2
	Diagnostic imaging and laboratory	26	$417.0	$339.9	24.3
	Medications	26	$869.7	$1,729.9	50.7
	Total cost	26	$1,716.4	$2,246.4	
2	Hospitalization	26	$269.7	$760.9	5.5
	Consultation	26	$81.8	$48.6	1.7
	Diagnostic imaging and laboratory	26	$409.8	$252.6	8.4
	Medications	26	$4,142.3	$4,592.9	84.5
	Total cost	26	$4,903.6	$4,943.0	
3	Hospitalization	24	$435.4	$1,478.8	6.4
	Consultation	24	$63.6	$38.6	0.9
	Diagnostic imaging and laboratory	24	$298.3	$173.2	4.4
	Medications	24	$6,037.6	$6,169.9	88.3
	Total cost	24	$6,834.8	$6,577.6	
4	Hospitalization	22	$421.2	$1,186.7	7.0
	Consultation	22	$65.4	$36.8	1.1
	Diagnostic imaging and laboratory	22	$295.6	$164.7	4.9
	Medications	21	$5,517.2	$5,074.0	91.2
	Total cost	22	$6,048.6	$5,657.4	
5	Hospitalization	20	$347.1	$849.0	7.1
	Consultation	20	$63.6	$49.7	1.3
	Diagnostic imaging and laboratory	19	$344.7	$376.9	7.1
	Medications	19	$4,348.6	$3,694.5	89.3
	Total cost	20	$4,869.3	$3,953.4	
6	Hospitalization	18	$180.3	$629.1	3.5
	Consultation	18	$46.9	$29.0	0.9
	Diagnostic imaging and laboratory	18	$258.6	$184.6	5.0
	Medications	18	$4,660.6	$4,787.6	90.6
	Total cost	18	$5,146.3	$4,744.6	
7	Hospitalization	14	$489.9	$1,321.8	10.7
	Consultation	14	$38.6	$33.3	0.8
	Diagnostic imaging and laboratory	14	$255.2	$244.0	5.6
	Medications	14	$3,783.0	$4,146.8	82.8
	Total cost	14	$4,566.7	$4,181.8	

(Continues)

Table 1. Annual direct medical costs by component and percentage *(continued)*

Year	Cost component	n	Mean	Standard deviation	%
8	Hospitalization	9	$698.4	$2,095.3	16.3
	Consultation	9	$91.6	$182.7	2.1
	Diagnostic imaging and laboratory	9	$306.0	$251.0	7.2
	Medications	9	$3,179.9	$3,265.3	74.4
	Total cost	9	$4,276.0	$3,465.9	
9	Hospitalization	7	$255.2	$675.2	5.9
	Consultation	7	$35.8	$18.2	0.8
	Diagnostic imaging and laboratory	7	$415.3	$316.4	9.6
	Medications	7	$3,638.0	$2,217.9	83.7
	Total cost	7	$4,344.3	$2,180.0	
10	Hospitalization	5	$-	$-	0.0
	Consultation	5	$29.0	$19.5	1.0
	Diagnostic imaging and laboratory	5	$212.6	$118.8	7.5
	Medications	5	$2,604.9	$2,761.5	91.5
	Total cost	5	$2,846.5	$2,816.2	
11	Hospitalization	3	$-	$-	0.0
	Consultation	3	$17.6	$20.1	6.8
	Diagnostic imaging and laboratory	3	$214.1	$62.3	82.6
	Medications	3	$27.6	$47.8	10.7
	Total cost	3	$259.2	$103.8	
12	Hospitalization	1	$-	$-	0.0
	Consultation	1	$13.2	$-	13.0
	Diagnostic imaging and laboratory	1	$88.4	$-	87.0
	Medications	1	$-	$-	0.0
	Total cost	1	$101.6	$-	
Promedio 10 años	Hospitalización				8.0
	Consulta				1.8
	Gabinete and laboratorio				8.4
	Medicamentos				82.7

The average of the first 10 years is reported because the information corresponding to years 11 and 12 primarily relates to patients in remission on conventional synthetic disease-modifying antirheumatic drugs, a situation that distorts the structure of cost components compared to the rest of the years.

the number of patients for each year (n). It is worth mentioning that because the population size is different for each component, it is not valid to attempt to sum the medians of each component to estimate the total DMC for each year; the latter is reported based on the median of the DMC variable. In the first 10 years of treatment, the total DMCs of patients with JIA have an average of USD 3,828 (SD = 1,492). For the different components, these presented the following costs: consultations USD 54.7 (SD = 17.3), imaging and laboratory studies USD 308.0 (SD = 52.0), hospitalization USD 2,348.5 (SD = 1,776.4), and finally medications USD 4,285.1 (SD = 2,008.4).

