Productos de investigación

2020

CUENTA DE ALTO COSTO

Fondo Colombiano de Enfermedades de Alto Costo

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Fondo Colombiano de Enfermedades de Alto Costo

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CONTENIDO

PRODUCCIÓN CIENTÍFICA CON IMPACTO EN LOS RESULTADOS DE LA GESTIÓN DE LAS ENFERMEDADES DE ALTO COSTO: **EL VALOR DE LA INVESTIGACIÓN CON DATOS DEL MUNDO REAL**

CUENTA DE ALTO COSTO
Fondo Colombiano de Enfermedades de Alto Costo

ENFERMEDAD RENAL CRÓNICA

CUENTA DE ALTO COSTO
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ERC Y PRECURSORAS

Air pollution, sociodemographic and health conditions effects on COVID-19 mortality in Colombia: An ecological study

Autores: Laura A. Rodriguez-Villamizar, Luis Carlos Belalcázar-Ceron, Julián Alfredo Fernández-Niño, Diana Marcela Marín-Pineda, Oscar Alberto Rojas-Sánchez. Lizbeth AlexandraAcuña-Merchán, Nathaly Ramírez-García, Sonia Cecilia Mangones-Matos, Jorge Mario Vargas-González, Julián Herrera-Torres, Dayana Milena Agudelo-Castañeda, Juan Gabriel Piñeros Jiménez, Néstor Y. Rojas-Roa, Victor Mauricio Herrera-Galindo

Revista: Science Total Environment (STOTEN)

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Trabajo colaborativo con la academia como actor de interés (Universidad Industrial de Santander)

Objetivo:

Determinar la asociación entre factores ambientales, sociodemográficos y condiciones de salud como la hipertensión y la mortalidad por COVID-19 en Colombia.

Principales hallazgos

- Asociación significativa entre exposiciones crónicas a contaminación ambiental y mortalidad por COVID-19.
- Población con edad >65 años, mayor índice de pobreza e hipertensa tienen mayores tasas de mortalidad a nivel municipal.

Relevancia de los hallazgos

- Identificación de población de alto riesgo de morir por COVID-19 desde una perspectiva de datos agregados.
- Acercamiento al trabajo colaborativo entre la CAC y la academia como actor de interés.
- Se reconoce la información de la CAC como insumo para la generación de investigación con datos nacionales de impacto internacional que aportan a la planeación de los servicios de salud ante la emergencia sanitaria.

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Air pollution, sociodemographic and health conditions effects on COVID-19 mortality in Colombia: An ecological study

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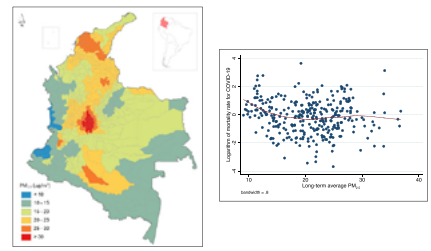
HIGHLIGHTS

- There was not a significant association between long-term exposure to $PM_{2.5}$ and COVID-19 mortality in Colombia.
- Demographic, health system, and social conditions are related to COVID-19 mortality.
- Population over 65 years, poverty index, and prevalence of hypertension are associated to the death rate.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective: The present study aimed to determine the association between chronic exposure to fine particulate matter ($PM_{2.5}$), sociodemographic aspects, and health conditions with COVID-19 mortality in Colombia.
Methods: We performed an ecological study using data at the municipality level. We used COVID-19 data obtained from government public reports up to and including July 17th, 2020. We defined $PM_{2.5}$ long-term exposure as the 2014–2018 average of the estimated concentrations at municipalities obtained from the Copernicus Atmospheric Monitoring Service Reanalysis (CAMSRA) model. We fitted a logit-negative binomial hurdle model for the mortality rate adjusting for sociodemographic and health conditions.
Results: Estimated mortality rate ratios (MRR) for long-term average $PM_{2.5}$ were not statistically significant in either of the two components of the hurdle model (i.e., the likelihood of reporting at least one death or the count of fatal cases). We found that having 10% or more of the population over 65 years of age (MRR = 3.91 95%CI 2.24–6.81), the poverty index (MRR = 1.03 95%CI 1.01–1.05), and the prevalence of

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Mortality
Colombia

hypertension over 6% (MRR = 1.32 95%CI1.03–1.68) are the main factors associated with death rate at the municipality level. Having higher hospital beds capacity is inversely correlated to mortality.
Conclusions: There was no evidence of an association between long-term exposure to $PM_{2.5}$ and COVID-19 mortality rate at the municipality level in Colombia. Demographics, health system capacity, and social conditions did have evidence of an ecological effect on COVID-19 mortality. The use of model-based estimations of long-term $PM_{2.5}$ exposure includes an undetermined level of uncertainty in the results, and therefore they should be interpreted as preliminary evidence.

1. Introduction

The SARS-CoV-2 is a new coronavirus responsible for the human coronavirus disease 2019 (COVID-19) initially reported in Wuhan, China, in December 2019. The rapid global spread of COVID-19 made the World Organization of Health (WHO) declare it a public health emergency of international concern (World Health Organization, 2020b). Up to and including July 20th 2020, 14,530,563 cases and 606,741 deaths have been reported in 188 countries (Johns Hopkins Coronavirus Resource Center, 2020). Approximately 80% of COVID-19 confirmed cases reported mild to moderate disease, and the average case fatality rate is 4.6%, with a wide variation across countries (Wang et al., 2020a).

Efforts to determine modifiable factors that could increase transmission, exacerbate symptoms, and increase the risk of COVID-19 mortality remain essential to guide public policies. Individual conditions such as age above 65 years and underlying chronic diseases, including diabetes, hypertension, cardiovascular disease, chronic lung disease, kidney failure, and cancer, have shown to increase the risk of mortality (Ruan et al., 2020; Lippi and Wong, 2020; Hussain et al., 2020; Zhou et al., 2020; Cheng et al., 2020). Environmental factors have also been explored with evidence of COVID-19 airborne transmission (Lu et al., 2020; Setti et al., 2020; Prather et al., 2020).

Short-term air pollutant concentrations, specifically particular matter (PM), might contribute to the spread of the pandemic by transporting viruses in aerosols (airborne transmission) to longer distances than the usual involved in close contacts transmitted through droplets (Zhang et al., 2020). In China, Zhu et al. (2020) conducted a time-series study with data of 120 cities during January and February of 2020. They found a positive association between the daily count of confirmed cases and concentrations of fine and coarse PM ($PM_{2.5}$ and PM_{10}, respectively), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) the two weeks before (lag 0–14). Similar findings for $PM_{2.5}$ and O_3 were reported in Italy by Borro et al. (2020) and Zoran et al. (2020) in studies analyzing data from 110 Italian provinces between February and March and data from Milan comparing correlations before and beyond lockdown. In the United States, Adhikari (2020) also found positive short-term associations between air pollutants and confirmed cases in New York. These studies suggest a significant relationship between air pollution and COVID-19 infection and PM's potential effect in airborne transmission. The role of PM as a potential carrier of the SARS-CoV-2 was analyzed for the pandemic in Italy. The authors compared PM10 concentrations and events in Lombardy (the region with a higher number of cases and deaths) and Piedemont (located near Lombardy with less affectation) before and during the first peak of the pandemic. The results showed that the cities in the Piedemont region had even more PM10 pollution events than the cities in the Lombardy region, suggesting that short-term concentrations of PM10 do not fully explain the spread and severity of the pandemic (Bontempi, 2020).

Long-term exposure to atmospheric pollution has been hypothesized as a contributing factor for explaining mortality related to COVID-19. This hypothesis is based on the evidence that chronic exposure to air pollutants is associated with chronic inflammatory response and overexpression of inflammatory cytokines and chemokines (Gouda et al., 2018) and with the development of chronic respiratory and cardiovascular diseases (Brunekreef and Holgate, 2002; Brook, 2008). These factors might increase infected people's susceptibility to SARS-CoV-2 and therefore, might mediate the pathway between chronic exposure to air pollution and COVID-19 mortality (See Supplementary material Fig. S1).

Italy was the first country affected by the pandemic in Europe, with an outbreak and mortality larger than the one observed in the city of Wuhan. The regions in Northern Italy exhibited the higher mortality rates for COVID-19 coinciding with the regions with higher air pollutant concentrations, suggesting that chronic exposure to air pollution might contribute to SARS-Cov-2 lethality (Conticini et al., 2020). Fattorini and Regoli (2020) assessed the correlation between chronicity of exposure to air pollution and COVID-19 mortality by using a regional distribution of the mean concentration NO_2, PM_{10}, $PM_{2.5,}$ and O_3 from 2016 to 2019, the number of days per year in which the regulatory limits of PM_{10} and O3 were exceeded, and the number of years during the last decade (2010–2019) in which limit value of PM_{10} was exceeded for at least 35 days. They found significant correlations between all three measurements, supporting early and preliminary evidence on the role of chronic exposure to air pollution on COVID-19 mortality. These studies provided meaningful results; however, they did not control for potential confounding factors involved in the relationship between chronic exposure to air pollution and COVID-19 mortality. Ecological studies conducted in China and United States controlling for a variety of sociodemographic and health conditions showed that chronic air pollution exposure, mainly to NO_2, $PM_{2.5}$ SO_2, increase the COVID-19 mortality risk by 11.2% (CI95%: 3.4%–19.5%), 15% (CI95%:5% - 25%) and 17.2% (CI95%:0.5%–36.9%), respectively (Wu et al., 2020; Yao et al., 2020; Liang et al., 2020).

The pandemic dynamics have had geographic transitions, from China to Europe and then to America, with a growing impact in Latin America and the Caribbean (World Health Organization, 2020a; Kirby, 2020). In developing countries of Latin America, average of air pollutant concentrations are usually higher than levels reported in high-income countries of Europe and North America, especially for $PM_{2.5}$ (World Health Organization, 2020c). Despite the known effect of chronic exposure to air pollution on the burden of cardiovascular and respiratory diseases (Cesaroni et al., 2014; Ballesteros-González et al., 2020), its potential effect on COVID-19 mortality has not been fully elucidated, particularly in low-and-middle-income countries. This study aimed to determine the association between chronic exposure to $PM_{2.5}$, and COVID-19 mortality in Colombia, South America, using an ecological approach and controlling for potential socioeconomic and health conditions confounders. The purpose of this study is to provide results to assess the hypothesis of the long-term effect of $PM_{2.5}$ on COVID-19 mortality in countries with different socioeconomic contexts and pollution levels.

2. Material and methods

2.1. Study population

Colombia is a country located in the extreme north of South America, consisting of 32 departments, 1122 municipalities. According to the National Administrative Department of Statistics (DANE, for its initials in Spanish), the population of Colombia in 2020 is estimated to be 50,372,424 inhabitants (Departamento Administrativo Nacional de Estadistica DANE, 2018). Estimations based on the national census of

2018 show that 51.2% of the total population in Colombia are women, 77.1% reside in urban areas, and 68.2% are between 15 and 64 years old.

2.2. Data sources

2.2.1. Air pollution data

Ninety-two out of 1122 municipalities measure air quality regularly in Colombia (Instituto de Hidrología MyEAI, 2017). Large cities such as Bogota, Medellin, Bucaramanga, Cali, and Barranquilla have air quality monitoring networks. Medium-size and smaller cities perform periodic manual measurements that are not readily available. Because of the scarcity of surface measurements in the country, we retrieved $PM_{2.5}$ surface concentrations from the Copernicus Atmospheric Monitoring Service CAMS Reanalysis (CAMSRA) and CAMS Near Real-Time (CAMSNRT) for this study. CAMSRA uses four-dimensional variational data assimilation techniques, combining satellite observations with a global scale atmospheric model to produce aerosol concentrations and mixing ratios of several gases at the surface and vertical gridded data (Flemming et al., 2017; European Centre for Medium-Range Weather Forecasts, 2020). CAMSNRT is evaluated every quarter, and evaluation reports are available at the COPERNICUS website (Copernicus Atmosphere Monitoring Service CAMS, 2020). We downloaded surface CAMSRA concentrations over Colombia for $PM_{2.5}$ using the ECMWF WebAPI and the Python script provided at this platform. We retrieved monthly average gridded data at a 0.125-degree resolution from January 2014 to December 2018. We estimated $PM_{2.5}$ concentrations at the centroid of each municipality by using a mathematical interpolation from the nearest four retrieved CAMSRA concentrations. Additionally, in order to evaluate the responsiveness of CAMS-based estimation of $PM_{2.5}$ concentrations, as a support for data validation, we evaluated exposure data for the quarantine period (between March 1 and August 31, 2020) using CAMSNRT.

2.2.2. Population and socioeconomic data

Total population, population by age groups, and area of residence (urban/rural) were retrieved at the municipality level from the estimation of population 2020 based on the Colombian census DANE 2018. We obtained cartographic information and maps from the DANE Geoportal public website (Departamento Administrativo Nacional de Estadistica DANE, 2020a), and the spatial data were created in ArcGIS 10.6.1® using the projection of Colombia in mode Custom Azimuth Equidistant and Datum WGS 1984. We used the Multidimensional Poverty Index as a socioeconomic ecologic measure at the municipality level. The poverty index ranges from 0 to 100 with higher percentages meaning privation of more indicators and dimensions. The higher the index, the higher the socioeconomic deprivation (Departamento Administrativo Nacional de Estadistica DANE, 2020b).

2.2.3. Health data

We obtained data related to the number of confirmed cases and deaths for COVID-19 and the number of RT-PCR tests to confirm positive cases of infected people from the National Institute of Health (INS) website (www.ins.gov.co). The database includes case-by-case information of report date, diagnosis date, date of first symptoms, department and municipality of origin, age, sex, clinical condition, and death date for fatality cases. Information about the number of tests was available at the department level. We used the crude period prevalence of arterial hypertension, diabetes mellitus, and chronic kidney disease data from the High-Cost Account created by the Ministry of Health and Social Protection; we calculated prevalences for the period between July 1st, 2018 and June 30th, 2019 for the 1122 municipalities of Colombia. Hospital beds capacity was measured as intermediate and intensive care beds per 100,000 inhabitants for each municipality, as a surrogate of the health system capacity. We obtained the data from the publicly available national registry of healthcare providers (Registro Especial de Prestadores de Servicios de Salud - REPS https://prestadores.minsalud.gov.co/habilitacion/).

2.2.4. Statistical analysis

The Colombian municipalities with at least one confirmed case of COVID-19 constituted the analytic sample. We calculated population-time at risk as the total population multiplied by the number of days since the first symptom for the first confirmed case at each municipality. We computed the mortality rate using the population-time at risk as a denominator. We described the geographic distribution of the deaths counts, and explored its fit to a Poisson distribution, using the variance test (VT) and the O_2 test. Based on the mean and variance of the death counts we rejected the null hypothesis in both tests ($p > 0.01$) finding evidence of overdispersion (range: 0–1402) and the presence of inflated zeros (58.5%).

Considering the high number of zeros and that from an epidemiological point of view, the first death of COVID-19 represents a phase of the pandemic for one specific municipality; we decided to fit a hurdle model regression for the death counts. We interpreted Hurdle models as a two-part model integrated into one model. The first part is typically a binary response model (logit), and the second part is usually a truncated-at-zero count model (Cameron and Tivedi, 1998). We fit a logit-negative binomial hurdle model and use the population-time at risk as the "offset" variable in the regression models. We used the continuous long-term average of $PM_{2.5}$ as the primary independent variable in the hurdle model. We performed a sensitivity analysis, running models using the $PM_{2.5}$ average as categorized variable and as a modeled variable with restricted cubic splines using three knots. We used the Akaike criterion to compare the models. We adjusted the effect of long-term $PM_{2.5}$ using the following confounding variables identified in the directed acyclic diagram (DAG, see supplementary material Fig. S1): percentage of population 65 years or older, percentage of the urban population, population density, poverty index, hospital beds capacity, number of COVID-19 tests at the department level, and prevalence (percentage) of hypertension, diabetes, and chronic renal failure. These variables were used as covariates. We ran the analysis clustered by department to account for potential correlation in municipalities within the same department. We conducted secondary analyses excluding the capital district of Bogotá, which holds the highest count of deaths, excluding Medellin, the city among three capitals for which CAMSRA underestimates land-based concentrations (see supplementary material Fig. S3a), and excluding municipalities with less than ten confirmed cases. Furthermore, to validate CAMS-based estimations, we analyzed their correlation with surface measurements of $PM_{2.5}$ during the study period as well as their responsiveness to the quarantine period (between March and August) in Bogota, Barranquilla, and Medellin. We ran all the analyses using STATA 15.

3. Results

There were 182,140 confirmed cases and 6288 confirmed deaths for COVID-19 in Colombia up to and including July 17th. Colombia had confirmed COVID-19 cases in 772 out of 1122 municipalities (68.8%) and deaths for COVID-19 were reported in 320 (41.5% of municipalities with cases). Table 1 summarizes the characteristics of the municipalities with COVID-19 confirmed cases. Mortality proportion for COVID-19 varies widely across municipalities with confirmed cases from 0 to 197.0 per 100,000; the mortality rate (using person-time at risk as the denominator) ranged between 0 and 38.4 per 1,000,000. Fig. 1(a) presents the mortality rate for COVID-19 by municipality. The long-term average exposure to $PM_{2.5}$ (2014–2018) in municipalities with COVID-19 confirmed cases was 20.0 $\mu g/m^3$ raging between 9.1 and 37.5 $\mu g/m^3$. Fig. 1(b) presents the long-term average exposure to $PM_{2.5}$ at the municipality level.

The geographic pattern of COVID-19 mortality proportion and the long-term average of $PM_{2.5}$ does not seem to have a good overlap at visual inspection as some municipalities with low levels of $PM_{2.5}$ exhibit high mortality proportions. The regions with higher mortality proportion are located in the Atlantic and Pacific coasts, and the Amazonian region. Fig. 2 shows the visual inspection of the relation between the

Table 1
Characteristics of the municipalities with COVID-19 cases in Colombia up to and including July 17th, 2020 (mean and SD).