Table 2. Annual cost of treatment

Year	Cost component	n	Median	P25	P75
1	Hospitalization	4	$1,519.8	$301.6	$4,132.3
	Consultation	20	$65.9	$26.4	$115.3
	Diagnostic imaging and laboratory	24	$356.3	$158.4	$703.9
	Medications	18	$148.8	$24.2	$2,132.8
	Total cost	26	$509.5	$182.6	$2,909.9
2	Hospitalization	5	$1,196.9	$221.7	$2,686.0
	Consultation	24	$92.3	$52.7	$115.3
	Diagnostic imaging and laboratory	26	$353.2	$262.0	$494.6
	Medications	24	$3,468.6	$207.7	$7,598.7
	Total cost	26	$3,824.1	$782.7	$7,676.7
3	Hospitalization	3	$4,373.9	$100.2	$5,975.3
	Consultation	24	$65.9	$39.5	$79.1
	Diagnostic imaging and laboratory	24	$296.1	$200.1	$406.4
	Medications	23	$3,971.0	$99.5	$12,410.3
	Total cost	24	$4,535.4	$380.9	$12,032.0
4	Hospitalization	3	$2,658.1	$1,792.5	$4,816.3
	Consultation	22	$59.3	$39.5	$92.3
	Diagnostic imaging and laboratory	20	$331.5	$227.7	$431.0
	Medications	20	$5,144.2	$542.1	$9,852.6
	Total cost	22	$5,673.8	$48.0	$8,747.7
5	Hospitalization	3	$2,259.0	$2,215.5	$2,468.3
	Consultation	20	$52.7	$26.4	$79.1
	Diagnostic imaging and laboratory	16	$282.9	$188.1	$475.3
	Medications	19	$3,087.6	$2,266.8	$6,029.1
	Total cost	20	$4,174.8	$9.9	$6,161.2
6	Hospitalization	2	$1,622.5	$610.7	$2,634.3
	Consultation	16	$52.7	$39.5	$65.9
	Diagnostic imaging and laboratory	17	$299.3	$80.5	$397.2
	Medications	13	$7,496.5	$1,632.8	$8,935.8
	Total cost	18	$4,589.0	$-	$8,254.5
7	Hospitalization	3	$1,783.2	$300.2	$4,775.3
	Consultation	12	$46.1	$13.2	$79.1
	Diagnostic imaging and laboratory	12	$251.2	$91.1	$441.3
	Medications	9	$6,575.3	$2,506.8	$7,914.6
	Total cost	14	$4,069.5	$-	$4,923.4

(Continues)

Table 2. Annual cost of treatment *(continued)*

Year	Cost component	n	Median	P25	P75
8	Hospitalization	1	$6,285.9	$6,285.9	$6,285.9
	Consultation	7	$39.5	$26.4	$79.1
	Diagnostic imaging and laboratory	9	$243.4	$107.8	$541.0
	Medications	6	$4,716.5	$2,961.2	$7,462.4
	Total cost	9	$4,277.5	$169.0	$208.6
9	Hospitalization	1	$1,786.3	$1,786.3	$1,786.3
	Consultation	7	$39.5	$13.2	$39.5
	Diagnostic imaging and laboratory	6	$403.9	$268.2	$719.0
	Medications	6	$4,600.0	$2,511.3	$5,833.7
	Total cost	7	$4,666.7	$3,186.1	$6,088.1
10	Hospitalization	0			
	Consultation	4	$32.9	$26.4	$49.4
	Diagnostic imaging and laboratory	5	$263.2	$86.5	$313.3
	Medications	4	$3,642.3	$562.1	$5,564.2
	Total cost	5	$1,966.1	$297.9	$5,835.3
11	Hospitalization	0			
	Consultation	2	$26.4	$13.2	$39.5
	Diagnostic imaging and laboratory	3	$244.7	$142.4	$255.0
	Medications	1	$82.9	$82.9	$82.9
	Total cost	3	$294.6	$142.4	$340.8
12	Hospitalization	0			
	Consultation	1	$13.2	$13.2	$13.2
	Diagnostic imaging and laboratory	1	$88.4	$88.4	$88.4
	Medications	0			
	Total cost	1	$101.6	$101.6	$101.6

Figure 1 shows the evolution of total DMCs for each year of follow-up obtained with both estimates, which are relatively consistent in the behavior of DMCs. However, it can be seen that the first estimate (mean) tends to overestimate the cost results compared to the second estimate (median). From the 2nd year onwards, treatment DMCs increase, remaining relatively stable, only decreasing after the 9th year.

Analyzing each component over time, we observe that in the hospitalization component, during the 12 years of follow-up, only 10 of the 26 patients (38.46% of the total) used hospitalization services, with a total of 123 hospitalization events. Hospitalizations occurred only in the first 9 years, with a mean cost of USD 2,348.6 (SD = 1,776.4) and a median of USD 1,784.8 (1,510-3,087) for the first 10 years. Compared to the 1st year, an increasing cost trend was found, with some peaks in years 3 and 8 (Fig. 2A).

The medication component constitutes the highest cost within the total DMC. A total of 43 different medications were administered to the patients, with a median number of medications administered being 9 (IQR = 4). The mean cost was USD 4,285.1 (SD = 2,008.4), and the median was USD 4,285.5 (3,457.13-5,502.0) per patient per year during the first 10 years. We found that the cost of medications gradually increased during the first 6 years and subsequently decreased until reaching a minimum below the cost reported in year 1 (Fig. 2B).

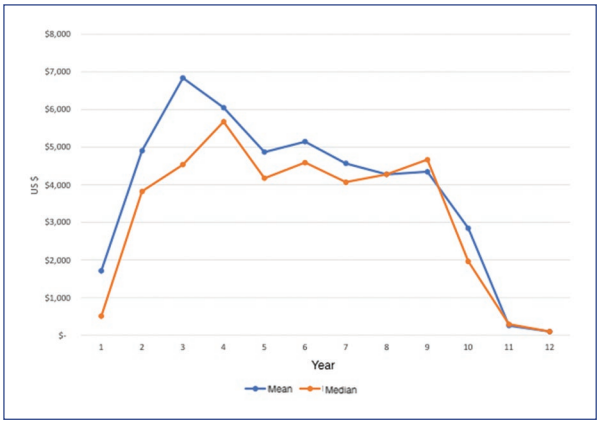

Figure 1. Evolution of direct medical costs for polyarthritis during 12 years of follow-up.