Variable	Total 772 municipalities	$PM_{2.5}$ < 20 μg/m³[a] 393 municipalities	$PM_{2.5}$ ≥20 μg/m³[a] 379 municipalities
COVID-19 mortality rate (per 1,000,000)	0.75 (2.23)	0.75 (2.60)	0.74 (1.76)
Time since symptoms in first case	66.15 (37.58)	62.48 (36.68)	69.96 (38.18)
% Population 65 or older	10.03 (3.64)	9.89 (3.75)	10.17 (3.53)
% Urban population	49.26 (24.71)	41.74 (22.53)	57.07 (24.48)
Population density per Km^2	229.98 (899.66)	116.38 (421.68)	347.78 (1119.66)
Poverty index	39.85 (17.73)	42.56 (18.72)	37.03 (16.19)
Hospital beds capacity (per 100,000)	71.95 (78.22)	70.78 (77.73)	73.15 (78.81)
% Hypertension	6.11 (3.74)	5.68 (3.19)	6.57 (4.19)
% Diabetes	1.57 (1.42)	1.43 (1.04)	1.73 (1.71)
%Chronic renal failure	0.94 (1.26)	0.86 (1.00)	1.04 (1.48)

[a] Mean 2014–2018 from Copernicus Atmospheric Monitoring Service Reanalysis model.

estimated long-term mean of $PM_{2.5}$ and the COVID-19 mortality rate logarithm. The patterns did not follow a linear trend, and increased log of mortality rates for COVID-19 are present at the lowest levels of mean $PM_{2.5}$. Using a binomial approach (having or no having deaths), the relation with mean $PM_{2.5}$ did not follow a linear trend but a line with different inflection points (See Supplementary material Fig. S2). Restricted cubic splines of $PM_{2.5}$ with three knots identified those points to be 12.6, 19.3, and 26.6 μg/m³.

We present the results of our primary analysis using hurdle models in Table 2. Estimated mortality rate ratios (MRR) for long-term average $PM_{2.5}$ were not statistically significant in either of the two components of the model: the logit component modeling the change of no having

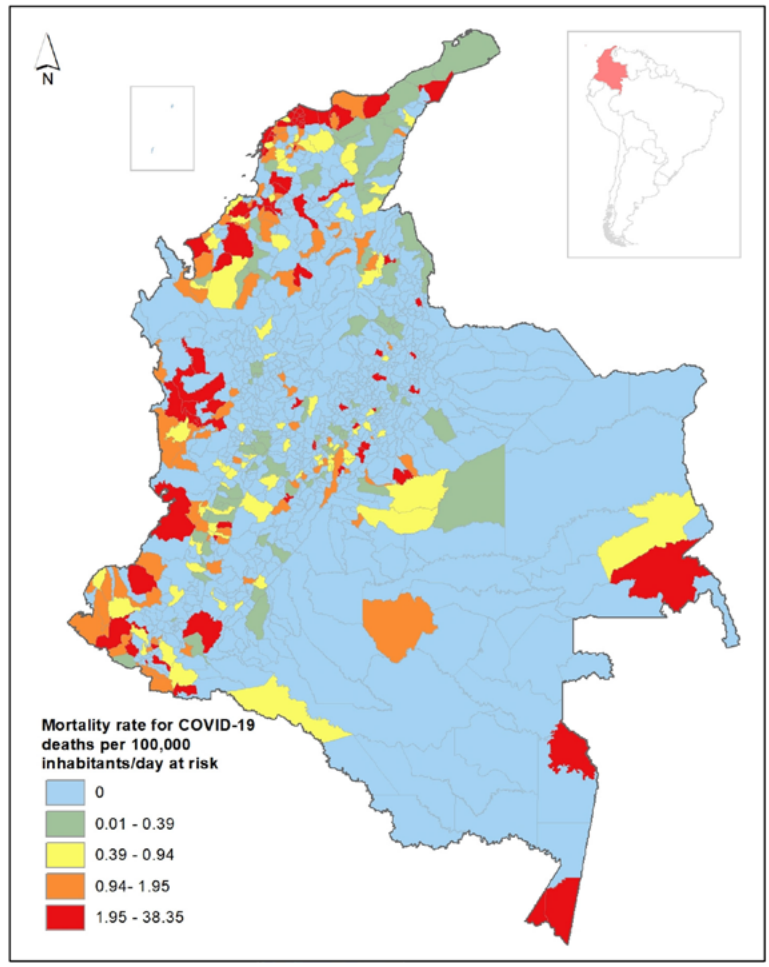

Fig. 1. Mortality for COVID-19 and $PM_{2.5}$ long-term average in Colombia at municipality level. (a) Mortality rate for COVID-19 by municipality in Colombia up to and including July 17th, 2020. (b) Long-term average of $PM_{2.5}$ concentrations (2014–2018) in Colombia (in μg/m³).

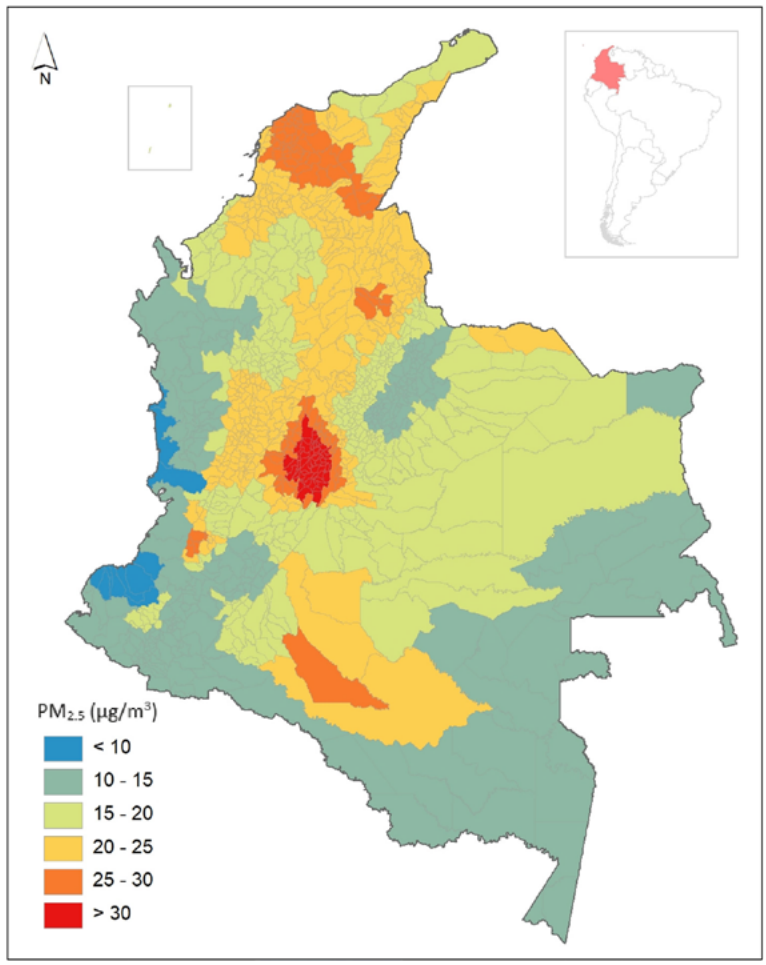

Fig. 1 (*continued*).

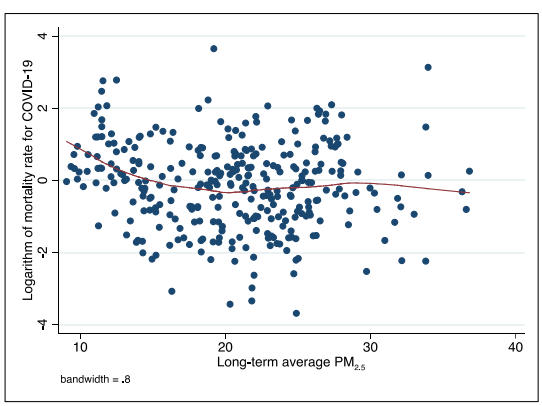

Fig. 2. Relation between mortality rate for COVID-19 and $PM_{2.5}$ in municipalities with COVID-19 confirmed cases in Colombia up to and including July 17th, 2020.

deaths to have at least one death (MRR = 1.00; 95%CI 0.92–1.08), and the negative binomial model of counts of deaths (MRR = 1.00; 95%CI 0.95–1.06). In the logit component, we found that in municipalities having 10% or more of the population over 65 years of age, the mortality rate is almost four times the mortality rate in municipalities with fewer percentages of the older population. The prevalence of hypertension over 6% is the other main factor associated with the death rate at the municipality level (RR = 1.32; 95% CI 1.03–1.68). On the other hand, having a higher percentage of urban population and higher hospital beds capacity are negatively correlated to mortality (Table 2). Once the municipality reaches at least one COVID-19 death, the main factors associated with the mortality rate are the percentage of urban population and the poverty index, which increases the mortality rate in 2% and 3%, respectively (Table 2). Also, a significant cluster (department) effect was identified in the data ($p < 0.01$).

We found that secondary analysis exhibits similar results to our primary analysis in terms of no evidence of increased risk of COVID-19 mortality rate associated with an increased long-term average of $PM_{2.5}$ at the municipality level (Table 3). Results similar to our primary analysis were also consistent in our sensitivity analysis using different approaches to model $PM_{2.5}$ long-term average exposure (See supplementary material Table S1).

Table 2
Mortality rate ratios in the main analysis using hurdle models for municipalities with COVID-19 cases in Colombia up to and including July 17th, 2020.

Variable	Component logit (0-at least one death)			Component negative binomial (counts of deaths>1)		
	MRR	95% CI	*P*-value	MRR	95% CI	P-value
Long-term average $PM_{2.5}$ ($\mu g/m^3$)	1.00	0.92–1.08	0.973	1.00	0.95–1.06	0.747
% Population 65 or older>10%	3.91	2.24–6.81	0.000	0.51	0.23–1.14	0.100
% Urban population	0.96	0.94–0.98	0.000	1.02	1.01–1.03	0.000
Population density (per Km2)	0.99	0.99–1.00	0.129	1.00	0.99–1.00	0.033
Poverty index	0.99	0.97–1.02	0.928	1.03	1.01–1.05	0.001
Hospital beds capacity (per 100,000)	0.99	0.98–0.99	0.000	1.00	0.99–1.01	0.052
% Hypertension						
spline 1 (2.09–5.97)	0.75	0.60–0.94	0.013	0.96	0.73–1.28	0.804
spline 2 (5.97–10.37)	1.32	1.03–1.68	0.026	1.00	0.70–1.45	0.960
% Diabetes>4%	0.29	0.01–9.97	0.495	1.74	0.43–6.95	0.434
%Chronic renal failure>3%	1.25	0.35–4.39	0.726	0.42	0.15–1.17	0.096
Number of test at department level	1.00	0.00–1.00	0.056	1.00	0.99–1.00	0.565

MRR: mortality rate ratio; CI: confidence interval.

We present a comparison between the estimated monthly average $PM_{2.5}$ concentration from CAMSRA model and surface levels during the study period (2014–2018) in three cities in the supplementary material (Figs. S3a). The results show that CAMSRA adequately reproduces the trends of surface $PM_{2.5}$, with correlation coefficients of 0.8 for Bogotá, and 0.6 for Medellín and Barranquilla, with a tendency to underestimate surface levels in Bogotá and Barranquilla. Fig. S3b presents the daily average concentrations of CAMSNRT and surface concentrations during the quarantine period, supporting that CAMSNRT responsiveness to changes in surface levels is adequate, with a tendency to underestimate surface levels at higher $PM_{2.5}$ surface concentrations.

4. Discussion

Our research presents the first ecologic nationwide study conducted in a developing country assessing the association between COVID-19 mortality and long-term exposure to $PM_{2.5}$. Our results did not find evidence of an association between higher concentrations of $PM_{2.5}$ and higher counts of deaths, controlling for nine socioeconomic and health indicators at the municipality level. The effect of socioeconomic and health conditions, such as the proportion of the population over 65 years, the poverty index, and the prevalence of hypertension, showed evidence of increasing the risk of deaths for COVID-19, while the hospital's capacity decreased such risk. The use of model-based estimations of long-term $PM_{2.5}$ exposure includes an undetermined level of uncertainty in the results, and therefore, they should be interpreted as preliminary evidence.

The first COVID-19 confirmed case occurred in Bogota, the capital district (Instituto Nacional de Salud (Colombia), 2020), where the highest number of cases have been reported, exceeding 45,000 by mid-July. The first cases identified in the capital district were related to returning flights from Europe, which were also related to the first cases identified in other main capital cities, including Medellin and Cali. Then, an additional infection source came from international cruises in the Port of Cartagena, where the epidemic spread to the Atlantic Coast. The epidemic in the Brazilian Amazonian region was the probable source of infection in Leticia, the capital of the Amazonas department, which is the municipality with the highest mortality proportion for COVID-19 in Colombia (195.02 per 100,000 inhabitants). Thus, the COVID-19 spread went from capital cities to small municipalities, where the mortality rates have been higher.

There was no evidence of an association between the long-term average of $PM_{2.5}$ and the mortality rate for COVID-19 in crude or adjusted models. Our results contrast with the reports of correlational studies conducted in Italy (Conticini et al., 2020; Fattorini and Regoli, 2020) and ecological studies in China (Yao et al., 2020) and the United States (Wu et al., 2020), which found positive associations between $PM_{2.5}$ and COVID-19 mortality after adjusting for four and 20 potential confounders, respectively. These studies supported the hypothesis that the effect of long-term exposure to $PM_{2.5}$ on COVID-19 mortality is largely mediated by comorbidities linked to chronic PM-related inflammation (Conticini et al., 2020; Tsai et al., 2019). In this regard, it has been proposed that chronic exposure to $PM_{2.5}$ causes alveolar ACE-2 receptor overexpression, which may increase viral load in patients exposed to pollutants (Frontera et al., 2020). Our findings revealed a significant effect of aging and poverty on COVID-19 mortality rate, factors related to failure in the mechanisms of acute immune humoral and cellular response at the individual level; and to a higher burden of chronic disease and lower capability of the healthcare system to treat complicated cases of infection, at the municipal level. These findings might suggest that the chronic effect of aging and poverty might have a stronger effect on COVID-19 complications and mortality in developing countries. However, our negative results related to pollution exposure might also be explained by the use of CAMSRA model-based estimations of long-term $PM_{2.5}$ exposure, which implies a measurement error and an unknown degree of uncertainty in the results.

Another possible explanation for our findings is that long-term exposure to $PM_{2.5}$ has less impact on biological susceptibility to COVID-19 complications and deaths compared to the effect of other air pollutants such as nitrogen dioxide (NO_2). Multipollutant models in Colombia have identified a stronger short-term effect of NO_2 on respiratory and cardiovascular morbidity compared to other pollutants (Rodriguez-Villamizar et al., 2019). A country-wide cross-sectional study in the United States using multipollutant models for the effect of $PM_{2.5}$, NO_2, and O_3 found a solid positive association between NO_2 and COVID-19 fatality and mortality but did not find significant associations with $PM_{2.5}$ and O_3 (Liang et al., 2020). The authors discussed that divergent results with the previous US nationwide study (Wu et al., 2020) are probably due to the use of multipollutant models and the adjustment for spatial trends, which might have

Table 3
Mortality rate ratios in secondary analysis using hurdle models for municipalities with COVID-19 cases in Colombia up to and including July 17th, 2020.

Long-term $PM_{2.5}$ ($\mu g/m^3$)	Component logit[a] (0 - at least one death)			Component negative binomial[a] (counts of deaths >1)		
	MRR	95% CI	P-value	MRR	95% CI	P-value
Excluding Bogotá	1.00	0.93–1.08	0.973	1.00	0.96–1.06	0.784
Excluding Medellín	1.00	0.93–1.08	0.973	1.01	0.95–1.06	0.759
Excluding municipalities with less than 10 confirmed COVID-19 cases	1.02	0.96–1.07	0.494	1.03	0.96–1.09	0.347

MRR: mortality rate ratio; CI: confidence interval.
[a] Adjusted for the percentage of population 65 years or older, percentage of urban population, population density, poverty index, hospital beds capacity, number of tests at department level, and prevalence of hypertension, diabetes, and chronic renal failure.

confounded the findings. Unfortunately, we did not count on reliable NO_2 and O_3 long-term exposure estimations, so we did not assess this effect in multi-pollutant models.

We found an independent and significant effect of the older age, the poverty index, and the prevalence of hypertension (over 6%) associated with the COVID-19 mortality rate. Several studies reported similar findings related to age and chronic diseases (Ruan et al., 2020; Lippi and Wong, 2020; Hussain et al., 2020; Zhou et al., 2020; Cheng et al., 2020). In Italy Conticini et al. (2020) discussed that factors such as the age structure of the affected population, the great differences between the Italian regional health systems, the capacity of intensive care units in the region, and prevention policies adopted by the government had played a major role in the spread of and mortality for SARS-CoV-2, presumably more than long-term air pollution itself. The effect of poverty on COVID-19 mortality is less described in the literature, but it represents a major risk condition in developing countries, probably related to unstable employment and income, lower health literacy, and limited access to preventive health services (Bong et al., 2020; Proaño, 2020). A few recent ecological studies in the US at the county level have reported a correlation between COVID-19 mortality rate and some social disparities such as poverty status and non-English speaking households and other ethnic minorities (Zhang and Schwartz, 2020; Fielding-Miller et al., 2020).

The strengths of this study include the use of nationwide public government data at the municipality level and the adjustment for nine sociodemographic and health conditions using a hurdle model. The main limitation of this study is the lack of empirical data for the long-term estimation of $PM_{2.5}$ exposure. The estimation of $PM_{2.5}$ concentration in this study comes from the CAMSRA model, which has been evaluated using independent measurements available in different world regions at the surface level and in the tropospheric column. These evaluations show that CAMSRA successfully reproduces levels and trends of aerosols and gases (Wang et al., 2020b). A recent research conducted to evaluate the performance of CAMSRA over the cities of Bogota, Medellin, and Barranquilla for $PM_{2.5}$, CO, and NO_2 concentrations comparing measurements from the air quality monitoring networks with retrieved CAMSRA concentrations showed that CAMSRA is able to reproduce $PM_{2.5}$ levels and trends in these three cities (Fig. S3a). However, the model largely underestimates NO_2 and CO concentrations (Vargas, 2020). Additionally, we compared the daily average concentrations of CAMSNRT with surface concentrations in the same cities during the quarantine period (Fig. S3b), and the results also indicate that CAMSNRT adequately reproduces the trends and levels of surface $PM_{2.5}$, with a tendency to underestimate surface levels at higher $PM_{2.5}$ concentrations during the dry season.

Although elevated levels of $PM_{2.5}$ are observed in urban areas, $PM_{2.5}$ distribution in Colombia shows that even medium-size and small municipalities have similar or even higher concentrations of $PM_{2.5}$. This behavior coincides with aerosols' geographical distribution reported in previous studies for Colombia (Ballesteros-González et al., 2020; Luna et al., 2018). These studies indicate that biomass burning is a critical source of $PM_{2.5}$ in Colombia and that both large and small cities are affected by this source. The $PM_{2.5}$ geographical distribution and trends presented in our study (Fig. 1b) line up with the results reported in those previous studies. Further research should confirm the validity of information from CAMSRA over other Colombian municipalities and highlights the need for a robust national air quality monitoring network. Even though CAMSRA seems to capture the heterogeneity and trend of concentration across municipalities during the study period, it had a moderate correlation to surface measurements in a selected sample of three of the largest cities. Therefore, the use of CAMSRA to estimate $PM_{2.5}$ exposure introduced a measurement error and uncertainty in the analysis, which might have partially attenuated any underlying association between $PM_{2.5}$ and COVID-19 mortality. Therefore, our results should be considered preliminary and need confirmation from further investigations.

Our study has other limitations. First, the ecological study's nature precludes the extrapolation of inferences from the empirical evaluation of hypotheses based on clusters (i.e., municipalities) to the individual level. Therefore, the absence of a relationship between long-term exposure to $PM_{2.5}$ and mortality among patients diagnosed with SARS-CoV-2 should at best be regarded as provisional. Second, in the absence of reliable NO_2 and O_3 long-term exposure estimations, we could not incorporate them into the analysis or evaluate the independent association of $PM_{2.5}$ and mortality in the context of multi-pollutant models. Third, mortality data reflect fatal cases among patients with a confirmatory diagnosis of the infection, excluding deaths among undiagnosed individuals (due to low testing rates or unreliable test results) and those occurring outside of hospitals. Systematic differences in municipalities' capability to comprehensively and correctly identify and register deaths attributable to the infection could have biased our estimate of effect. Although this issue could not be directly addressed in the analysis, adjusting for testing rates and hospital beds capacity should have partially corrected for differential readiness of municipal health systems to cope with the epidemic.

5. Conclusions

There was no evidence of an association between long-term exposure to $PM_{2.5}$ and mortality rate for COVID-19 at the municipality level in Colombia. Demographics, health system capacity, and social conditions did show an ecological effect on COVID-19 mortality. The use of model-based data to estimate the long-term $PM_{2.5}$ exposure is an important source of uncertainty in this study, and therefore, results should be considered preliminary evidence. The lack of air pollutants' surface data in most municipalities reveals the need to strengthen the country's air quality monitoring systems.

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Data sharing statement

Data will be made available upon request.

CRediT authorship contribution statement

Laura A. Rodriguez-Villamizar: Conceptualization, Methodology, Formal analysis, Writing - original draft. **Luis Carlos Belalcazar-Ceron:** Methodology, Validation, Data curation, Writing - original draft. **Julián Alfredo Fernández-Niño:** Conceptualization, Methodology, Formal analysis, Writing - original draft. **Diana Marcela Marín-Pineda:** Conceptualization, Methodology, Formal analysis, Writing - original draft. **Oscar Alberto Rojas-Sánchez:** Conceptualization, Data curation, Writing - original draft. **Lizbeth Alexandra Acuña-Merchán:** Data curation, Writing - review & editing. **Nathaly Ramirez-Garcia:** Data curation, Writing - review & editing. **Sonia Cecilia Mangones-Matos:** Data curation, Writing - review & editing. **Jorge Mario Vargas-Gonzalez:** Methodology, Validation, Data curation, Writing - review & editing. **Julián Herrera-Torres:** Methodology, Validation, Data curation, Writing - review & editing. **Dayana Milena Agudelo-Castañeda:** Writing - review & editing. **Juan Gabriel Piñeros Jiménez:** Conceptualization, Writing - review & editing. **Néstor Y. Rojas-Roa:** Conceptualization, Writing - original draft. **Victor Mauricio Herrera-Galindo:** Conceptualization, Methodology, Formal analysis, Writing - original draft.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.144020.

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VIH

CUENTA DE ALTO COSTO
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VIH

Caracterización epidemiológica y clínica en menores de 13 años que viven con VIH en Colombia. 2018: un estudio de corte transversal

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Revista: Infectio

Ámbito: Nacional

Trabajo colaborativo con los expertos clínicos

Objetivo:

Describir las características epidemiológicas y clínicas de los niños que viven con el VIH/sida en Colombia.

Principales hallazgos

- La transmisión materno fetal continúa siendo la principal fuente de transmisión en esta población (89% de los casos).
- La cobertura de la TAR fue del 83%.
- El 50% alcanzaron la indetectabilidad.
- El 49% de los niños analizados han progresado a sida.

Relevancia de los hallazgos

- La disminución de la transmisión materno fetal es una meta mundial. En el país, es necesario fortalecer las intervenciones dirigidas a la prevención de la misma.
- Además de optimizar las estrategias de prevención y detección temprana, se debe garantizar el seguimiento de los niños con VIH para evitar su progresión a sida.
- Es necesario acercar estos hallazgos a las entidades y articularlo a las demás actividades de apoyo técnico para tomar decisiones informadas que se traduzcan en mejores resultados en esta cohorte.

ARTÍCULO ORIGINAL

Caracterización epidemiológica y clínica en menores de 13 años que viven con VIH en Colombia. 2018: un estudio de corte transversal

Julieth Carolina Castillo[1,*], Alexandra Sierra[2], Nathaly Ramírez[3], Ana María Valbuena[4], Lizbeth Acuña[5]

Resumen

Objetivo: Describir las características epidemiológicas y clínicas de los niños que viven con el VIH/sida, en Colombia.

Métodos: Estudio observacional retrospectivo de tipo corte transversal analitico, realizado en los menores de 13 años que viven con el VIH /sida y que fueron reportados a un organismo técnico colombiano en el 2018. Se estimó la prevalencia del VIH/sida y se caracterizaron los niños con VIH y niños con sida.

Resultados: 655 niños tenían la infección. La prevalencia de VIH/sida fue de 0,05 (IC 95% 0,04 – 0,07) por 1.000 niños. El 50,08% pertenecían al sexo femenino y el 79,85% al régimen subsidiado. La transmisión materno infantil predominó en el 89,16%. El 83,21% usaban tratamiento antirretroviral. El 50,08% se encontraba indetectable. Las principales enfermedades que definieron el sida fueron la neumonía y el síndrome de desgaste. La región de residencia, el último conteo de linfocitos T CD4+ y el diagnóstico temprano de VIH mostraron diferencias estadísticas entre los grupos.

Conclusión: La reducción de la transmisión materno infantil del VIH ha sido una meta mundial; sin embargo, fue el principal mecanismo de transmisión en los menores de 13 años en Colombia. Las acciones deben dirigirse a la prevención de la transmisión y al diagnóstico temprano del VIH.

Palabras clave: VIH, epidemiología, niños, transmisión vertical de enfermedad infecciosa, Colombia *(fuente: DeCS BIREME)*.

Epidemiological and clinical characterization in minors under 13 years living with HIV in Colombia. 2018: a cross-sectional study

Abstract

Objective: To describe the epidemiological and clinical characteristics of children living with HIV / AIDS in Colombia.

Methods: Retrospective observational study of analytical cross section, carried out in children under 13 years of age living with HIV / AIDS and who were reported to High Cost Diseases Fund in 2018. The prevalence of HIV / AIDS was estimated and children with HIV and children with AIDS were characterized.

Results: 655 children had the infection. The HIV / AIDS prevalence was 0.05 (95% CI; 0.04 - 0.07) per 1,000 children. 50.08% were female and 79.85% to the subsidized insurance. Mother-to-child transmission predominated in 89.16%. 83.21% of children used antiretroviral treatment and 50.08% were undetectable. The main diseases that defined AIDS were pneumonia and wasting syndrome. The region of residence, the last CD4 T cells counts and early diagnosis of HIV showed statistical differences between the groups.

Conclusion: Reducing mother-to-child transmission of HIV has been a global goal; however, it was the main transmission mechanism in the children under 13 in Colombia. Actions should be directed to prevent transmission and early diagnosis of HIV.

Keywords: HIV; epidemiology; children; Infectious Disease Transmission, Vertical; Colombia *(source: MeSH NLM)*.

Introducción

La infección por el virus de inmunodeficiencia humana (VIH) en los niños, además de atacar el sistema inmune y progresar más rápido a un síndrome de infecciones y enfermedades oportunistas (sida)[1], genera otras manifestaciones atípicas produciendo mayor severidad de las enfermedades propias de la infancia[2]. En Colombia los niños, al igual que los adultos, son atendidos en un sistema de salud que funciona bajo un modelo de aseguramiento con una alta cobertura universal, donde las personas con capacidad de pago y sus familias son afiliadas en el régimen contributivo y cuando no se cuenta con los recursos se accede al régimen subsidiado que ofrece el Estado. Independiente de la afiliación, la atención de las personas que viven con VIH (PVV) está justificada por las recomendaciones de las Guías de Práctica Clínica

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para la atención de la infección por VIH[2,3]. La Cuenta de Alto Costo como un organismo técnico del Sistema General de Seguridad Social colombiano[4], realiza el seguimiento a esta cohorte en cumplimiento a la normatividad que obliga a las entidades de salud a reportar las principales características sociodemográficas y clínicas de las personas que viven con VIH (PVV); sin embargo, aún no se ha caracterizado la población menor de 13 años.

La evidencia muestra que, los niños con VIH son más vulnerables a pobres resultados en salud, debido al estigma y la discriminación[5], cuentan con un riesgo de morir 30 veces mayor que la población pediátrica general y alcanzan una mortalidad hasta del 87% a los 5 años del diagnóstico sin terapia antirretroviral (TAR)[6]. La supervivencia infantil depende en este caso de un diagnóstico temprano, el inicio rápido de la TAR[7], el mantenimiento de un sistema inmune y la supresión de la carga viral[8].

Dado lo anterior, el objetivo de este estudio fue describir las características epidemiológicas y clínicas de los niños menores de 13 años que viven con el VIH y sida, que fueron atendidos y reportados por el Sistema General de Seguridad Social en Salud de Colombia, con el fin de poner en evidencia la situación actual de los niños y dar un sustento en la toma de decisiones basadas en las características propias de los casos colombianos.

Materiales y métodos

Se realizó un estudio observacional retrospectivo de tipo corte transversal analítico, de las personas que viven con el VIH (PVV) menores de 13 años reportados a la Cuenta de Alto Costo entre el 1º de febrero de 2017 al 31 de enero de 2018, por parte de las Entidades Administradoras de Planes de Beneficios y Entidades Obligadas a Compensar. Dicha información fue ingresada a un sistema de validación que revisó la calidad, consistencia y coherencia de los datos solicitados según la resolución 273/2019 del Ministerio de Salud y Protección Social "Por la cual se establecen disposiciones para el reporte de información relacionada con la infección por el Virus de la Inmunodeficiencia Humana - VIH y el Síndrome de Inmunodeficiencia Adquirida - SIDA con destino a la Cuenta de Alto Costo"; posteriormente los casos fueron auditados contrastándolos con los soportes de historia clínica que fueron cargados por las entidades en el repositorio dispuesto por la CAC para tal fin. Se incluyeron todos los casos confirmados para el diagnóstico de VIH, según el algoritmo definido en la Guía de Práctica Clínica basada en la evidencia científica para la atención de la infección por VIH en niñas y niños menores de 13 años de edad[2]. En aquellas variables donde no coincidió lo reportado contra lo soportado, se realizó la corrección en la base de datos según la fuente primaria. Culminado el proceso de auditoría, la base de datos fue entregada a los investigadores de manera anonimizada, garantizando la confidencialidad de la información durante el análisis. Se excluyeron del análisis los niños en los que no se podía determinar el estadio VIH o sida.

Entre las variables sociodemográficas seleccionadas para el análisis se incluyeron: el sexo, el grupo de edad, el régimen de afiliación al sistema de salud y la región de residencia. Las variables clínicas fueron: el mecanismo de contagio, el diagnóstico temprano (definido como las PVV con conteo de linfocitos T $CD4^+$ mayor o igual a 500 células por microlitro (µL) al momento del diagnóstico), el recuento actual de los linfocitos T $CD4^+$, la presencia de las principales enfermedades definitorias del sida, el tiempo entre el diagnóstico y el inicio del tratamiento, el uso de la TAR, los esquemas antirretrovirales usados y la carga viral actual.

Análisis estadístico

Se calculó la prevalencia del VIH en los niños menores de 13 años con diagnóstico confirmado, teniendo como referencia la población estimada por el Departamento Administrativo Nacional de estadística (DANE)[9] para el 2017 de 12.021.170 niños menores de 13 años. Se realizó la caracterización de los niños diferenciando entre VIH y sida en los casos en los que se reportó el estadio de la enfermedad. Para las variables cuantitativas se presentaron las medidas de tendencia central y dispersión, según la distribución marginal de la variable. Las variables categóricas fueron presentadas en valores absolutos y relativos.

Análisis bivariado

Se realizaron pruebas de significancia estadística entre las variables estudiadas con la condición de VIH o sida, para lo cual, se emplearon pruebas de contraste de hipótesis para observaciones independientes: la prueba $\chi 2$ de Pearson o la exacta de Fisher, para las variables cualitativas; y la prueba no paramétrica U de Mann-Whitney, para las variables continuas que no presentaron una distribución normal dentro de cada una de las categorías de la variable de respuesta de acuerdo a pruebas gráficas y numéricas. Para todos los análisis se consideró significancia estadística a un valor de p menor que 0,05. Los análisis estadísticos se realizaron utilizando Stata 13.1 (Stata Corporation, College Station, TX, USA).

Resultados

Del total de PVV fueron identificados 691 menores de 13 años, para una prevalencia de 0,05 casos de VIH/sida (IC 95% 0,04 – 0,07) por 1.000 menores de 13 años (691 menores de 13 años con VIH/sida/12.021.170 niños menores de 13 años). En 655 (94,79%) niños se reportó el estadio de la enfermedad. El 49,31% (n=323) se encontraban en estadio sida. El 50,08% pertenecían al sexo femenino y según el grupo de edad, el 82,75% era población escolar (5 a 12 años). El 79,85% fue reportado por el régimen subsidiado, es decir población sin capacidad de pago afiliada al sistema de salud colombiano, y la principal región de residencia fue la región Caribe (45,49%).

En cuanto a la fecha de diagnóstico, solo se contó con información en el 48,24% (n=316) de los casos reportados, de estos 200 casos (30,53%) fueron diagnósticados temprana-

Tabla 1. Caracterización sociodemográfica y clínicas de los menores de 13 años que viven con VIH y sida Colombia. 1 de febrero de 2017 al 31 de enero de 2018

Variables	VIH (n=332)	Sida (n=323)	p§
	n (%)	n (%)	
Características sociodemográficas			
Sexo (masculino)	162 (48,80)	165 (51,08)	0,56
Edad (años)[a]	8,71 (5,88-11,01)	8,87 (6,40-11,10)	0,58
Categorías de edad[b]			0,24
Primera infancia (0-4 años)	63 (18,98)	50 (15,48)	
Escolares (5-12 años)	269 (81,02)	273 (84,52)	
Régimen de afiliación[c]			0,37
Contributivo	56 (16,87)	59 (18,27)	
Subsidiado	270 (81,33)	253 (78,33)	
Excepción	6 (1,81)	11 (3,41)	
Región de residencia[d]			**<0,01**
Bogotá D.C.	22 (6,63)	29 (8,98)	
Caribe	150 (45,18)	148 (45,82)	
Central	53 (15,96)	66 (20,43)	
Oriental	45 (13,55)	27 (8,36)	
Pacífica	55 (16,57)	35 (10,84)	
Otros departamentos	7 (2,11)	18 (5,57)	
Características clínicas			
Conteo de linfocitos T CD4+ actuales (Células/µL)[a]	893 (653,5-1 167)	769 (495,5-1 073,5)	**<0,01**
Categorías de linfocitos TCD4+ actuales (Células/µL)			**<0,01**
<200	0 (0,00)	14 (4,33)	
200-499	30 (09,03)	64 (19,81)	
≥500	258 (77,71)	226 (69,97)	
Sin dato	34 (10,24)	19 (5,88)	
Diagnóstico temprano de VIH (linfocitos TCD4+ ≥500) (Células/µL)			**<0,01**
Sí	126 (37,95)	74 (22,91)	
No	27 (8,13)	89 (27,55)	
Sin dato	179 (53,92)	160(49,54)	
Tiempo entre la fecha de diagnóstico y la fecha de inicio de la primera TAR (días)[a]	30 (0-127)	29 (1,50-90,50)	0,91
Carga viral actual			0,09
Indetectable (menor de 50 copias/µL)	178 (53,61)	150 (46,44)	
Detectable pero menos de mil copias	62 (18,67)	69 (21,36)	
Mil o más copias	63 (18,98)	68 (21,05)	
No se ha realizado en los últimos 6 meses	7 (2,11)	16 (4,95)	
Sin dato	22 (6,63)	20 (6,19)	
Recibe terapia antirretroviral			0,50
Sí	287 (86,45)	258 (79,88)	
No	9 (2,71)	11 (3,41)	
Sin dato	36 (10,84)	54 (16,72)	
Esquema antirretroviral por principios activos			0,60
Lamivudina/lopinavir/ritonavir/ zidovudina	95 (33,10)	81 (31,40)	
Abacavir/lamivudina/lopinavir/ritonavir	82 (28,57)	84 (32,56)	
Otros esquemas	110 (38,33)	93 (36,05)	
Mecanismo de transmisión			0,07
No se conoce	8 (2,41)	13 (4,02)	
Transmisión sexual	22 (6,63)	16 (4,95)	
Transfusión	0 (0,00)	5 (1,55)	
Transmisión materno infantil	297 (89,46)	287 (88,85)	
Violación o abuso sexual	5 (1,51)	2 (0,62)	

a Mediana (rango intercuartílico)

b Agrupación según la Encuesta Nacional de Situación Nutricional[10]

c En Colombia los afiliados al sistema de salud pertenecen a un tipo de régimen, en el contributivo se encuentran los empleados y personas con capacidad de pago, así como sus familias; en el subsidiado, la población sin capacidad de pago; y en el de excepción, los empleados de entidades como las fuerzas militares, la policía, el magisterio y Ecopetrol.

d División acorde al producto interno bruto definido por el Departamento Administrativo Nacional de Estadística para el año 2017.Las divisiones son: **Región Caribe**: Atlántico, Bolívar, Cesar, Córdoba, Sucre, Magdalena, La Guajira. **Región Central**: Caldas, Risaralda, Quindío, Tolima, Huila, Caquetá, Antioquia **Región Oriental**: Norte de Santander, Santander, Boyacá, Cundinamarca, Meta. **Región Pacifica**: Chocó, Cauca, Nariño, Valle. **Otros departamentos**: Amazonas, Arauca, Casanare, Guainía, Guaviare, Putumayo, San Andrés, Vaupés, Vichada[11]

§ Valor de p obtenido mediante la prueba $\chi 2$ **de Pearson** o la prueba exacta de Fisher en el caso de variables categóricas, la prueba U de Mann-Whitney para las variables cuantitativas sin distribución normal. Nivel de significancia 0,05.