The medication groups from highest to lowest cost (percentage share) are biological disease-modifying drugs (abatacept, adalimumab, etanercept, secukinumab, and tocilizumab) representing 95.6%, followed by synthetic disease-modifying drugs (hydroxychloroquine, leflunomide, MTX, and sulfasalazine) representing 2.04%, concomitant medications (calcitriol, calcium carbonate/Vitamin D3, carboxymethylcellulose, ferrous fumarate, mycophenolate sodium, prednisone, polyethylene glycol/propylene glycol, and tobramycin) 1.7%, prophylactic treatments (folic acid, rifampicin, rifampicin/isoniazid, cholecalciferol, and Vitamin D) 0.5% of the total, pharmacotherapy for addressing adverse effects of other medications (esomeprazole and omeprazole), treatment for inflammation and pain (acetylsalicylic acid, diclofenac, etoricoxib, ibuprofen, naproxen, and acetaminophen) 0.1%, and medications for treating disease complications (alendronic acid and colchicine) (Fig. 3). According to clinical management, biological disease-modifying drugs are gradually incorporated from the 2nd year of treatment, which coincides with the pattern of cost increase for this component (Fig. 2B).

The consultation component represents the lowest DMC for the institution, with a mean of USD 54.7 (SD = 17.3) and a median of USD 52.7 (39.5-65.9) in the first 10 years of follow-up. However, this component shows an increase in the 2nd year (40%), a cost that subsequently decreases until reaching 20% of that reported in the initial year (Fig. 2C).

Finally, the diagnostic imaging and laboratory studies component presents a mean of USD 308.0 (SD = 52.0) and a median of USD 297 (262.8-353.9). In this component, we observe that costs decrease consistently over time; in the 12th year, the cost represented 25% of the initial year's cost (Fig. 2D).

Discussion

There are no reports on the estimation of DMC for JIA of the polyarthritis subtype from the perspective of public health service providers in Latin America. This study represents one of the first efforts to estimate these costs and demonstrates that the medication component represents 82.7% of the total DMC for care in the first 10 years of these patients, with biological disease-modifying drugs accounting for 95.6% of the total cost.

In this study, medical records were retrospectively analyzed over 12 years; only the studies by Luca et al. 2016[24], Mars et al. 2019[25], and Kip et al. 2021[14] conducted cost follow-ups over long periods of 5, 9, and 10 years, respectively. The study by Kip et al. Only examined costs derived from the use of synthetic and biological disease-modifying drugs. In contrast, Luca et al. 2016[24] study included costs of consultations, laboratory tests, and hospitalizations. Other studies that analyzed the same cost components are those by Thornton et al. in 2008[a], Thornton et al. in 2008[b16,18], and Minden et al. in 2009[19], although the latter presents these components in a more disaggregated form. The duration of this study offers us a broader panorama of treatment throughout the disease and includes the estimation of the same components, so it can be considered to have a good design and allows comparability with these studies.

This study did not include estimates related to the rehabilitation process, as this stage of care is carried out in another hospital unit. Bernatsky et al. 2007[15] and Thornton et al. 2008[a16] did include these types of costs without specifying the proportion relative to the total DMC. Only the study by Yucel et al. 2012[11] mentions that rehabilitation costs (physiotherapist) represent 0.5% of the DMC. While the lack of cost information for the rehabilitation component could be considered a weakness in the present study, as it represents a percentage of 0.5% of the cost reported in another study[11], it should not affect the DMC estimation and distort the estimated relative weight of participation of the four components estimated here. Although the consultation component has the lowest participation within the DMC, it is a key component since the treatment of patients with JIA is mainly carried out on an outpatient basis, a period during which, in addition to clinical assessments of patients, the delivery and application of pharmacological treatments are performed.