Tabla 2. Enfermedades oportunistas definitorias de sida en los menores de 13 años que viven con VIH. Colombia. 1 de febrero de 2017 al 31 de enero de 2018

Enfermedades oportunistas definitorias de sida	Número de casos con sida (n=323)	Porcentaje de enfermedades oportunistas entre las personas con sida
Neumonía bacteriana recurrente	67	20,74
Síndrome de desgaste	63	19,50
Tuberculosis	41	12,69
Diarrea por *Isospora belli* o *Cryptosporidium* de más 1 mes de evolución	38	11,76
Neumonía por *Pneumocystis jiroveci*	34	10,53
Candidiasis esofágica	24	7,43
Toxoplasmosis cerebral	10	3,10
Neumonía intersticial	1	0,31

mente. El principal mecanismo de transmisión fue el materno infantil con el 89,16% de los casos. En cuanto a las características clínicas, se halló que el 73,89% de los menores de 13 años tenían un conteo de linfocitos T CD4+ mayor de 500 células/µL. El 83,21% usaban TAR, siendo el principal esquema: lamivudina/lopinavir/ritonavir/zidovudina en el 32,29% de los casos. El 50,08% de los casos tenían menos de 50 copias/ml (indetectabilidad).

Al comparar las variables entre el grupo con VIH y sida (Tabla 1), se evidenció diferencias estadísticamente significativas en la región de residencia, el último conteo de linfocitos T CD4+ y en el diagnóstico temprano de VIH.

En cuanto a los niños en estadio sida, predominaron las enfermedades oportunistas como la neumonía bacteriana recurrente, el síndrome de desgaste y la tuberculosis (Tabla 2).

Discusión

Este primer estudio realizado en Colombia para el año 2018 en población pediátrica, evidenció el reporte a la Cuenta de Alto Costo de 691 niños menores de 13 años con infección por VIH, para una prevalencia de 0,05 por 1.000 niños menores de 13 años. No fue posible realizar directamente la comparación de estos datos con otra evidencia, pues los análisis en pediatría se reportan en menores de 15 años, pero en Colombia las GPC establecen un corte a los 13 años que impacta en el reporte de la información. Estudios mundiales han mostrado prevalencias del VIH en niños pero en un subgrupo específico, como son los niños menores de 15 años en condición de calle o explotados sexualmente, con prevalencias de la enfermedad entre 50 niños por 1.000 niños menores de 15 años en regiones de América hasta 3.700 niños por 1.000 niños menores de 15 años en países de Europa[12].

Esta caracterización muestra que el 49,31% de los niños en Colombia han progresado a sida, siendo este un factor de riesgo para mortalidad[13]. Se observaron más PVV en el sexo femenino, cuando generalmente la literatura presenta más casos en el masculino en edades menores de 15 años[14]. De otro lado, si comparamos estas diferencias en el sexo con respecto a los adultos en Colombia, esta relación es inversa, existiendo una relación de 2 hombres por 1 mujer[15] en los adultos. Una cohorte de niños y niñas seguida en 32 países[16] evidenció que solo en la región de Asia-Pacífico el mayor porcentaje de VIH ocurría en las niñas menores de 19 años (51,5%).

Se identificó que el 16% de los niños con VIH/sida no tienen TAR, posiblemente porque el país está a la espera de la actualización de las GPC que recomiendan "diagnosticar y tratar"[17]. Aun así, nuestros resultados muestran un mayor porcentaje de TAR comparado con otras regiones; por ejemplo, una cohorte de 130.000 niños menores de 15 años con VIH[16], identificó que el 73,4% habían iniciado tratamiento y puso en evidencia diferencias porcentuales entre las regiones de la Organización Mundial de la Salud, pues América Latina inició TAR en el 88,6% mientras que en la región de África Central fue del 63,1%. Chile estimó un 65% (IC 95% 53 - 80%) de TAR en pediatría[18]. Esto pone en evidencia el incumplimiento del segundo 90 (aumentar al 90% la proporción de personas bajo tratamiento antirretroviral) en la estrategia de eliminación del virus planteado por el Programa Conjunto de las Naciones Unidas sobre el VIH/sida – ONUSIDA-[19]. De otro lado, al comparar mundialmente el acceso a la terapia entre niños y adultos, se evidencia una brecha en el acceso, pues en el 2018 la cobertura de TAR en menores de 15 años fue del 54% (IC 95% 37–73%), cuando en los adultos fue del 62% (47% - 75%)[20].

Nuestro estudio también evidenció en las PVV , mayor número de casos con neumonía bacteriana, síndrome de desgaste y de tuberculosis (TB). Estos hallazgos son similares a los encontrados en otros estudios[6,21] donde además se relacionan tiempos de supervivencia más cortos por estas enfermedades oportunistas. Algunos factores de riesgo para la aparición, por ejemplo, de TB se han relacionado con el estadio clínico en fase 3 (sida), el bajo nivel de adherencia a la terapia y el inicio tardío de la TAR[21]. En contraste, un estudio en España determinó que la TB ocurre en países endémicos en todos los grupos de edad, independientemente del estado del VIH[22].

Entre las fortalezas del estudio está la disponibilidad de información gracias a la normatividad que obliga a las entidades encargadas de la población, el reporte de las PVV a la CAC , permitiendo la realización de este tipo de análisis que pueden orientar la toma de decisión. Además de los sesgos propios de los estudios transversales, puede existir un sesgo de información que hace que la CAC no conozca todo el universo de la población pediátrica con VIH, dado por las barreras en el acceso a los servicios de salud, así como una posible omisión del reporte por parte de las entidades pese a la obligatoriedad de la norma. Otra limitación está en la comparabilidad de nuestros datos con otra evidencia, por no contener el mismo punto de corte de la edad con otros estudios.

En conclusión, pese a que la reducción de la transmisión materno infantil del VIH ha sido una meta mundial, sigue siendo este el principal mecanismo de transmisión en los niños menores de 13 años en Colombia. Este analisis también evidencia diferencias en el estadio de la enfermedad en algunas regiones de residencia, en el diagnóstico temprano y en el estado inmune de los niños. Las acciones deben estar dirigidas a la prevención de la transmisión en niños, al diagnóstico temprano y el seguimiento de los casos para reducir el riesgo de progresión de la enfermedad o evitar mortalidades. Futuras investigaciones deben analizar las brechas en la atención de la población pediátrica.

Responsabilidades éticas

Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

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

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

Conflicto de intereses. Los autores declaran no tener ningún conflicto de intereses.

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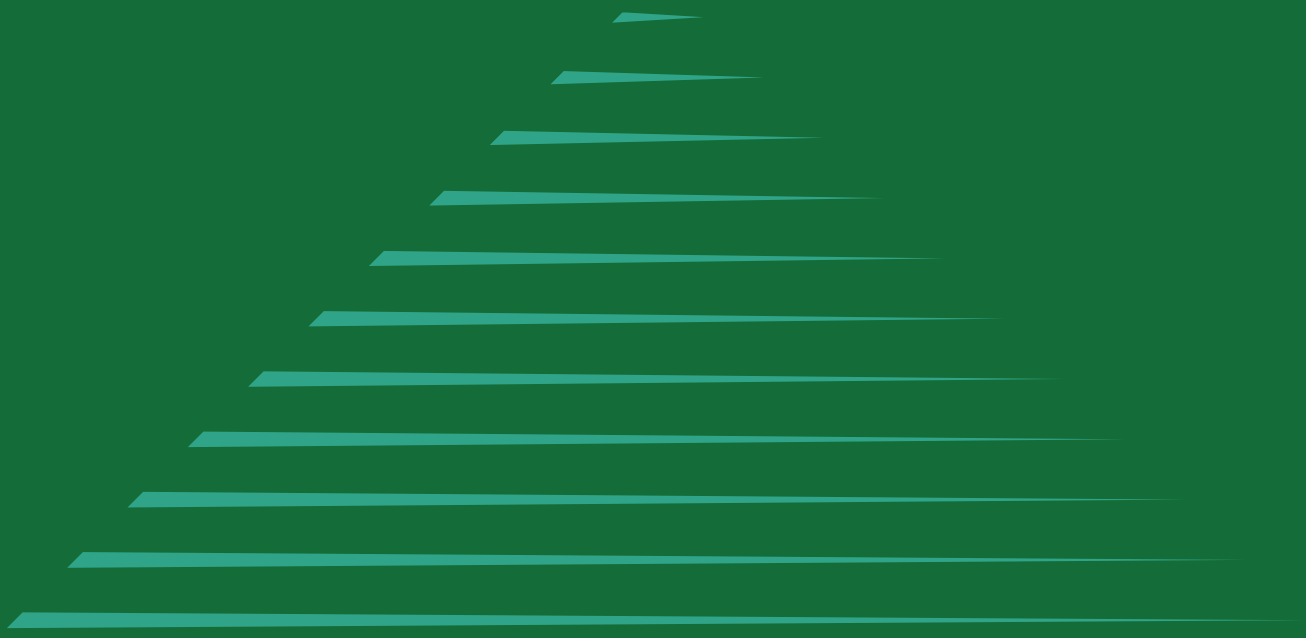

CUENTA DE ALTO COSTO
Fondo Colombiano de Enfermedades de Alto Costo

CÁNCER

Space-time clustering of childhood leukemia in Colombia: a nationwide study

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Revista: BMC Cancer

Alcance: internacional

Trabajo colaborativo con la academia como actor de interés (Universidad Industrial de Santander)

Objetivo:

Evaluar la presencia de grupos de casos de leucemias pediátricas en Colombia.

Principales hallazgos

- Entre 2009 y 2017, la tasa de incidencia promedio de leucemia pediátrica fue de 33 casos por millón de años-persona en niños de 0-14 años.
- Se identificaron cinco regiones que agrupan el mayor número de casos de leucemias pediátricas.

Relevancia de los hallazgos

- Consolidación del trabajo colaborativo con la academia.
- La identificación de áreas geográficas con mayor número de casos permite la intensificación de la captación de casos.
- Las regiones identificadas pueden requerir una red de prestación más robusta y articulada, que ofrezca una mayor cobertura.
- Estos resultados pueden ser traducidos en acciones concretas de mitigación del riesgo y detección temprana desde la perspectiva de los tomadores de decisiones y los aseguradores.

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Space-time clustering of childhood leukemia in Colombia: a nationwide study

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Abstract

Background: Leukemia is the most common cancer in childhood. The estimated incidence rate of childhood leukemia in Colombia is one of the highest in America and little is known about its spatial distribution.

Purpose: To explore the presence of space-time clustering of childhood leukemia in Colombia.

Methods: We included children less than 15 years of age with confirmed diagnosis of acute leukemia reported to the national surveillance system for cancer between 2009 and 2017. Kulldorff's spatio-temporal scan statistics were used with municipality and year of diagnosis as units for spatial and temporal analysis.

Results: There were 3846 cases of childhood leukemia between 2009 and 2017 with a specific mean incidence rate of 33 cases per million person-years in children aged 0–14 years. We identified five spatial clusters of childhood leukemia in different regions of the country and specific time clustering during the study period.

Conclusion: Childhood leukemia seems to cluster in space and time in some regions of Colombia suggesting a common etiologic factor or conditions to be studied.

Keywords: Leukemia, Childhood, Cluster analysis, Epidemiology, Colombia

Background

Leukemia is the most common cancer in childhood. According to the World Health Organization (WHO), the age-standardized cancer incidence rate for 2001–2010 was 140.6 cases per million in children aged 0–14 years, being leukemia the most common cancer (rate = 46.4), followed by tumors of the central nervous system (rate = 28.2), and lymphomas (rate = 15.2) [1]. World estimated childhood leukemia (CL) incidence rates increased 13% in the period 2001–2010 compared to the 1980s rates, and for the recent period, the rates in South America are the highest (33.8 cases per million) in the world, followed by West Asia (33.7 cases per million) [1, 2].

Despite leukemia being the most common cancer in childhood, little is known about its etiology. Genetic, infectious, and environmental factors are the most implicated factors for leukemia. During the last decade, the use of molecular profiling and panel-based testing for detection of germ line syndromes allows the identification of people, and families, with predisposition to hematopoietic malignancies. Furthermore, the WHO included the familial hematopoietic malignancies as an essential component of leukemia diagnosis with reference to specific leukemia predisposition genes [3, 4]. Despite the recognized importance of genetic factors in the occurrence of leukemia, some authors affirm that environmental factors might account for the 85–96% of all cancers in childhood, including leukemia [5–7]. Environmental factors associated with leukemia incidence include ionizing radiation, pesticides exposure, parental smoking, traffic fumes, and household chemicals [8]. The current standardized incidence rates for leukemia in children aged 0–14 years are higher in developing countries where exposure to environmental agents associated with leukemia incidence is probable higher than in developed countries [2]. It is expected that spatial variation in exposure to environmental factors might yield to spatial variations of cancer incidence. Therefore, exploring and describing the spatial distribution and clustering of CL is an important step to explore potential environmental causes related to CL incidence.

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Previous studies have described the spatial distribution and clustering of CL in different countries of Europe and North America [9–13]. Most of these studies found evidence of space-time clustering of cases related to the time at birth or the time at diagnosis using different geographical units of analysis (from large administrative areas to exact geocodes or residential locations). These studies have provided evidence that CL tends to cluster in space and time, providing solid bases for further studies focusing on identifying etiologic factors.

The estimated incidence rate of CL in Colombia is one of the highest in Latin America and the Caribbean with an estimated age-standardized rate of 58.4 cases per million of children under 15 years of age during 1992–2013 based on the report of four cancer registries in Colombia [2]. According to the 2017 childhood cancer report of the National Institute for Health in Colombia, there are departments with leukemia incidence rates over 85 cases per million children [14]. National analysis are routinely reporting estimated rates by region and departments but little is known about the spatial distribution of CL in Colombia at a smaller geographic unit; despite the high incidence rates the analysis of potential clustering of CL is not available. Therefore, the objective of this study was to explore the presence of space-time clustering of incident cases of acute childhood leukemia (ACL) in Colombia between 2009 and 2017.

Methods

Population and data sources

The study was conducted in Colombia, a country with a population of approximately 48 million of people located at north of South America [15]. The country has 32 departments and 1122 municipalities with administrative and political autonomy. The health system is part of the Social Protection System, which is regulated by the Ministry of Health and Social Protection. The health system was reformed in 1993 conceiving health as a public service to be provided on a market-regulation basis with the participation of health promoting insurance companies (EPS, for its initials in Spanish); during the last decade the main advances of the health system were the expansion of insurance coverage (98% in 2016), the recognition of health as a constitutional right, and the harmonization of health benefit plans for beneficiaries of paid and subsidized insurances systems [16]. Since 2010 the health care for childhood cancer was declared a health priority in Colombia and there is specific regulation for guarantee the timely access to diagnosis, treatment, and rehabilitation [17].

We included incident confirmed cases of ACL (acute lymphoblastic leukemia and acute myeloid leukemia) diagnosed in children less than 15 years old registered in the National Surveillance System of Childhood Cancer (NSSCC) between 2009 and 2017. The NSSCC is a national registry of childhood cancer that started in 2008 as a national surveillance registry for ACL only and in 2014 was converted into the NSSCC, which collects reports for all types of cancer for children and adolescents from 0 to 18 years old in Colombia. The NSSCC is part of the National Surveillance System in Public Health (SIVIGILA, for its name in Spanish) that is led by the National Institute for Health in Colombia [18]. The NSSCC receive reports of probable and confirmed childhood cancers from the health institutions country-wide on a weekly basis. The confirmation of cases is done based on reports of myelogram, immunotypification, histopathology, and cytogenetic tests. The NSSCC compile the reports, eliminate duplicates, and confirm the cases and the date of diagnosis. We obtained anonymous data from the NSSCC that contained the age, sex, the code of the international classification of disease (ICD-10), date of diagnosis, and the municipality of residence at the time of diagnosis for all ACL cases.

In Colombia there are four cancer population-based registries validated by and reporting to the International Agency for Research on Cancer (IARC); these registries are located in the cities of Cali, Bucaramanga, Manizales, and Pasto, and offer high quality information of cancer for these cities; in the case of Bucaramanga the registry includes the four municipalities of the metropolitan area [19]. The cancer registry of Cali was created in 1962, being the oldest cancer registry in Latin America and the pioneer in implementing cancer registry methods in Colombia [20]. The Colombian High Cost Diseases Fund (CAC, for its name in Spanish), a national organization affiliated to the Ministry of Health Protection in Colombia, started in 2015 a National Cancer Registry (NCR), which collects data of all types of cancer cases (children and adults) reported by the health insurance companies, municipalities, and special health regimes, country-wide on a yearly basis [21]. The population coverage in Colombia of the health insurance companies is about 94% [22]; therefore, the NCR was created to be a population-based registry in Colombia. The CAC compile the reports, eliminate duplicates, and confirm the cases and their health service provision by reviewing the medical history and histopathological report for all cancer cases. Thus, the NCR is complementary to other cancer data sources and its main objectives are to assess the cancer risk (magnitude and tendency) and the access to health services. We conducted an analysis of the underreporting of ACL and childhood cancer in the NSSCC, by comparing the ACL reports of the NSSCC with the reports of the cancer population-based registries of Cali and Bucaramanga for both cities during 2010–2015. In addition, we obtained anonymous data from the NCR for 2016 so we were able to conduct a

complementary analysis comparing all childhood cancer cases reported to the NCR and the NSSCC during 2016.

Data for the population at risk were obtained from the National Department of Statistics (DANE, for its name in Spanish). Census population projections for children less than 15 years were obtained annually for the study period (2009–2017) for all 1122 municipalities in Colombia [23]. We calculated the geometric centroid coordinates (longitude and latitude) for each polygon of municipality by using the ArcGIS software version 10.3.

Statistical analysis

Descriptive statistics including mean annual specific incidence rates of ACL and Bayesian smoothed incidence morbidity ratios were calculated by municipality. We used Moran's Index for calculating global spatial autocorrelation and Kulldorff's circular scan test to detect local clusters [24]. We used the SaTScan® software version 9.6. In this study we used Kulldorff's spatio-temporal scan statistics to conduct the first exploratory analysis of childhood cancer clusters in Colombia because: 1) spatial scan statistic are commonly used to detect spatial and/or temporal disease clusters in epidemiological studies and are appropriated for detecting regularly shaped clusters which we expect to find if clusters are related to localized environmental exposures at municipality level; 2) Kulldorff's scan statistics have very good performance to detect large compact clusters of rare diseases in large territories compared to other scan methods [25]; 3) it has a open software to implement the analysis which make it highly reproducible [26], and 4) it have been widely used for assessing clusters of health events worldwide. We ran the Kulldorff's test using a retrospective space-time analysis, scanning for clusters with high rates using a discrete Poisson model. The space unit was the municipality of residence and the time unit was the year of diagnosis. The upper limit for the radii was set to include within the circles the 25% of the total number of ACL cases. The significant level for the test was 0.05.

Results

There were 3915 confirmed incident cases of ACL notified to the SIVIGILA between 2009 and 2017. Nine cases were excluded of the analysis for being residents outside Colombia and 60 cases were excluded because they were identified from a specific department but not at a specific municipality. Therefore 3846 incident cases of ACL were included in the analysis. We identified cases in 629 out of the 1122 municipalities in Colombia (56%).

Most cases were male (54%) and 48% of cases occurred in children under 6 years old. The mean annual incidence rate was 33.15 cases per million for children under 15 years old in Colombia during 2009–2017, and the rate ranged from 24.71 in 2009 to 39.41 in 2016. The district of Bogotá, followed by the departments of Antioquia, Valle, and Santander, were the sites with the highest proportion of cases. The departments of Amazonas, Casanare, and Santander had the highest mean incidence annual rate of ACL during the study period. Bayesian smoothed incidence morbidity ratios by municipality ranged from 0.45 to 2.43 (Fig. 1). Table 1 shows the main characteristics of the study population.

Clustering results

The Moran's I was 0.43 ($p = 0.049$) for global spatial autocorrelation of total ACL cases 2009–2017 using municipality as spatial unit. The spatio-temporal scan test identified five clusters with statistical significance. The clusters were of different size and located mainly across the Andean región of the country (Fig. 2). Cluster 1 has the largest number of municipalities and was located at the center of Colombia, including Bogotá, the capital district; this cluster contained 558 ACL cases when a number of 369 cases was expected. Cluster 2 was located at the northeast of the country including a large area of 124 Km and 137 cases in municipalities of Santander and Norte de Santander. Cluster 3 was located at the southwest of the country inlcuding municipalities of Cauca, Valle and Tolima with 135 cases. Cluster 4 was identified in the department of Huila at the south of the country including 30 cases and 11 municipalities. Cluster 5 was identified in the city of Medellín including 62 cases. There were two clusters identified around Leticia in Amazonas, and Cartagena in Bolívar, that did not reach statistical significance in the hypothesis tests. Three out of the five clusters identified ocurred also clustered in time between 2015 and 2017 (Table 2).

Analysis of underreporting for the NSSCC

We compared the number of ACL cases registered in the cancer population-based registries of Cali and Bucaramanga during 2010–2015 with the number of cases of ACL reported to the NSSCC for both cities during the same period. During this period 52 ACL cases were reported for Bucaramanga and 167 for Cali by the cancer registries compared to 51 and 163 reported to the NSSCC, respectively for both cities. Therefore the NSSCC captured and registered 97% of all confirmed incident cases of ACL in both cities during 2010–2015.

A complementary analysis compared the reports of the NCR and the NSSCC for all childhood cancer cases reported during 2016. During this year 1394 incident cases of childhood cancer were identified and 1206 (86.5%) of them were reported to the NSSCC. Among the cases reported to the NSSCC only 54 (3.8%) were discarded due to errors in the notification of diagnosis (not cancer cases) or the year of diagnosis (not incident cases). Therefore the NSSCC captured and registered 83% of all incident cases of childhood cancer in Colombia during 2016.

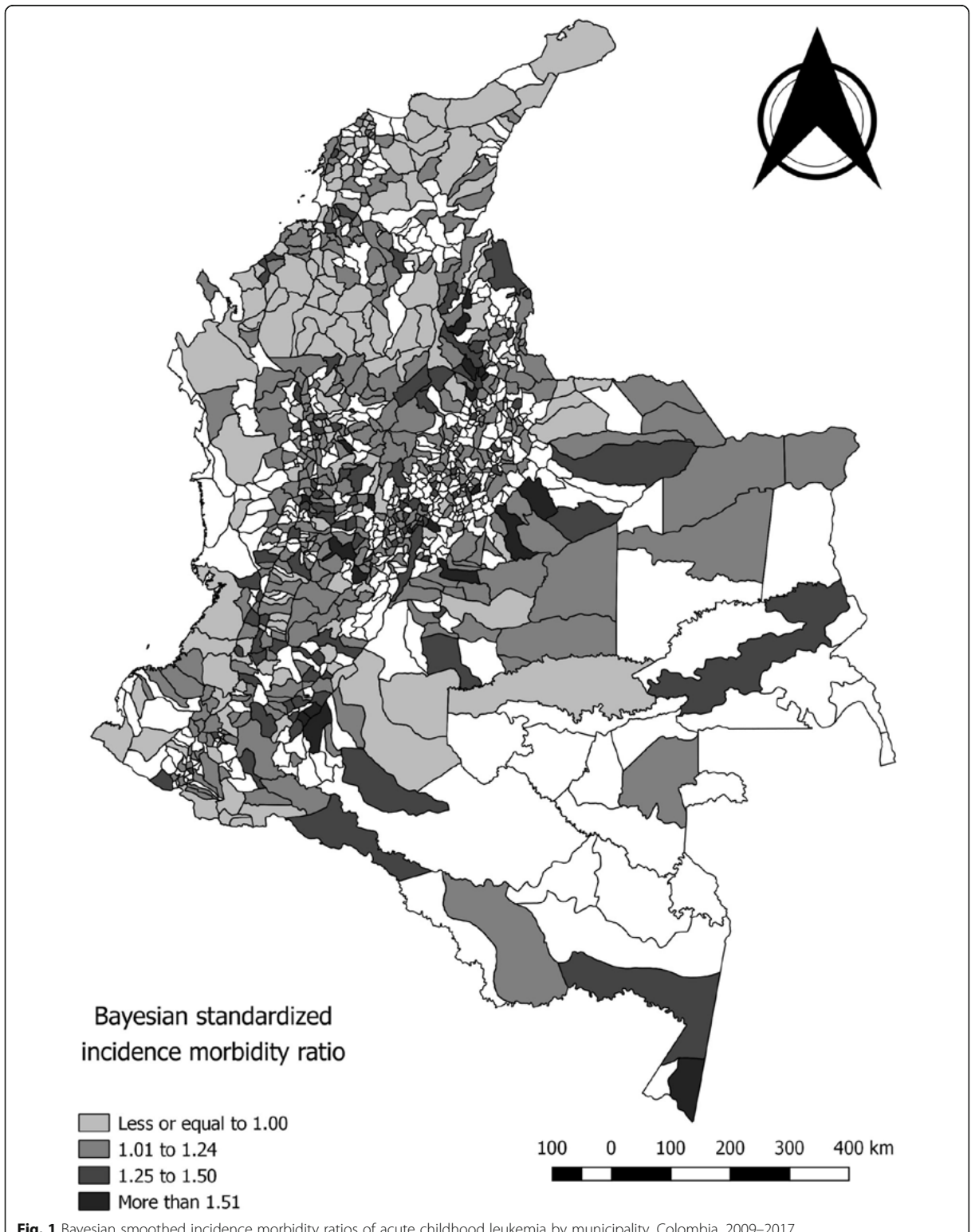

Fig. 1 Bayesian smoothed incidence morbidity ratios of acute childhood leukemia by municipality, Colombia, 2009–2017

Table 1 Characteristics of the study population

Variable	No. cases	% ($n = 3846$)	Cumulative %
Sex			
Female	1763	45.84	45.84
Male	2083	54.16	100
Age (years)			
0	153	3.98	3.98
1	230	5.98	9.96
2	392	10.19	20.15
3	429	11.15	31.31
4	351	9.13	40.43
5	300	7.8	48.23
6	250	6.5	54.73
7	249	6.47	61.21
8	199	5.17	66.38
9	191	4.97	71.35
10	190	4.94	76.29
11	228	5.93	82.22
12	194	5.04	87.26
13	219	5.69	92.95
14	271	7.05	100
	No. cases	%	IR per million
Year of diagnosis			
2009	323	8.4	24.71
2010	355	9.23	27.28
2011	405	10.53	31.24
2012	437	11.36	33.82
2013	452	11.75	35.06
2014	392	10.19	30.45
2015	503	13.08	39.10
2016	507	13.18	39.41
2017	472	12.27	36.66
	No. cases	Population 2013	MIR per million
Department			
Amazonas	17	28,949	65.25
Antioquia	442	1,575,200	31.18
Arauca	23	96,456	26.49
Atlántico	113	650,420	19.30
Bogotá, D.C.	706	1,809,750	43.35
Bolívar	164	616,314	29.57
Boyacá	102	355,591	31.87
Caldas	96	244,793	43.57
Caquetá	51	158,253	35.81
Casanare	63	107,970	64.83
Cauca	108	396,099	30.30
Cesar	74	329,697	24.94
Chocó	18	188,626	10.60
Córdoba	112	520,461	23.91
Cundinamarca	235	713,766	36.58
Guainía	5	15,028	36.97
Guaviare	4	40,556	9.72
Huila	130	339,341	10.96
La Guajira	29	331,338	42.57
Magdalena	36	417,689	9.58
Meta	113	270,616	46.40
Nariño	109	496,285	24.40
Norte de Santander	128	389,382	36.53
Putumayo	24	116,821	22.83
Quindío	39	137,954	31.41
Risaralda	61	231,248	29.31
San Andrés	1	19,197	5.79
Santander	235	512,955	50.90
Sucre	74	252,122	32.61
Tolima	150	392,101	42.51
Valle del Cauca	374	1,093,126	38.02
Vaupés	4	16,683	26.64
Vichada	6	27,502	24.24

IR Incidence Rate, *MIR* Mean annual Incidence Rate 2009–2017

Discussion

This nation-wide study assessed the presence of space-time clustering of ACL in Colombia during 2009–2017 using information of the NSSCC. Using Kulldorff's circular scan test we found five space-time local clusters in different regions of the country during specific time windows. To the best of our knowledge, this is the first study assessing the presence of clusters of ACL at national level in South America.

World childhood leukemia (CL) estimated rates for the period 2001–2010 showed the highest rates in South America (33.8 per million), followed by West Asia (33.7 million) [1]. The estimated incidence rate of CL in Colombia is one of the highest in Latin America and the Caribbean with an estimated standardized rate of 58.4 per million (Colombia four registries 1992–2013) [2]. Using information from the NSCC we found a mean annual incidence rate of 33.15 per million-person year for children under 15 years old for Colombia during 2009–2017. This estimated country rate is similar to the reported by IARC for South America but lower for the estimated rate for Colombia based on the report of the four population-based cancer registries reporting to the IARC. The difference is probably explained by the national coverage of the NSSCC that includes information for all 1122 municipalities in Colombia since 2009, giving a mean

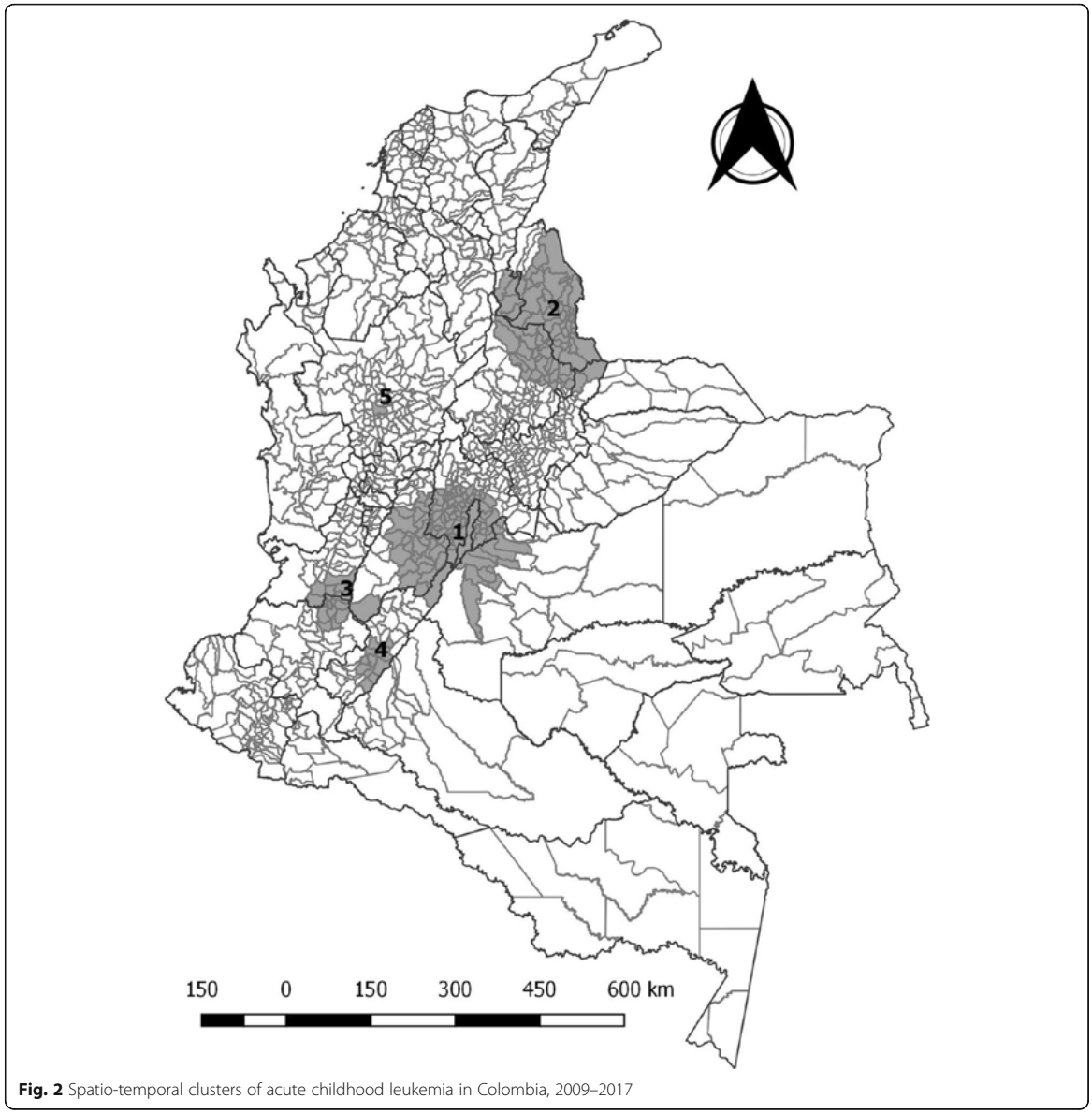

Fig. 2 Spatio-temporal clusters of acute childhood leukemia in Colombia, 2009–2017

Table 2 Results of scan test for spatiotemporal clusters of acute childhood leukemia in Colombia, 2009–2017

Clusters	*Ratio (Km)*	*N° municipalities*	*RR*	*Time*	*P value*
1	106.9	109	1.60	2013 to 2016	< 0.001
2	124	73	1.95	2015 to 2017	< 0,001
3	48.9	18	1.74	2015 to 2017	0.001
4	43.1	11	3.14	2010 to 2013	0.018
5	0	1	2.10	2015 to 2016	0.021

estimated for the country and mixing municipalities with high and low incidence of CL. In contrast, the IARC estimates for Colombia are based on four registries that provide high quality information for seven selected municipalities: four in the metropolitan area of Bucaramanga, and the cities of Cali, Pasto and Manizales [19].

The report of ACL cases to the NSSCC is considered of good quality due to the continuous training and quality-assurance process of SIVIGILA in all regions of Colombia. In addition, the complementation of ACL cases report with an active institutional surveillance of ACL-compatible diagnosis favors the identification of

ACL cases in early stages [27]. Nevertheless, there is a probability of ACL underdiagnosis that might be mediated by limitations of access to health care facilities in remote rural areas; according to the national study of childhood cancer in 2017 there were no cases of acute lymphoblastic leukemia (82% of total ACL cases) in three departments with remote population (Guainía, Guaviare and San Andres Island). In addition, this study reported that 99.4% of acute lymphoblastic leukemia prevalent cases were covered by health insurance companies, the time between clinical suspicion and the confirmatory diagnosis was on average 21.8 days (median 7 days) and the time between the diagnosis and first treatment was on average 32.1 days (median 3 days) [28].

According to the report of the population-based cancer registry of Cali (the oldest cancer registry in South America) there was an annual increase of 0.7% in the ACL incidence between 1977 and 2011 [29]. The estimated survival proportion for CL is about 55% at 5 years (registries of Colombia 2005–2009) compared to 85% reported by registries in United States during the same period [30]. Taking into account the incidence, trends, and survival of childhood cancer in Colombia, the national goverment have prioritized regulations related to guarantee the health care access, treatment, and follow-up for childhood cancer; however, only few institutions comply with national standards of comprehensive health care for childhood cancer [31]. As part of the national strategies for cancer prevention, treatment and control, the government create the NSSCC starting in 2014 to include the mandatory report of all types of childhood cancer; between 2008 and 2013 the mandatory notification the the national system was exclusive for ACL [18]. Primary prevention of cancer in Colombia is based on tabacco control, HPV vaccination, health style promotion (diet, alcohol, physical activity), and control of exposure to ionizing radiation and known carcinogens in occupational settings (industries) [30]. No specific prevention strategy is directed to environmental exposures related to childhood cancer, probably due to the evidence for those associations still being incipient in the world literature and absent in Colombia.