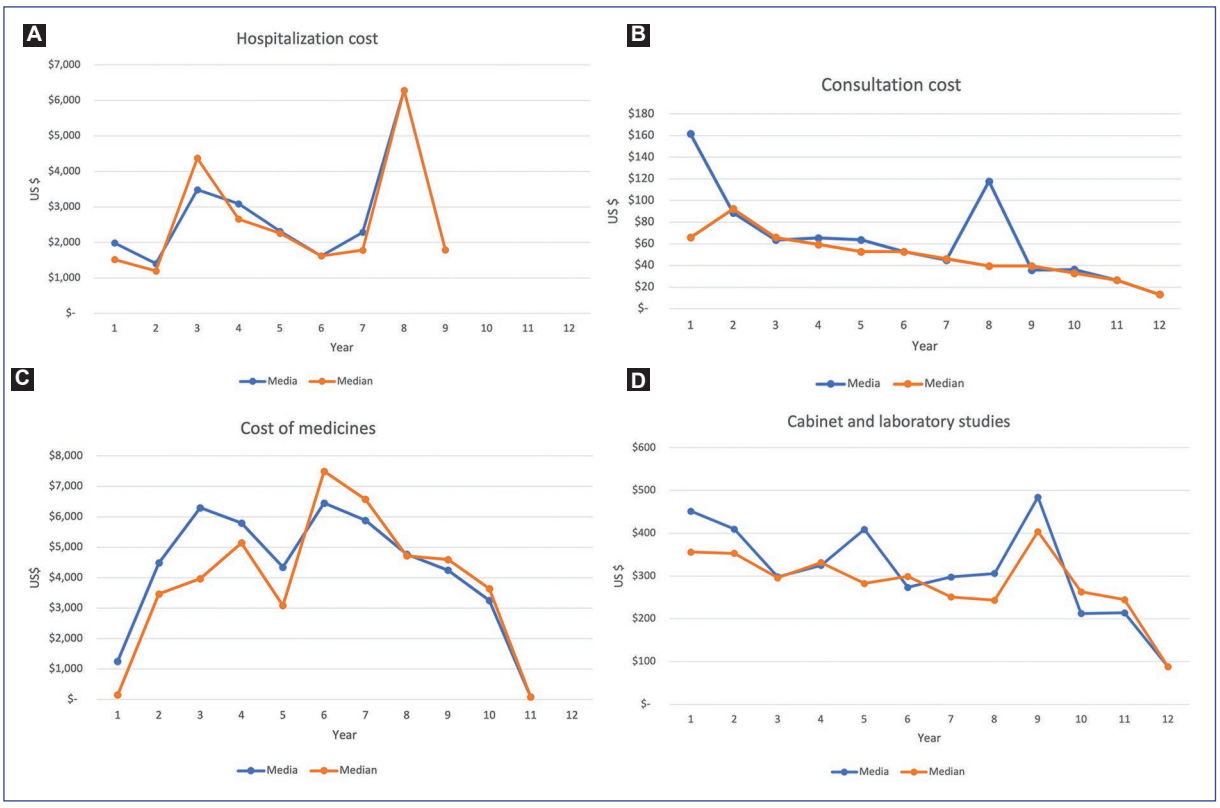

Figure 2. Evolution of the different cost components of polyarthritis. **A:** hospitalization. **B:** medications. **C:** consultations. **D:** cabinet and laboratory studies.

Among the limitations of our study, it should be considered that in recent years, a smaller number of patients were observed compared to the initial years. Therefore, the results of the last 3 years could be considered less robust. When analyzing the information, it should be considered that the results are representative of the disease for the first 10 years of illness. It is worth noting that the two cases of patients with Remission on Conventional Synthetic DMARDs occur in years 11 and 12, which is why, in those years, there is a modification in the relative weight of resource use and DMC within the disease. Another limitation of the study is that the average costs/recovery fees reported by ISSEMyM mainly contemplate the variable costs of services or procedures offered by the institution, not the fixed costs. However, considering the conditions of most public institutions in Mexico, which generally, due to their age, already have depreciated equipment and infrastructure and considering the type of disease management, we believe that underestimating fixed costs in this case does not affect the estimated results.

For the present study, the median annual DMC per patient amounted to a mean of USD 4,555.2 (SD = 1,456.7) and a median of USD 3,828 (SD = 1,492) in the first 10 years of treatment. These costs are similar to those previously reported[26]. However, there are studies in which the reported costs are below those reported in the present work and preceding studies. One of these is the study by Ens et al. 2013, which reports costs well below those reported in the present study. Nevertheless, the work of this group was conducted from the family's perspective, not from the service provider's perspective. The study by Khatun et al.[9] also reported lower costs, with annual DMCs of USD 193. In that study, few individuals used biological disease-modifying drugs; however, in cases where this medication was used, costs doubled, although they remained low despite this.

Another prospective study conducted in the United Kingdom in patients with polyarthritis, which compared the change in DMC during the first 6 months of treatment in 1989 and 10 years later, showed that the average DMC per patient was USD 1,003 in 1989 and almost doubled by 1999, with a cost of up to USD 2,578 (adjusted for exchange rate and inflation to 2021)[27]. Through the data from the present study, we identified that the median costs increase exponentially from the