Childhood leukemia seems to have higher incidence in Latin Americans than in other racial groups. The reported incidence of CL in Guadalajara metropolitan area during 2010–2014 was 64 per million in children under 15 years of age [32]. Similarly, high CL incidence have bee reported in Latin population living in USA [33]. Higher incidence compared to other world regions might be related to genetic factors but also might be related to exposure to environmental factors such as radiation, pesticides, children and parental exposure to toxics, and infections [9, 34–36] that might be present more commonly in Latin American countries compared to developed countries. The occurrence of epidemics of infections disease has been related to space-time clustering of leukemia and other childhood cancers [37, 38]. For leukemia and central nervous system tumors, ionizing radiation in high doses is the only environmental exposure established as a risk factor in the literature [39], while others remained under study such as exposure pesticides, volatile organic compounds such as benzene, and traffic-related air pollution [35, 40–42].

Mapping of disease is part of the descriptive epidemiologic analysis of cancer and any other diseases; however, assessing the pattern of disease occurrence in terms of clustering is less common. Space-time cluster analysis rationale is based on Tobler's first law of geography, which proposes that "things that are closer to each other are more alike that things that are further apart" [43]. Therefore, assessing space-time clustering helps to uncover disease patterns that might not be evident when routinely mapping the disease using large administrative units for analysis. Furthermore, cluster studies might provide clues of etiologic factors such as common exposures or conditions present in populations. The environmental factors potentially related to ACL show space-time variability and, consequently, variations in exposure to these factors might result in space-time aggregations of ACL cases if the relationship among exposure and ACL is present. Thus, analyzing geographic clusters of ACL might provide key information related to potential etiologic factors.

Most studies assessing clustering of childhood cancer have focused on clustering of leukemia [9, 44]. Childhood leukemia clusters have been identified in different countries but none of these studies have been conducted in South America where the incidence rates of ACL are higher. In United Kingdom, Knox & Gilman studied clustering of CL during 1966 and 1983 and found short-range clustering of ACL at place of notification and at birth and suggested two types of etiologic factors: familiar susceptibility and focal environmental hazards [45]. In Hong Kong, Alexander et al., assessed CL clustering during 1984 and 1990 and found spatial clustering for acute lymphoblastic leukemia suggesting an infectious etiology related to the childhood peak and population mixing [46]. The EUROCLUS project aimed to assess spatial clustering of CL in 17 European countries during 1980–1989 and found evidence of spatial clustering in small census areas [44]. In Switzerland, Kreiss et al., found space-time clustering of childhood leukemia between 1985 and 2010 [11]; they found clustering at birth but not at diagnosis suggesting a common etiologic factor early in life. In Mexico, Tlacuilo-Parra et al., found three spatial clusters of ACL at time of diagnosis within the municipality of Guadalajara during 2010–2014 [32].

Our results found five space-time clusters at time of diagnosis in different regions of the country and three of them were clustered in time after 2015. The spatial clustering might provide information of potential underlying risk factors and the time clustering might provide information related to windows of susceptibility and latent periods [47]. The evidence of spatial clustering at diagnosis for ACL in some regions of Colombia might suggest the presence of potential local environmental exposures which are closer to the time of diagnosis and that the latent periods for those exposures might be relatively short. In this regard, it is important to note that in the four clusters detected that involve different municipalities, the cluster core corresponded to municipalities with predominance of rural areas that are expanded to capital cities such as Bucaramanga, Cali and Bogotá. Most rural municipalities included in these clusters have crops in which the use of pesticides is a common practice [48]. It is suggested that further studies assessing the potential relationship between pesticides' use and the incidence of ACL might be conducted in those areas. In the case of the city of Medellin, the city itself was identified as a defined spatial cluster with predominant timing between 2015 and 2016. Being that Medellin is a capital city characterized for their manufacturing industry and high levels of intra-urban air pollution, the potential relation of ACL with other potential risk factors such as exposure to volatile organic compounds, other chemicals, or traffic-related air pollution is also matter of further research within the city. A case-control study conducted in the cities of Bogotá and Bucaramanga found an association between parental occupational exposure to carcinogens, especially carcinogenic hydrocarbons before conception, and the occurrence of childhood acute lymphoblastic leukemia [36]. Therefore, occupational exposure to carcinogens and occupational and environmental exposure to pesticides are factors that might explain difference of ACL across regions in Colombia. These factors should be explored in detail by future studies.

In contrast to our findings, other studies did not find any leukemia clustering [49–51]. A recent study conducted by Konstantinoudis et al. [47] assessed spatial clustering of all childhood cancers other than leukemia in Switzerland between 1985 and 2015 and did not found any evidence of space clustering at birth or diagnosis after adjusting for multiple testing of different cancer groups. Lack of clustering of leukemia and other childhood cancers should be interpreted with care. In most cases, divergence of results in epidemiology is seen as lack of consistency and therefore low credibility for associations between potential etiologic factors and diseases [52]. Childhood cancer are a group of diseases that do not have clear etiology and might be related to potential environmental factors that are uneven distributed across places. When assessing spatial distribution of these types of diseases, the heterogeneity of findings must be seen as valuable information about the differential distribution of potential etiologic factors that leads to differential distribution (negative or positive clustering) of disease. Therefore, spatial clustering should be seen as an exploratory analysis that open the window to new potential hypothesis at specific places and should be studied in more detail using other study designs to assess association or causation.

Strengths and weaknesses

The main strength of this study is that it is a nationwide study utilizing registries of the NSSCC, which is a national registry with coverage across all municipalities in Colombia. Using the population-base cancer registries as references for underreporting analysis [53], we provided evidence of low percentage (3%) of underreporting of ACL in the NSSCC in two capital cities during 2010–2015; this result implies that the NSSCC is not a fully population based registry but the health care coverage is very high, and therefore the cases included in the NSSCC are a good representation of the total incident cases in Colombia and provide useful information for making geographical analysis and estimations. However, the low percentage of underreporting for ACL observed in the two capital cities does not imply that the same underreporting pattern applies to other non-capital municipalities. We used a long period of analysis (2000–2015) to assess spatial clusters of CL at a reasonable period of time that was not affected by short-term variations of the CL incidence. The use of Kulldorf's circular spatial scan, the most widely used cluster scan test, let us assess and identify local clusters at municipality level, and the time and quantity of ACL cases provided sufficient power to detect space-time clusters.

We were able to confirm the municipality of residence at time of diagnosis for all cases; however, the residential address and municipality during the pregnancy or at birth was not available from the registries and therefore we were not able to conduct analyses of space-time clustering at an earlier window of susceptibility. The place of residence at diagnosis, however, can be a good representation of earlier place of living, as previous studies on CL in Colombia suggested that residential mobility usually occurs after the time of diagnosis related to access to specialized treatment [54]. Therefore, it is less probable that residential mobility occurs before the diagnosis and, if present, previous studies conducted in Colombia report intra-city mobility more than residential mobility outside the municipality [55]. Spatio-temporal analysis using regional count data may vary depending on the areal and time unit selected (modifiable areal and temporal unit problem) [56]; in our study we used municipality as the

unit of analysis which is highly variable in terms of population; therefore the analysis were conducted for rates using as estimates of population at risk the number of population at municipality level. Kulldorff's scan test assessed only circular shapes and thus clusters of irregular shape might not be adequately identified in this study.

Conclusions

Acute childhood leukemia seems to cluster in space and time in some regions of Colombia suggesting a common etiologic factor or conditions to be further studied. Future work should be focused on assessing the presence of spatio-temporal clusters of childhood cancer at smaller geographical areas within the regions identified in this study, and assessing the comparison of results using different cluster detection methods. We suggest that adding cluster analysis of disease should be considered as part of the routine surveillance system analysis for childhood leukemia.

Abbreviations

ACL: Acute childhood leukemia; CAC: Colombian High Cost Diseases Fund (CAC, for its name in Spanish); CL: Childhood leukemia; DANE: National Department of Statistics (DANE, for its name in Spanish); NCR: National Cancer Registry; NSSCC: National Surveillance System of Childhood Cancer; SIVIGILA: National Surveillance System in Public Health (SIVIGILA, for its name in Spanish)

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Source of map

The maps depicted in Figs. 1 and 2 were created for the authors for the publication. The maps were created using ArcGIS software and open (public) shape files from the National Department of Statistics of Colombia (DANE) available at DANE geoportal.

Authors' contributions

LARV designed, coordinated the study and conducted statistical analyses data; MPRD & PRB managed cancer cases records at SIVIGILA and CAC and compiled databases for the study; FEMR support the geo-statistical analysis and made maps; LARV, MPRD, PRB & LAAM interpreted results and contributed to discussion. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the national and international ethical standards and ethical approval of the study was granted by the Ethical Committee for Research of the Universidad Industrial de Santander (CEINCI-UIS). Informed consent for participation in the study was not obtained from the parent or guardian of children as the data was obtained at aggregated level (number of cases per municipality) from administrative health databases of NSSCC and CAC.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Childhood Leukemia in Small Geographical Areas and Proximity to Industrial Sources of Air Pollutants in Three Colombian Cities

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Trabajo colaborativo con la academia como actor de interés (Universidad Industrial de Santander)

Objetivo:

Identificar grupos de casos de leucemias agudas pediátricas y su asociación con la proximidad a fuentes industriales de contaminación de aire en Bucaramanga, Cali y Medellín durante 2000-2015.

Principales hallazgos

- La exposición a la contaminación del aire, procedente de fuentes industriales, puede contribuir a la incidencia de la leucemia aguda en población pediátrica en centros urbanos.
- La tasa de incidencia fue mayor en Bucaramanga.

Relevancia de los hallazgos

- Resultados consistentes con el trabajo previo con respecto a la identificación de grupos con mayor concentración de casos.
- Apoyo a la planeación de los servicios bajo un enfoque centrado en el riesgo.
- La identificación de factores relacionados con la calidad del aire y exposición a contaminantes ambientales es fundamental para la generación de políticas públicas enfocadas en la reducción de su impacto.

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Article

Childhood Leukemia in Small Geographical Areas and Proximity to Industrial Sources of Air Pollutants in Three Colombian Cities

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Abstract: Acute leukemia is the most common childhood cancer and has been associated with exposure to environmental carcinogens. This study aimed to identify clusters of acute childhood leukemia (ACL) cases and analyze their relationship with proximity to industrial sources of air pollution in three capital cities in Colombia during 2000–2015. Incident ACL cases were obtained from the population cancer registries for the cities of Bucaramanga, Cali, and Medellín. The inventory of industrial sources of emissions to the air was obtained from the regional environmental authorities and industrial conglomerates were identified. The Kulldorf's circular scan test was used to detect city clusters and to identify clusters around industrial conglomerates. Multivariable spatial modeling assessed the effect of distance and direction from the industrial conglomerates controlling for socioeconomic status. We identified industrials sectors within a buffer of 1 km around industrial conglomerates related to the ACL clusters. Incidence rates showed geographical heterogeneity with low spatial autocorrelation within cities. The spatio-temporal tests identified one cluster in each city. The industries located within 1 km around the ACL clusters identified in the three cities represent different sectors. Exposure to air pollution from industrial sources might be contributing to the incidence of ACL cases in urban settings in Colombia.

Keywords: leukemia; childhood; cluster analysis; air pollution; industrial pollution; Colombia

1. Introduction

Leukemia is the most common childhood cancer worldwide [1]. According to the most recent report of the Global Cancer Observatory, it is estimated that 7745 new cases of leukemia were diagnosed in 2018 in Latin America and the Caribbean in children under 15 years old. The age-standardized rate of leukemia in this region is estimated in 49 cases per million, only exceeded by North America and Europe (58 and 50 cases per million, respectively). In terms of mortality due to childhood leukemia, the Latin America and the Caribbean region has an estimated age-standardized mortality rate of 20 deaths per million children under 15 years old, the highest mortality rate for leukemia shared with the Asia region [2].

In Colombia it is estimated that acute childhood leukemia (ACL) accounts for 36% of the total incident childhood cancer cases, followed by the central nervous system tumors (16%) and lymphomas (14%) [3]. The estimated age-standardized incidence rate for leukemia in Colombia was 68.4 cases per million for children between 0 and 14 years old during 1992–2013 [4]. According to the long-term data of the population-based cancer registry of Cali, Colombia, the incidence of childhood leukemia had an annual percent change of 1.0 (95% confidence interval (CI): 0.2–1.8) between 1977 and 2011, while the mortality had an annual percent change of –1.2 (95% CI: −2.6–0.3) during the same time [5].

The causes of ACL and their biological pathways are not yet well understood. However, there is evidence that genetic conditions, infectious and environmental exposures are the most important contributors for leukemia [6,7]. Environmental factors associated with leukemia incidence include ionizing radiation, pesticides exposure, parental smoking, air pollution, and household chemicals [8]. The report of the World Health Organization on air pollution and child health highlights the fact that air pollution has a terrible impact on child health and survival as 93% of children live in environments with air pollution levels above the WHO guidelines [9].

Several studies conducted in Europe and the United States have evaluated the relationship between air pollution exposure and the childhood cancer risk, especially of ACL. The first published study (1989) was conducted in Denver, USA, and found an increased risk of childhood cancer and leukemia using traffic counts at the home address at the time of diagnosis as pollution exposure [10]. Most of studies in the following 15 years focused mainly on assessing traffic-related air pollution using case-control and ecologic designs and provided mainly negative evidence for the relationship with childhood cancer [11]. Then, a meta-analysis of seven case-control studies assessing specifically residential traffic exposure and risk of childhood leukemia found positive associations among studies using a postnatal exposure window and no association among studies using prenatal exposure window [12]. Another comprehensive review and meta-analysis of outdoor air pollution and childhood leukemia risk included six ecologic and 20 case-control studies using different exposure measurements. They found an increased risk of childhood leukemia related to high traffic density, increased risk of acute lymphoblastic leukemia related to nitrogen dioxide exposure, and of acute myeloid leukemia related to benzene exposure [13].

In contrast, studies estimating the effect of industrial air pollution on childhood cancer are less common. Initial ecologic studies from Great Britain found a geographic association of leukemia and solid cancers with petroleum-derived volatiles and effluents of combustion engines [14]. Studies published in the last five years in Spain suggest a relationship between industrial pollution and childhood cancer. A population-based case-control study assessing the effect of residential proximity to industrial pollution found an increased risk of childhood leukemia for children living near to specific types of industries [15]. A study assessing proximity to air-polluting industries using cluster analysis and small geographical areas in the Region of Murcia, found a possible association between proximity to specific industries and childhood cancer [16]. More evidence from other world regions is needed before establishing the relationship between industrial pollution and childhood leukemia.

The use of spatial epidemiological studies is useful for exploring geographical patterns of disease, opening the possibility for studying potential associations with underlying conditions that might differ across places. A recent study identified spatial clusters of childhood leukemia in five regions

of Colombia when using municipalities as spatial units of analysis. The clusters identified included four of the five largest cities in Colombia: Bogotá, Cali, Medellín, and Bucaramanga [17]. However, little is known about the clustering of cases within cities and their relation with industrial pollution sources. This study aimed to identify clusters of ACL cases, using a spatial analysis based on small geographical areas, and analyze their relationship with proximity to industrial sources of air pollution in three capital cities in Colombia during 2000–2015.

2. Materials and Methods

2.1. Study Areas, Population, and Geographical Data

This ecologic and spatial analysis study centers in Colombia, a country located at the northern extreme of South America, with a population of approximately 48 million people. The study areas included the cities of Bucaramanga, Cali, and Medellín. These three cities were chosen because they were previously identified as municipalities with clusters of leukemia [17] and the existence of population-based cancer registries. Bucaramanga, the capital city of the department of Santander locates in the northeast of Colombia and has a population of approximately 529,000 people. Cali, the capital city of the department of Valle del Cauca, locates in the southwest of the country and has a population of approximately 1,823,000 people. Medellín, the capital city of the department of Antioquia, locates in the northwest of the country and has approximately 2,373,000 people [18].

Data for the population at risk came from the National Census 2005, National Department of Statistics (DANE, for its name in Spanish). Census population annual projections of children less than 15 years were obtained from DANE for the study period (2000–2015) for the three cities [19]. Population data was available from Census 2005 at section, sector, and block level. The census sector (CS) is the intermediate geographical territorial unit for an urban area that corresponds to the area delimited by the census perimeter and is made up of census blocks, which is the smaller geographical census unit. Census sectors do not have a specific size or population. We used CS as the spatial unit for cluster analysis in this ecologic study as it offers an adequate small-area unit of analysis for health outcomes and preserves the privacy of cases. We performed linear interpolation for estimating the annual population for each CS during the study period based on the linear interpolation of DANE projections of the population between 0 and 14 years old for the cities.

We worked with the geographic coordinates (latitude and longitude) of population-based CS centroids. The distance and direction between the location of each "industrial conglomerate" and the CS centroids were calculated using the Euclidean distance (in meters) and angle (in geodetic degrees) in ArcGIS 10.6.1® (Environmental Systems Research Institute ESRI, Redlands, CA, USA). The maps of the three cities at CS level were obtained from the DANE Geoportal public website [20], and the spatial data were created in ArcGIS 10.6.1® using the projection of Colombia in mode Custom Azimuth Equidistant and Datum WGS 1984. The socioeconomic status data were obtained from the municipalities at the neighborhood level and then the predominant socioeconomic status (SES) from the neighborhoods in each CS (usually between 2 and 3), represented the whole CS SES. The SES data uses the DANE "socioeconomic strata" classification of the socioeconomic resources of residential places [21], which range from one to six being one the strata with higher socioeconomic deprivation.

2.2. Acute Childhood Leukemia Data

In Colombia there are four Population-Based Cancer Registries validated by and reporting to the International Agency for Research on Cancer (IARC). These registries are located in the cities of Cali, Bucaramanga, Manizales, and Pasto, and offer high-quality information about cancer for these cities. The population-based cancer registry of the metropolitan area of Bucaramanga was created in 2000 and registers cases of Bucaramanga and the other three municipalities of the metropolitan area. The cancer registry of Cali was created in 1962, is the oldest cancer registry in Latin America and the pioneer in implementing cancer registry methods in Colombia [22]. The cancer registry of Antioquia is

a population-based cancer registry created in 2000, which register cancer cases for Medellín and all municipalities in Antioquia.