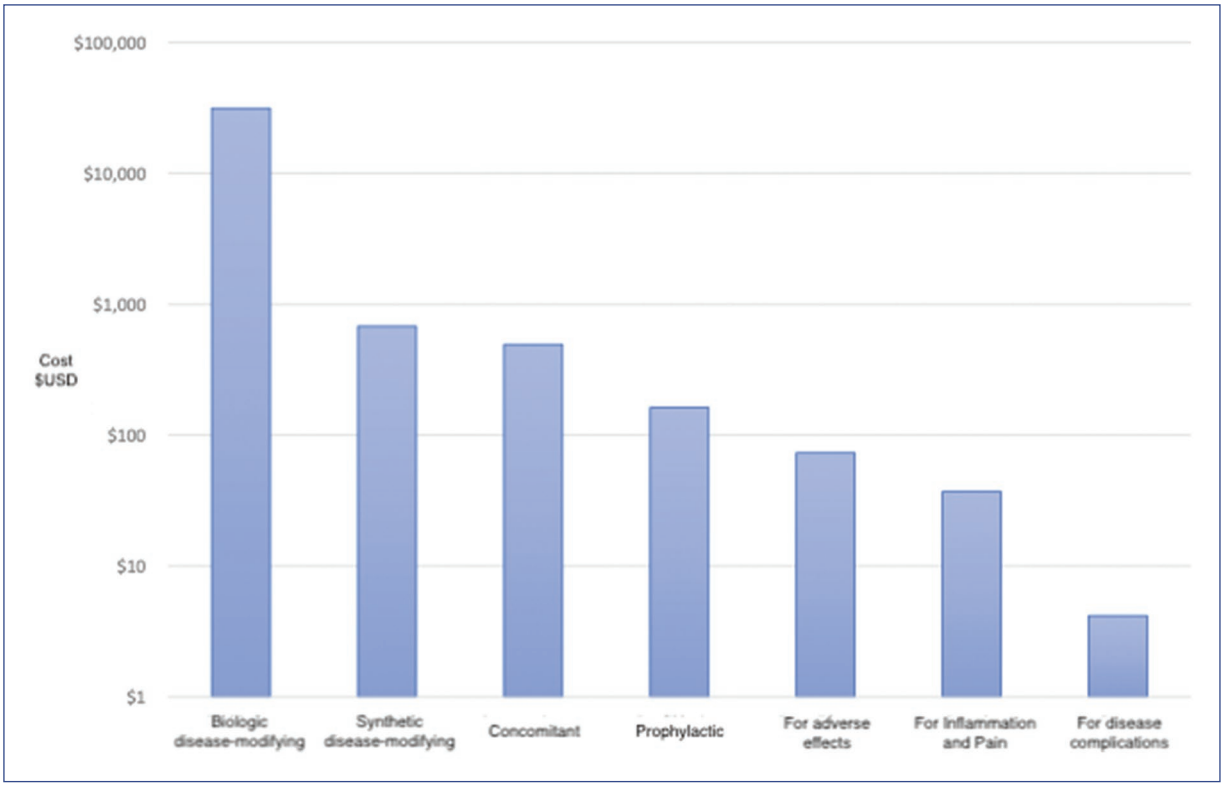

Figure 3. Cost by type of medication.

1st year, with the 4th year being where the median cost is ten times higher than the 1st year. After that year, the median costs decrease gradually until reaching values similar to those obtained during the 1st year, between years 11 and 12. These data are similar to those reported by Nikiphorou et al. 2015[27], in which it is observed that as time passes, patients incorporate biological disease-modifying drugs into their treatment, thereby increasing the costs of the medication component. This coincides with what was observed in years 3 and 4 of our study and with other studies reporting that when this type of medication is incorporated, there is an increase in the cost of between 200%[9] and 300%[13] compared to the non-use of these biological drugs. In our study, an increase of 550% is observed between the 1st and 2nd years, and the total DMC increases by about 651%. However, the increase in the cost of the medication component is 2,327%, which is well above what was expected even when not compared to the value of the 7th year of treatment, where the maximum value is found (4,930%). This leads us to believe that this increase is due to the low prices of disease-modifying drugs (non-biological) during the 1st year or to the excessive increase observed in the cost of biological disease-modifying drugs from the 2nd year onward.

The pharmacological component represents a very high percentage (82.7%) of the total DMC, a figure that is very similar to that reported by Yucel et al. (85%)[11]. In other studies, this component represents a highly variable percentage, between 9 and 54%[9,10,15,16,20,27]. Considering that the total DMCs are relatively similar, we are inclined to think that this variability is due to an overpricing of medications in the Mexican health system.

Based on these results, we suggest replacing patented biological disease-modifying drugs with effective and safe generic medications that can generate savings for the health institution and expand current coverage. If this is not possible, public health institutions should conduct a detailed review of purchase prices from pharmaceutical companies.

According to other authors, the polyarticular clinical subtype of JIA is the most expensive among the different subtypes, followed by the polyarthritis and systemic arthritis subtypes[19,20]. These figures suggest that the estimated cost of polyarthritis could overestimate the average DMC of the disease if it were used

for the rest of the JIA patient subtypes in Mexico, except the polyarthritis and systemic arthritis subtypes, according to the cost differences reported in other studies[11,19,20,28].

We consider that future studies should make estimates for other JIA subtypes in the Mexican context. Likewise, it is suggested to make estimates of out-of-pocket expenses or indirect costs, which could be useful to estimate the cost of the disease from the user's and/or society's perspective. In addition, it would be interesting to include the costs and disease burden on caregivers. Finally, because the natural course of polyarthritis continues into adulthood, it would be important to estimate the costs over the lifetime of these patients.

Conclusion

Patients with JIA of the polyarthritis subtype at HMI presented an annual mean DMC of USD 4,555.2 (SD = 1,456.7) and a median of USD 3,828 (SD = 1,492) in the first 10 years of the disease.

The main component of DMC in the first 10 years of treatment was the medication component (82.7%), followed by diagnostic imaging and laboratory studies (8.4%), hospitalization (8.0%), and finally, the consultation component (1.8%).

The cost of biological disease-modifying drugs represented 95.6% of the DMC within the medication component and is reflected in the 2nd year of treatment. Therefore, it is important to include generic medications or review purchase prices by Mexican public health institutions from pharmaceutical companies.