The ACL data were obtained from the population-based cancer registries of the Bucaramanga metropolitan area, Cali and Antioquia, for the cities of Bucaramanga, Cali, and Medellín, respectively. Incident confirmed ACL cases diagnosed from 1 January 2000, to 31 December 2015, from residents in the cities were included in the study. For the cancer registries and this study, resident ACL cases are those who have been living six months or more in the city before the date of ACL diagnosis. The information available in the cancer registries for ACL cases that were used for this study included the type of ACL, sex, date of birth, date of diagnosis, and place of residence at the time of diagnosis. When the address or neighborhood of residence was not available in the cancer registries files, the information was obtained by the cancer registry professionals from the health institutions who reported the cases. The address or neighborhood of residence at the time of diagnosis served to determine the CS of residence at the time of diagnosis for ACL cases.

2.3. Industrial Facilities Data

The list (inventory) of industrial sources of emissions to the air was obtained from the regional environmental authorities for the cities: Corporación para la Defensa de la Meseta de Bucaramanga (CDMB) in Bucaramanga, Corporación Autónoma Regional del Valle del Cauca (CVC) and Departamento Administrativo de Gestion del Medio Ambiente (DAGMA) in Cali, and Area Metropolitana del Valle de Aburrá (AMVA) in Medellín. There were 32 industrial facilities identified in Bucaramanga, 289 in Cali, and 144 in Medellín. Data obtained included the address, coordinates, and industrial activity type of industrial facilities. We used distance to facilities as proxy measure of exposure because quantitative data of emissions to the air were not available for the industries during the study time window (2000–2015). Historical data for industrial emissions is available only for one year (2011) for Cali and two years (2011 and 2013) for Medellin. The industrial facilities were aggregated according to their geographical location in 4, 26 and 14 "industrial conglomerates" within Bucaramanga, Cali, and Medellín, respectively. The coordinates of the centroids (latitude and longitude) of the "industrial conglomerates" areas were used as the industrial location for focal cluster and multivariable spatial analysis of the cases.

2.4. Statistical Analysis

Descriptive analysis was conducted by calculating mean annual specific incidence rates of ACL and age-sex standardized rates by city. The standardized rates calculation used the direct method using the Colombian population with intervals of 5 years of age up to 14 years as the standard population. Bayesian smoothed incidence morbidity ratios were also calculated by CS to reduce heterogeneity when estimating the risk of ACL and then mapped as choropleth maps. We used the global Moran's Index for calculating global spatial autocorrelation and local Moran's Index for identifying spatial clusters of CS with high ACL rates. Statistical analyses were calculated in Stata 15® and maps were created using ArcGIS 10.6.1®.

We used the Kulldorff's circular scan test to detect local clusters within the cities and its focal mode for identifying clusters around "industrial conglomerates" [23]. We ran the Kulldorff's test using a retrospective space-time analysis, scanning for clusters with high rates using a discrete Poisson model. The spatial unit was the CS of residence, and the time unit was the year of diagnosis. We set as the upper limit for the size of those corresponding to a circle that included the 25% of the total number of ACL cases. Then centroid coordinates of the "industrial conglomerates" created grids for the focused tests. The significant level for the test was 0.05. This hypothesis test for clustering was selected based on its good performance to detect compact clusters of rare diseases and its widespread use in spatial epidemiological studies [24]. We used the SaTScan ® software version 9.6 (Kulldorff M. and Information Management Services, Inc., Boston, MA, USA).

We also conducted multivariable modeling with spatial variables using the CS as the unit of analysis aimed to assess the effect of distance and direction from the "industrial conglomerate" on the ACL incidence. The distance variable represented the measured distance in Km from the centroid of the "industrial conglomerate" to the centroid of each CS. The direction was modeled using the sine (longitude) and cosine (latitude) functions of the angle between both centroids. We used a Poisson model using the log of the expected cases by CS as an offset variable. A basic model was built for the effect of distance and subsequent models added other spatial functions (direction and interactions between distance and direction). Then, the effects of spatial variables were adjusted by the predominant SES of the CS. We used the Akaike information criterion as parameters for model selection. Models were built separately for all the "industrial conglomerates" that showed significant clusters in the focused Kulldorf's scan tests. These analyses were conducted using Stata 15® (Stata Corporation, College Station, TX, USA).

We identified the industrial sectors in proximity to the ACL clusters by identifying the industrial facilities located within a buffer of 1 km around the centroid of the "industrial conglomerates" that showed statistical significance of the distance variable in the multivariable model and were included within the spatio-temporal clusters identified for each city.

2.5. Research Ethics

All procedures performed in this study followed the national and international ethical standards and the Ethical Committee for Research of the Universidad Industrial de Santander (CEINCI-UIS) granted ethical approval of the study. Informed consent was not required due to the nature of the study and data sources. For those cancer cases missing place of residence information, data were obtained by the cancer registries from the administrative health databases of the health provider institutions. The cancer registries managed all personal data and the information was anonymized and compiled to a small area level (census sector) for analysis.

3. Results

There were 140,469 and 314 confirmed ACL cases during 2000–2015 in Bucaramanga, Cali, and Medellin, respectively. The annual mean age-standardized incidence rate per million children under 15 years was higher in Bucaramanga (70.03), followed by Cali (52.68) and Medellín (41.24). Most cases occurred in males with a mean age of six years old at the time of diagnosis. Table 1 shows the characteristics of ACL cases in terms of age, sex, time of diagnosis, and the number of census sectors (CS) with ACL cases. Bayesian smoothed rates of ACL by CS shows geographical heterogeneity within cities (Figure 1). The Moran's Index was –0.005 ($p = 0.349$) for Bucaramanga, 0.038 ($p < 0.001$) for Cali, and 0.041 ($p < 0.001$) for Medellín, suggesting a low spatial autocorrelation of ACL cases among CS in Cali and Medellín.

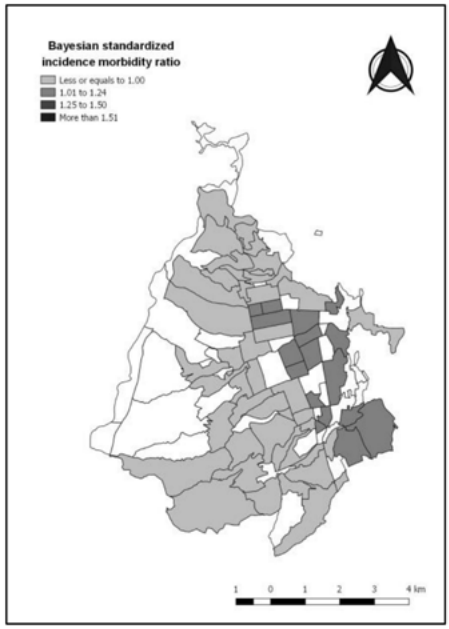
Table 1. Characteristics of acute childhood leukemia cases in three capital cities, Colombia 2000–2015.

Variable	Bucaramanga	Cali	Medellín
Estimated mean population (children under 15 years)	126,483	559,217	481,612
Total incident cases	140	469	314
Age in years			
Median (IQ range)	5 (3–10)	6 (3–10)	6 (3–11)
Mean (SD)	6.1 (4.04)	6.45 (4.28)	6.7 (4.30)
Male (%)	84 (60.00)	251 (53.52)	192 (61.15)
Age groups *n* (%)			
0–4 years	60 (42.86)	193 (41.15)	127 (40.45)
5–9 years	44 (31.43)	148 (31.56)	83 (26.43)
10–14 years	36 (25.71)	128 (27.29)	104 (33.12)
Time period cases *n* (%)			
2000–2007	71 (50.71)	243 (51.82)	79 (25.15)
2008–2015	69 (49.29)	226 (48.18)	235 (74.85)
Specific incidence rate (annual mean per million)	69.17	52.41	40.75
ASR (annual mean per million)	70.03 (58.90–82.65)	52.68 (48.24–56.27)	41.24 (36.79–47.07)
Cases geolocated n (%)	122 (87.85)	445 (94.88)	309 (98.4)
No. census sectors	99	404	266
No. census sectors with cases n (%)	66 (66.6)	205 (50.74)	143 (53.75)

ASR: Age standardized incidence rate.

Table 2 shows a summary of Kulldorff's circular scan tests results. The test for localized spatial clusters identified one in Bucaramanga, two in Cali and Medellín. The spatio-temporal tests identified one cluster in Bucaramanga (for the period 2010–2011), one in Cali (for the period 2003–2006), and one in Medellin (for the period 2002–2005). Figure 2 illustrates the location of clusters and their geographical relation with locations of "industrial conglomerates" within cities. Supplementary tables (Tables S1–S3) present details of the clusters identified in the cities. The ACL spatio-temporal cluster identified in Bucaramanga locates in the northwest of the city; in Medellín the cluster is located in the city center and extends towards the southwest; and in Cali the cluster is identified at west of the city (Figure 2). The results of the local Moran's Index also identified the same spatial cluster in the west of Cali. In Medellin, the cluster was identified in the center of the city, which is a more localized region included in the spatial cluster identified by the circular scan test immediately above the industrial conglomerate 8. An additional CS with a high rate was identified at south of the city in the south border of the spatial cluster identified by the scan test.

(a)



(b)

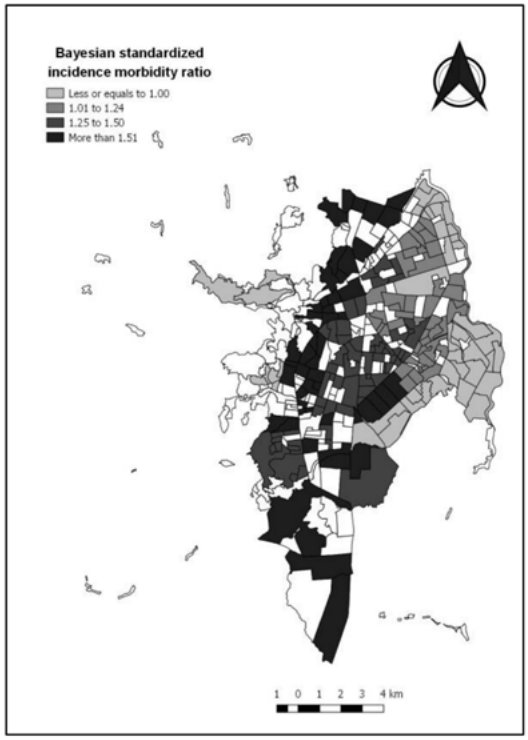


Figure 1. *Cont*.

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(c)

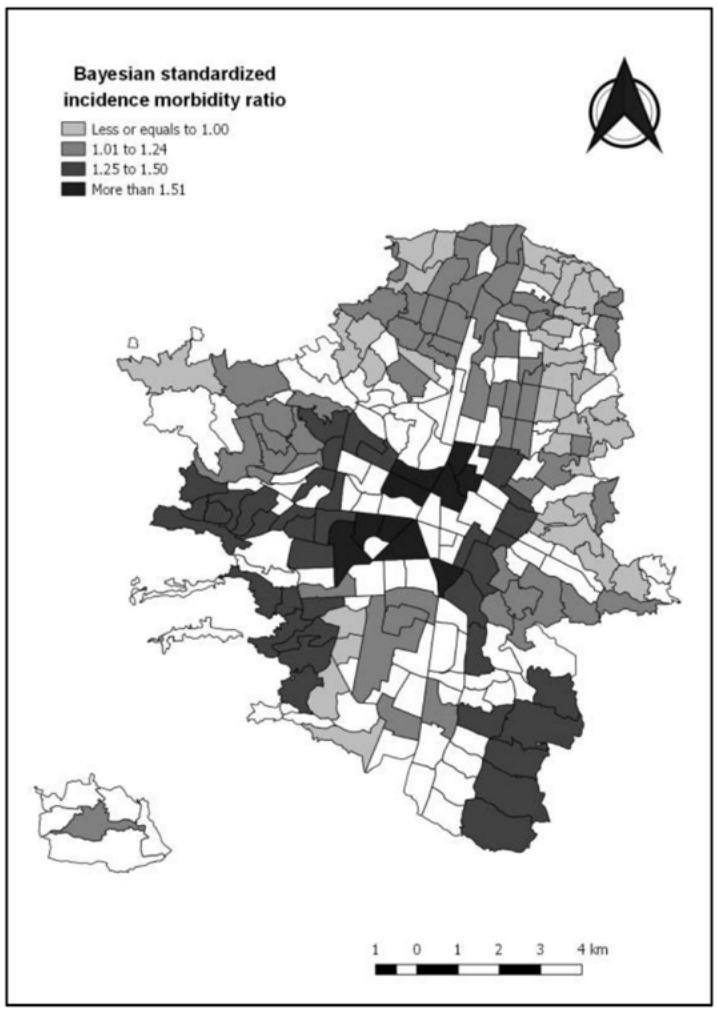

Figure 1. Bayesian smoothed rates of acute childhood leukemia in urban sectors of three capital cities, Colombia 2000–2015. (**a**) Bucaramanga; (**b**) Cali; (**c**) Medellín.

Table 2. Results of scan tests for spatial and spatiotemporal clusters of acute childhood leukemia by city, Colombia 2000–2015.

Type of Cluster Analysis (n)	Bucaramanga	Cali	Medellín
Localized spatial clusters	1	2	2
Localized spatio-temporal clusters	1	1	1
Industrial conglomerates	4	26	14
Industrial conglomerates with spatial clusters	1	13	5
Industrial conglomerates with significant spatial clusters in multivariable model	1	8	4

(a)

(b)

Figure 2. *Cont*.

(c)

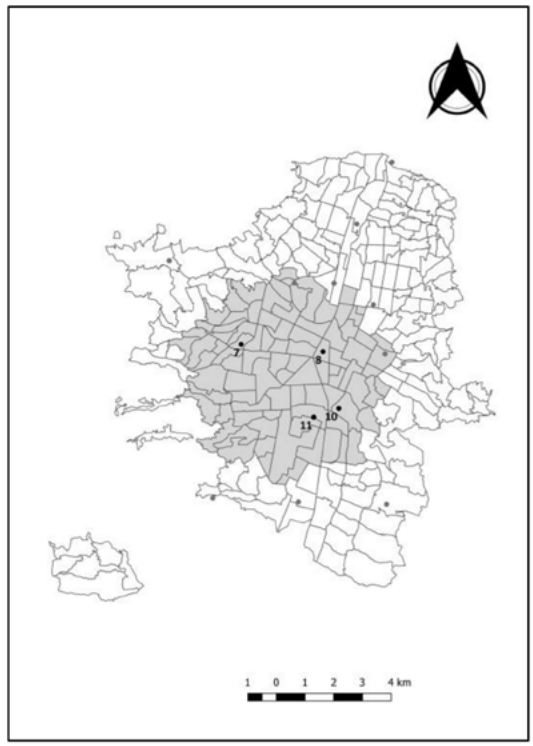

Figure 2. Localized spatio-temporal clusters of acute childhood leukemia and industrial conglomerates in urban sectors of three capital cities, Colombia 2000–2015. (**a**) Bucaramanga; (**b**) Cali; (**c**) Medellín. Note: industrial conglomerates are shown as points and the conglomerate's numbers are presented only for conglomerates with statistically significant result in cluster analysis.

Results of multivariable modeling with spatial variables using the CS as the unit of analysis are in Table 3. Controlling for spatial direction (latitude and longitude of the angle between the industrial conglomerate and the CS centroid) and predominant SES in the CS, there were industrial conglomerates spatially related to a higher incidence of ACL: one in Bucaramanga, eight in Cali, and four in Medellín. The industrial facilities within a buffer of 1 Km of the Bucaramanga's industrial conglomerate #1 are related to the processing of raw agricultural products. The industrial facilities within a buffer of 1 Km of the Cali's industrial conglomerates #17–20 include predominantly energy power plants fueled with diesel (mainly in conglomerate #19 located within the cluster 1) with some paints and food processing industries. The Cali's industrial conglomerates #23–26 are not included within any ACL spatio-temporal cluster. In Medellín the industrial conglomerate #7 includes facilities of the chemical and food sector; conglomerate #8 includes facilities of the metalworking, pharmaceutical, and textile sector; conglomerate #10 includes facilities of the textile and car repairing sector, both using tinctures and paints; and conglomerate #11 includes facilities of the textile, rubbers, and leather sector. According to the inventory of industrial sources of emissions to the air of the cities, the industrial conglomerates spatially related to the clusters were stable across the time window of the study (2000–2015) as most of them were in place at the beginning of the 2000 decade and were still active in the inventory list for 2012.

Table 3. Multivariable models for spatial clusters around industrial conglomerates in three capital cities, Colombia 2000–2015.

City	Industrial Conglomerate	Crude Coefficient [1]	Adjusted Coefficient [2]	95% CI	*p*-Value
Bucaramanga	Bucaramanga 1	−0.509	−0.220	−0.367–−0.070	0.003
Cali	Cali 17	−0.093	−0.047	−0.096–−0.002	0.059
	Cali 18	−0.106	−0.066	−0.118–−0.015	0.011
	Cali 19	−0.091	−0.056	−0.097–−0.016	0.006
	Cali 20	−0.090	−0.069	−0.113–−0.026	0.002
	Cali 23	−0.066	−0.045	−0.076–−0.0136	0.005
	Cali 24	−0.058	−0.047	−0.076–−0.018	0.001
	Cali 25	−0.063	−0.046	−0.076–−0.015	0.004
	Cali 26	−0.057	−0.045	−0.075–−0.015	0.003
Medellín	Medellín 7	−0.038	−0.657	−0.892–−0.421	0.000
	Medellín 8	−0.188	−0.667	−0.823–−0.512	0.000
	Medellín 10	−0.032	−0.625	−0.921–−0.329	0.000
	Medellín 11	0.015	−0.436	−0.756–−0.116	0.008

[1] Distance coefficient (per 1 km) for acute childhood leukemia cumulative incidence rate per million. [2] Distance coefficient (per 1 km) adjusted by direction (latitude and longitude) and predominant socioeconomic status.

4. Discussion

This study assessed the presence of space and space-time clustering of ACL cases in three capital cities of Colombia and their proximity to industrial air pollution sources. Using census sectors as the small-geographical area units for the spatial analysis, we identified one ACL cluster in each city; we also identified the predominant industrial sectors in proximity to these clusters. The lack of data of estimated industrial emissions to the air in the three cities during most of the study period leads to uncertainty in the results. Therefore they should be considered as preliminary evidence. To the best of our knowledge, this is the first study assessing the relationship between ACL clusters and proximity to industrial facilities at a small geographical level in South America.