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Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

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CLINICAL CASE

Graft-versus-host disease variety toxic epidermal necrolysis. Case report

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Abstract

Background: *We present the case of a patient who underwent hematopoietic progenitor cell transplantation from a fully compatible unrelated donor and subsequently developed Grade IV skin graft-versus-host disease (GVHD) resembling toxic epidermal necrolysis (TEN).* **Clinical case:** *An 11-year-old female, post-transplantation of hematopoietic progenitor cells from a 100% compatible unrelated donor, developed rash-like skin lesions on the trunk and extremities on day +35. A skin biopsy revealed dermal atrophy, vacuolization of the basal layer, and confluent apoptotic keratinocytes with mononuclear inflammatory cells in the dermoepidermis, confirming the diagnosis of TENlike acute cutaneous GVHD.* **Conclusion:** *The patient experienced an 80% remission of symptoms following dynamic management of immunosuppressants.*

Keywords: *Toxic epidermal necrolysis. Graft-versus-host disease. Hematopoietic stem cell transplantation.*

Enfermedad de injerto contra hospedero cutánea variedad necrólisis epidérmica toxica. Reporte de caso

Resumen

Introducción: *Se presenta el caso de paciente post trasplantado de células progenitoras hematopoyéticas de donador no relacionado 100% compatible con desarrollo de enfermedad, injerto contra hospedero cutánea grado IV tipo necrólisis epidérmica tóxica.* **Caso clínico:** *Femenino de 11 años, post trasplantada de células progenitoras hematopoyéticas donador no relacionado 100% compatible realizada el 01.02.23, en su día +35 inicia con lesiones dérmicas exantemáticas en tronco y extremidades, biopsia de piel que reporta atrofia de dermis, vacuolización de la capa basal, queratinocitos apoptóticos confluentes con células inflamatorias mononucleares en dermoepidermis, confirmando así el diagnóstico de enfermedad injerto contra huésped cutánea tipo Necrólisis Epidérmica Tóxica.* **Conclusión:** *Paciente presenta remisión de la sintomatología en un 80%, posterior al manejo dinámico de los inmunosupresores.*

Palabras clave: *Necrólisis epidérmica tóxica. Enfermedad injerto contra huésped. Trasplante de células progenitoras hematopoyéticas.*

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Introduction

Bone marrow transplantation represents a therapeutic option for refractory malignant neoplasms; one of the most frequent complications is graft-versus-host disease (GVHD). The cutaneous manifestation of this disease can be severe with generalized erythroderma, desquamation, and blisters that mimic toxic epidermal necrolysis (TEN). The variety that simulates TEN is extremely rare, occurring in approximately 0.4-1.2/ million people, causing almost 100% mortality.

Clinical case

An 11-year-old female patient post-transplanted with hematopoietic stem cell transplantation from an unrelated donor with 100% human leukocyte antigen (HLA) compatibility, with a history of acute lymphoblastic leukemia with early relapse to bone marrow and central nervous system. On day +35, she developed a disseminated dermatosis on the head, trunk, and upper extremities, affecting the cheeks, anterior chest, and anterior aspect of the arms. The dermatosis was characterized by a plaque composed of macules and papules on an erythematous base with irregular and poorly defined borders, disappearing with digital pressure, with acute evolution, and associated with mild pruritus.

A skin biopsy was performed, which reported epidermal atrophy, basal layer vacuolization, focally confluent apoptotic keratinocytes, no vesicle formation, and a dermo-epidermal junction with mononuclear inflammatory cells arranged around blood vessels (Fig. 1).

A disseminated dermatosis was observed, extensively affecting various body areas, including the head, face, ears, neck, anterior chest, arms, forearms, hands, thighs, and genitals. The morphology of the lesions was heterogeneous and characterized by the following findings: erythematous plaques formed by the confluence of macules and papules. The macules were erythematous, flat, and non-palpable, while the papules were raised and also erythematous. Both had well-defined and regular borders. In addition, flaccid blisters were present, indicating an intraepidermal or subepidermal lesion. Furthermore, a positive Nikolsky sign was observed, where applying pressure or rubbing on apparently healthy skin induced epidermal detachment, indicative of severe epidermal fragility (Fig. 2).

Upon admission, the patient received systemic steroid treatment at 2 mg/kg/day; however, due to a poor evolution, immunomodulatory management was initiated with Sirolimus 1 mg/kg/day, Tocilizumab 8 mg/kg (4 doses), Infliximab 5 mg/kg (7 doses), Ruxolitinib 5 mg every 12 h, and human immunoglobulin 2 mg/kg (3 doses). At the time of this report, on day +65, the patient showed evident cutaneous improvement (Fig. 3).

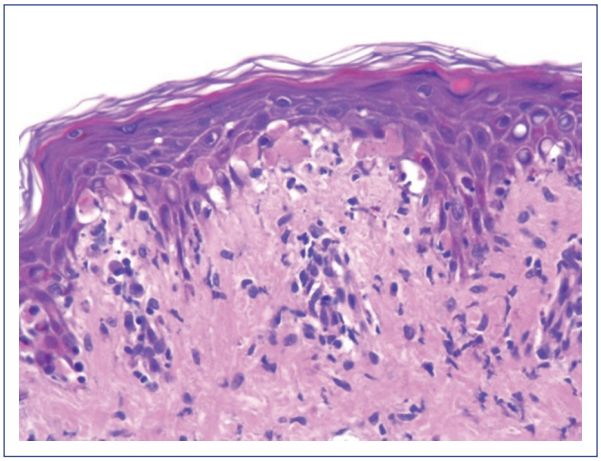

Figure 1. The image shows a section of the dermo-epidermal junction observed in a skin biopsy with hematoxylin and eosin staining. There is significant vacuolization of basal cells. A slight separation between keratinocytes is observed, suggesting intracellular edema. Keratinocyte necrosis is seen in the upper layers of the epidermis, indicating apoptosis. In the papillary dermis immediately adjacent to the epidermis, an inflammatory infiltrate composed predominantly of lymphocytes is observed. This is consistent with a T cell-mediated immune response, which is characteristic of graft-versus-host disease.

Discussion

Acute GVHD is a multisystemic disorder that occurs within 100 days following hematopoietic cell transplantation. In this condition, donor T lymphocytes play a central role in the immunological attack on host tissues. The main risk factors include HLA incompatibility, prophylaxis regimen, intensity of the conditioning regimen, sex disparity between donor and recipient, cell origin, cellular inoculum number, and advanced age of the donor or recipient. The most important risk factor is the difference in HLA system antigens between the donor and the recipient[1].

The cutaneous presentation initially shows an acral predilection, affecting the dorsum of hands and feet, palms, soles, forearms, face, ears, retro auricular area, and upper third of the trunk. Afterward, it can become

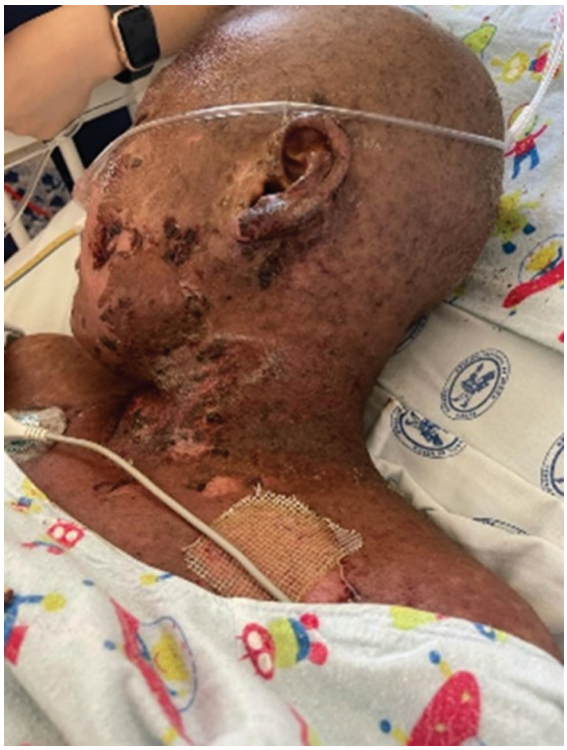

Figure 2. Day +55 post-hematopoietic stem cell transplantation: The lesions significantly affect the skin of the scalp, face, neck, and upper chest. Extensive areas of diffuse erythema with multiple erosions and ulcers are visible, some showing adherent hematic crusts. There are also areas of epidermal detachment, suggesting a severe cutaneous compromise.

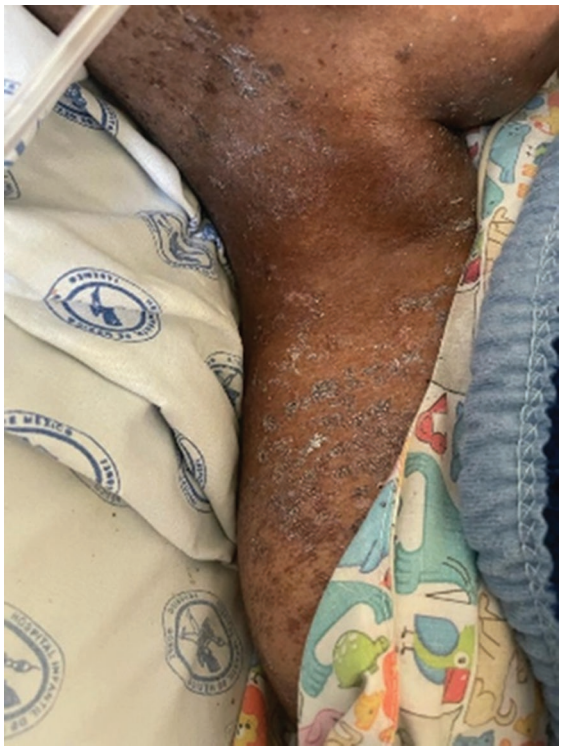

Figure 3. Day +65 post-hematopoietic stem cell transplantation: The lesions are located in the lateral region of the neck, with partial extension to the upper chest. Erythematous and desquamative plaques with a rough appearance are observed. The skin shows areas of irregular hyperpigmentation, as well as patches of fine, dry desquamation, suggesting an inflammatory process.

generalized. Regarding morphology, it manifests as a maculopapular rash, with diffuse macules that blanch or a morbilliform rash. It can progress to erythroderma with a folliculocentric pattern; in rare forms, it presents with blisters[1,2].

The patient's case was initially classified as acute, presenting on day +35, and stage 1 according to the degree of involvement, initially affected 12% of the body surface area. It subsequently progressed, exhibiting characteristics of stage 4 due to the presence of blisters and denuded areas, affecting 50% of the body surface area, as well as a positive Nikolsky sign, despite management with systemic steroids and sirolimus. With these findings, a diagnosis of cutaneous GVHD of the TEN type was made, which is a rare and of poorly described complications[3].

In the presence of TEN, it is important to rule out infections, which can also act as precipitating cofactors. Herpes simplex virus, some *Mycoplasma* species, mumps vaccine, and other genetic factors can act as predisposing factors in the pathogenesis[4].

Treatment is multidisciplinary and based on the immunosuppression of donor T cells, which are responsible for the clinical manifestations of GVHD. Regarding the skin, first-line treatment for stages I and II includes topical steroids and calcineurin inhibitors, as well as symptomatic management with antihistamines. In cases of cutaneous and systemic involvement, systemic steroid management is suggested until resolution of the condition. If there is no response, human immunoglobulin, rituximab, infliximab, and extracorporeal photopheresis can be considered. Treatment may include steroids, monoclonal antibodies, JAK inhibitors, and immunoglobulin[5].

In Mexico, no published studies have been found analyzing the incidence or mortality associated with this variant. An exhaustive search was conducted in scientific databases through the PubMed search

engine, covering the past 10 years, without identifying relevant publications from Mexico.

Conclusion

A pesar de que la necrólisis epidérmica tóxica en el contexto de un trasplante de células progenitoras tiene una alta tasa de mortalidad, nuestro paciente presentó remisión de la sintomatología en un 80%, posterior al manejo dinámico de los inmunosupresores, lo cual demuestra que con un manejo oportuno y dinámico se puede mejorar la sobrevida de estos pacientes.

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Conflicts of interest

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Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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LETTER TO THE EDITOR

Liver enzyme levels in adolescents with obesity and insulin resistance: a commentary

Niveles de enzimas hepáticas en adolescentes con obesidad y resistencia a la insulina: comentario

*Katherine Ning-Li**

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Dear Editor,

We read with great interest the article "Liver enzyme levels in adolescents with obesity and insulin resistance (IR): a propensity score matching analysis[1]."

This study effectively addresses obesity in adolescents, a significant concern in modern healthcare. With 365 participants aged 10-18 years, including 229 with IR, the research provides a robust sample size for meaningful analysis. This focused approach enables a deeper understanding of metabolic processes in this vulnerable population.

The study's comprehensive analysis of physical parameters, serum insulin, lipids, and liver enzymes-specifically aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase-offers a holistic view of these adolescents' metabolic profiles. This multi-faceted approach is essential for understanding the complex interplay between obesity, IR, and liver function during adolescent development.

A key strength of this research lies in comparing liver enzyme levels between obese adolescents with and without IR. This comparative analysis helps isolate IR's specific effects on liver function, independent of obesity. Notably, the use of propensity score matching to eliminate body mass index impact on liver enzyme levels enhances the study's validity by controlling for a major confounding factor, thereby enabling a more precise assessment of the relationship between IR and liver enzyme levels.

The study's most significant finding reveals higher AST levels in the insulin-resistant group compared to the non-insulin-resistant group among obese adolescents. This suggests that AST might serve as a risk factor for IR, potentially offering new opportunities for early detection and intervention in pediatric metabolic disorders. The elevated serum ALT and AST levels observed in obese adolescents with IR further support this hypothesis, indicating that AST alterations may constitute a potential risk factor for IR development.

While AST levels could potentially serve as a biomarker for IR in obese adolescents, several limitations warrant consideration. The cross-sectional design demonstrates only an association between IR and liver enzyme levels, rather than establishing causality. Consequently, the study cannot definitively determine whether elevated transaminases cause IR or vice versa.

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In addition, the absence of non-alcoholic fatty liver disease (NAFLD) assessment in study participants represents a significant limitation. NAFLD is closely associated with both IR and elevated liver enzyme levels, particularly in obese populations. This omission creates uncertainty in interpreting the observed liver enzyme elevations, as increased AST and ALT levels might indicate underlying NAFLD rather than direct associations with IR. Future studies should incorporate NAFLD screening to better elucidate these relationships.

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LETTER TO THE EDITOR

Anemia in children with obesity: is there a higher risk compared to eutrophic children?

Anemia en niños con obesidad: ¿existe un mayor riesgo en comparación con los niños eutróficos?

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Dear Editor,

Childhood obesity is a global public health problem, recognized as a chronic inflammatory multisystemic disease associated with other cardiometabolic conditions[1]. We conducted an observational study analyzing clinical records of children aged 2-18 years who were admitted to the pediatric service at Hospital General "Dr. Eduardo Vázquez N" during 2023. On admission, nutritional status was assessed using body mass index percentiles (Eutrophic: 5th-84.9th percentile; Overweight: > 85th percentile; and Obesity: > 95th percentile). Anemia was determined according to the World Health Organization (WHO) recommendations (< 2 standard deviations from age-and sex-specific hemoglobin levels). Student's t-tests were used to compare hemogram values across nutritional status categories, and Chi-square tests were performed to assess anemia risk.

Data from 295 pediatric patients were included, with a median age of 108 months. Females represented 49.2% (n = 145) of the sample. Among participants, 70.5% (n = 208) were eutrophic and 29.5% (n = 87) were overweight or obese. Overall, 16.6% of patients presented with anemia according to the WHO criteria. Anemia was present in 12.5% (n = 26) of eutrophic children and 26.4% (n = 23) of overweight and obese children. Children diagnosed with overweight and obesity showed an Odds Ratio of 2.51 (95% CI: 1.341-4.720; p = 0.004) for anemia. No significant differences were found in hemogram parameters between overweight/obese and eutrophic children, likely due to the comparison of absolute rather than percentile-adjusted values and the wide age range analyzed. These findings align with previous publications reporting high anemia prevalence in children with obesity[2,3].

In conclusion, overweight and obese children demonstrate a higher risk of anemia at hospital admission compared to eutrophic children, potentially due to the low-grade inflammation present in obesity. This condition may lead to additional comorbidities or increase the

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need for medical interventions, such as blood transfusions[4]. Further studies measuring inflammatory markers and iron deficiency parameters are needed to validate our findings.

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