Industrial sectors associated with ACL clusters seem to be different across the three cities. In Cali, the main ACL cluster was located in the proximity of an industrial conglomerate with the predominance of energy power plants. These energy-generating plants are fueled by diesel and besides potential benzene emissions probably generate a relevant electromagnetic field. Some ecological, case-control and cohort studies conducted in Asia and Europe have found associations between residential proximity to electromagnetic fields of high voltage power plants and lines with the increased risk of childhood leukemia [25]. In Medellin, there is a large cluster of ACL cases in proximity to industrial conglomerates that are located within the city around the river with the predominance of metalworking, chemical, and textile-leather industries with the use of tinctures and paints. Emissions of these industries might include volatile organic compounds, such as benzene, that have been implicated in leukemia incidence [26]. In Bucaramanga, the least industrialized of the three cities, the cluster identified was small and in proximity to an industrial conglomerate that processes raw agricultural products; during this process volatile organic compounds might be produced and pesticides from raw products might be emitted to the air. Studies conducted in Europe and North America have found associations between increased risk of leukemia and brain tumors and exposure to agricultural and domestic pesticides [25,27].

Some childhood cancers have shown variations in incidence according to the extent of socio-economic development. In the case of leukemia is has been observed that incidence increases with countries' socioeconomic development [28]. The placement and expansion of industries might explain this situation that in the early phases of the development are not well controlled by government authorities. Therefore, territories start growing by mixing industrial and residential areas. Populations around industrial areas are predominantly poor, which places them at double risk

for childhood cancer: poverty and exposure to industrial activities and emissions [29]. In this regard, it is essential to clarify that for the cities included in the study, and in general for Colombia, the national and local government during the last decade have been working in the delimitation and separation of industrial areas as a public policy to regulate industries and protect public health. Our results suggest that the 2000–2015 ACL incidence could be reflecting previous exposures that were stable and still present at the beginning of the 2010s decade. The urban growth of most capital cities in Colombia was not planned, and despite land use definitions, control for avoiding and eliminating industrial sources from residential places is relatively recent. Thus, industries were located in some cities within residential areas, or industrial areas were surrounded by residential new developments related to city growth. Thus, people living in cities might have been exposed to industrial air pollution emission for long periods.

Spatial clusters of leukemia have been identified in other countries. The EUROCLUS project assessed the spatial clustering of childhood leukemia in 17 European countries between 1980 and 1989 and found evidence of clustering within small census areas with intermediate population density [30]. In Spain, using a case-control study and place of residence at birth in five autonomous regions between 1996 and 2011 there was no evidence of the clustering of childhood cancer [31]. In contrast, clustering of acute childhood leukemia at the place of residence during pregnancy was identified in the region of Murcia, Spain between 1998 and 2013, suggesting that environmental exposure in utero might be important determinants for ACL [32]. In Switzerland a nationwide study assessed the presence of clustering childhood cancers using both, place of residence at birth and at the time of diagnosis during 1985–2010, and identified significant space-time clusters of childhood leukemia at birth but no at diagnosis, suggesting an etiologic factor present in early life [33]. Some studies in the United States have identified clusters of leukemia in Ohio [34] and Nevada [35] where the spatio-temporal patterns identified at the time of diagnosis suggest the hypothesis of a possible infectious cause. In California a case-control cluster analysis identified evidence of clustering of acute lymphoblastic leukemia diagnosed at 2–6 years of age between 1997 and 2007 in the San Francisco Bay Area by using the birthplace of children [36].

In Latin America, there is also some evidence of clustering for childhood leukemia: in Argentina, significant clusters of childhood leukemia were identified in the province of Cordoba using the residential address at the time of diagnosis between 2004 and 2013 [37]; in Mexico, clustering of ACL at the time of diagnosis between 2010 and 2014 was identified in the city of Guadalajara [38]; in Colombia a nationwide study at municipality level and time of diagnosis identified ACL clusters in five regions [17]. A recent systematic review and pooled analysis of space-time clustering studies of childhood cancer included 47 studies of childhood leukemia published before July 2016 and concluded that significant clusters are present at both time of diagnosis and birth; the clusters were identified especially for children aged 0–5 years for a spatial lag of 5 km and temporal lag of 6 months, suggesting that the pattern of clustering close to the time of diagnosis might be compatible with an infection cause to be identified [39].

Childhood leukemia has been associated with proximity to industrial complexes in other countries. During the 1990s Knox reported in England a childhood leukemia cluster close to railways, petrochemical plants and steelwork industries [40]. Clusters of childhood leukemia and solid cancers occurred in proximity to oil refineries and petroleum-related facilities, motor car factories and repair facilities, industries that use kilns and furnaces, including industries that produced smoke, gases and effluents from internal combustion engines; the identified clusters manifested when considering the place of birth between 1953 and 1980 [14]. In Taiwan, Weng et al., identified an increased risk of childhood deaths for leukemia between 1995 and 2005 in municipalities with the highest levels of petrochemical air pollution [41]. In Spain, a study found an increase of risk in childhood leukemia in children living up to 2.5 km of industries related to glass and mineral fibers, surface treatment using organic solvents, galvanization, and production and processing of metals. The study was a population-based case control study of childhood leukemia was conducted in four autonomous regions

for the period 1990–2011 using place at the time of diagnosis and assessing the effect of residential proximity to both industrial and urban pollution, and taking into account industrial groups and substances released. [15].

A review of 25 studies of childhood cancer and residential proximity to potential environmental hazards concluded that for leukemia the environmental exposures with evidence of association were: (1) traffic-related pollution, petrochemical plants, gas stations or car repair garages, in relation with benzene exposure; (2) pesticides exposures; (3) nuclear power plants; (4) and landfill sites [42]. A meta-analysis of exposure to benzene in utero and early life exposure identified evidence of consistent associations of childhood leukemia with different metrics of benzene exposure, including traffic-pollution, occupational and household use of solvents [43]. Our results for the city of Medellín are consistent with these studies as industries around the cluster identified might be related to benzene emissions. The finding of one cluster in the city of Cali related to energy power plants fueled by diesel might reflect exposure to benzene and electromagnetic fields (EMFs). In this regard, different studies have addressed the association between residential magnetic fields and childhood leukemia, and a pooled analysis reported small but consistent increased risk with EMFs exposures above 0.3 uT [44]. In the case of the city of Bucaramanga, the cluster identified might be associated with emissions of facilities' furnaces, exposure to benzene for being an area of high traffic, or indirect exposure to pesticides presents in agricultural raw products. The evidence of an association between exposure to pesticides and childhood leukemia has been specific for outside herbicide exposure and indoor residential insecticides [45]; a recent case-control state-wide study California for ACL cases between 1998–2011 showed evidence of elevated risk of acute lymphocytic leukemia for exposure to a variety of pesticides during pregnancy. However, this evidence is specific for rural and not urban areas [46].

Our findings and those reported in the literature, suggest that the potential associations relate to specific chemicals and physical factors instead of individual sectors. These observations also point out that each city has a different pattern of hazards that may call for regulatory actions tailored to tackle each location's specific conditions.

There are some strengths worth mentioning of this study. First, we used ACL high-quality data coming from population-based cancer registries with rigorous quality control [22]. The high coverage of the cancer registries along with the high percentage of geolocation of census sectors for the cases allowed us to include in the analysis more than 85% of cases for Bucaramanga and more than 95% of cases for Cali and Medellín. Second, we used spatial analysis tools for descriptive, hypothesis testing, and multivariable modeling that allowed to identified clusters and estimate effects of proximity to industrial conglomerates. Third, we controlled the proximity effect by the potential confounding effect of the socioeconomic status, which is recognized as a critical confounder at the ecological and individual level for studies assessing the effect of environmental exposures on childhood cancers [47].

This study's main limitation is the lack of quantitative data on air pollutants emissions from the industries during the study period. Unfortunately, there is no historical data available for industrial emissions for the decade 2000–2010 in the three cities included in the study. For the period 2011–2015, there is only one year available (2011) for Cali and two years (2011 and 2013) for Medellin reporting pollutants that might be relevant to our study. According to the total emission's inventory for Medellin and the Aburrá Valley in 2011, industries emitted 89% of $SO_{x,}$ 20% of $PM_{2.5}$ and 10% of volatile organic compounds (VOC) emissions with higher concentrations in the center and south of the city. The textile, ceramic and glass and food sectors contributed around 80% of the estimated annual industrial emissions of PM_{10}, VOC, and SOx. These 2011 emission patterns relate to the location and type of industries found spatially related to Medellin's ACL clusters in our study [48]. The Cali's 2011 industrial emissions inventory reports that the estimated highest releases of SOx and PM_{10} belong to industries from the textile sector while metalworking sector released most of the VOC. More than 70% of SOx and PM_{10} emissions occurred in the city center and >70% of VOCs were released north in the city. These patterns have no relation to the ACL cluster locations found in this study [49].

Emissions inventories and characterization of air pollutant composition became available for the cities of interest in recent years. For this reason, our spatial analysis is based only on distances, and therefore it has to be considered an exploratory study with no causal association. In contrast to Europe and North America, most Pollution Release and Transfer Registries are recent or starting to operate in developing countries. Therefore the availability of these data will provide critical information for further studies with enough quantitative data.

Knowing that residential mobility might affect children's exposure adds another limitation of this study since we lacked ACL cases residential address during pregnancy and at birth. The use of residential location at the time of diagnosis allowed us to identify potential hazards close to the time of diagnosis but not necessarily those related to early life exposures. Although we did not systematically analyze mobility in all cities, a sub-analysis of residential mobility in Bucaramanga [50] showed that most cases were living in the same address in the previous two years, and half of them lived in the same address since birth. Another limitation is the lack of control for the potential confounding effect of the traffic-related air pollution and the residential proximity to gas stations at the small-area level since this information is not available for the cities. Finally, we did not include the wind direction as part of the spatial multivariable models' spatial variables. Therefore we were not able to assess its effect on the ACL incidence. Further studies incorporating the chemical nature of the industrial emissions, meteorological and traffic-related air pollution variables would support the hypothetical associations described in this paper.

5. Conclusions

Acute leukemia is the most common childhood cancer in Colombia, and we identified clusters of ACL cases in three departmental capital cities. These clusters were associated with proximity to specific industrial conglomerates within the cities but with different industrial sectors patterns. Our results suggest that exposure to air pollution from industrial sources might contribute to the incidence of ACL cases in Colombia's urban settings. These results are based only on proximity (distance) analysis and provide preliminary evidence with no causal association. Further studies incorporating recent available data on pollution emissions to the air and dispersion models would provide more robust evidence. Therefore, this study's results reinforce the need for a continuous commitment of environmental and health authorities to maintain and improve the instruments needed to measure, surveil, regulate and control industrial emissions to the air to protect the children's current and future health.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/21/7925/s1, Table S1. Results of scan tests for spatial and spatiotemporal clusters of acute childhood leukemia in proximity to industrial sources of air pollution in Bucaramanga (n = 122 cases); Table S2. Results of scan tests for spatial and spatiotemporal clusters of acute childhood leukemia in proximity to industrial sources of air pollution for Medellin (n = 309 cases); Table S3. Results of scan tests for spatial and spatiotemporal clusters of acute childhood leukemia in proximity to industrial sources of air pollution for Cali (n = 445 cases).

Author Contributions: Conceptualization, L.A.R.-V.; data curation, C.J.U.P., M.R.B.B., H.I.G.G. and L.E.B.; formal analysis, L.A.R.-V., F.E.M.-C. and A.M.V.-G.; funding acquisition, L.A.R.-V.; methodology, L.A.R.-V. and F.E.M.-C.; project administration, L.A.R.-V. and J.N.V.; resources, C.J.U.P., M.R.B.B., H.I.G.G. and L.E.B.; software, F.E.M.-C. and R.G.O.M.; supervision, L.A.R.-V.; validation, L.A.R.-V. and A.M.V.-G.; visualization, F.E.M.-C.; writing—original draft, L.A.R.-V., F.E.M.-C. and A.R.O.-V.; writing—review and editing, A.M.V.-G., C.J.U.P., M.R.B.B., H.I.G.G., L.E.B., R.G.O.M., A.R.O.-V. and J.N.V. All authors have read and agreed to the published version of the manuscript.

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CÁNCER

Patterns of breast, prostate and cervical cancer incidence and mortality in Colombia: an administrative registry data analysis

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Alcance: internacional

Trabajo colaborativo con la Asociación Colombiana de Hematología y Oncología (ACHO) como actor de interés

Objetivo:

Describir la distribución de los casos nuevos y los fallecimientos en la población con cáncer de mama, próstata y cérvix, por las regiones y los departamentos del país.

Principales hallazgos

- El cáncer de mama fue el tipo más frecuente entre los casos nuevos y los fallecimientos reportados en el país.
- La región Oriental tuvo la menor PCNR y mortalidad para todos los tipos de cáncer que el país.
- Se observó una heterogeneidad importante en la distribución de los casos nuevos y las muertes a nivel municipal.
- El patrón de heterogeneidad fue mayor en el cáncer de cérvix, con mayor PCNR y mortalidad en la zona sur del país.

Relevancia de los hallazgos

- El patrón de distribución de casos nuevos y muertes para los tres tipos de cáncer de mayor frecuencia en el país es fundamental para mejorar la cobertura de los programas de tamización y su focalización en áreas de mayor riesgo.
- Adicionalmente, este mapeo es útil para mejorar las estrategias de detección temprana y fortalecer la red de prestadores que permita el acceso oportuno al tratamiento.

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RESEARCH ARTICLE Open Access

Patterns of breast, prostate and cervical cancer incidence and mortality in Colombia: an administrative registry data analysis

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Abstract

Background: Cancer is widely recognized as a global public health problem. Breast, prostate, and cervical cancer are among the most frequent types in developing countries. Assessing their incidence and mortality by regions and municipalities is important to guide evidence-based health policy. Our aim was to describe the incidence and mortality trends for breast, cervical, and prostate cancer across regions and municipalities in Colombia during 2018.

Methods: *We performed* a cross-sectional analysis with data from people with breast, prostate, or cervical cancer, reported to the National Administrative Cancer Registry during 2018. A descriptive analysis was performed. Age-standardized incidence and mortality rates were estimated at national, regional, and municipal levels. Finally, we identify the regions and municipalities with significantly higher or lower incidence and mortality rates compared to national estimations.

Results: Breast cancer was the most frequent type among all new cases and deaths in Colombia. Breast, prostate and cervical cancer incidence and mortality rates per 100,000 were: 18.69 (CI 95%: 18.15–19.25) and 10.48 (CI 95%: 10.07–10.91); 11.34 (CI 95%: 10.90–11.78) and 7.58 (CI 95%: 7.22–7.96); 5.93 (CI 95%: 5.62–6.25) and 4.31 (CI 95%: 4.05–4.58), respectively. Eastern region had both, incidence and mortality rates, significantly lower than national for all types of cancer. By municipalities, there was a heterogeneous pattern. Nonetheless, Agua de Dios (Cundinamarca), had one of the highest incidence rates for all types.

Conclusions: We observed clear differences in cancer incidence and mortality across regions and municipalities, depending on each type of cancer. Our findings are important to improve screening coverage, early detection, and treatment in the country.

Keywords: Cancer, Epidemiology, Incidence, Mortality, Registries

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Background

Cancer is one of the major public health concerns worldwide because its incidence and mortality, as well as its impact on life expectancy across populations, are rapidly increasing. Besides aging, population distribution, and changes in the frequency of the main risk factors for cancer can explain this trend and heterogeneity between regions, especially in countries with low socioeconomic development [1]. According to the Global Cancer Observatory (GLOBOCAN), in 2018, there were 18.1 million new cases and 9.6 million cancer deaths worldwide. For both sexes, lung cancer was the most frequent type with 2.1 million and 1.8 million incident cases and deaths, respectively. Global 5-year prevalent cases were 43.8 million [2].

Regarding region, Asia concentrates the highest number of new cases (8.8 million) and deaths (5.5 million), while Latin American and the Caribbean (LAC) is in the fourth place with 7.8% of incidence (1.4 million cases) and 7.1% (672 thousand deaths) of mortality worldwide [2]. In terms of the burden of the disease, cancer caused 233.5 million DALYs (Disability-Adjusted Life-Years) in 2017, of which 97% came from YLLs (Disability-Adjusted Life-Years) and 3% from YLDs (Years Lived with Disability) [3].

Globally, there were more new cases and deaths in men (9.5 and 5.4 million, respectively) than women (8.6 and 4.2 million, respectively). Lung cancer accounts for 14.5 and 22.0% of incidence and mortality in men. Further, 13.5 and 10.9% of new cases were diagnosed with prostate and colorectal cancer. Otherwise, in women, the most common incident cancers were breast (24.2%), colorectal (9.5%), and lung (8.4%), and breast and lung cancer were the leading cause of cancer death (15.0 and 13.8%, respectively) [2].

Concerning mortality, despite it has been declined in most higher-income countries, this progress has been deficient in low- and middle-income countries, where the Sustainable Development Goals have not been reached. It is well known that cancer is a complex disease with mortality patterns which vary importantly across countries and specific types of cancer. Variations depend on differences in lifestyles, such as smoking, and structural conditions of the health systems of each country. In most higher-income countries, mortality rates have decreased mainly due to interventions focused on screening, early prevention, and timely diagnosis while in countries in transition, such us Colombia they are rising or stable for many types, including breast, prostate, and colorectal cancer [4].

As we mentioned, cancer distribution by region is heterogeneous. In fact, in LAC, breast (14.1%) and prostate cancer (13.5%) were the most common types among new cases. Prostate and breast cancer grouped 27.9 and 27.4% of incidence in men and women, respectively [2]. This pattern is similar for all countries in the region, including Colombia, due to the ongoing sociodemographic transitions and health care conditions: advanced stage at diagnosis and limited access to diagnosis and treatment strategies [5]. Morbidity and mortality trends within countries are similar and their analysis is important for health care planning to reduce disparities in cancer distribution and impact on populations.

Therefore, we aim to describe the incidence and mortality trends for breast, cervix uteri and prostate cancer across regions and municipalities in Colombia during 2018.

Methods

Data sources

A cross-sectional analysis was performed on data compiled by the National Administrative Cancer Registry (NACR) administered by the High-Cost Diseases Fund (CAC-in its Spanish acronym) from January 2nd, 2018 to January 1st, 2019. The NACR was created by the Ministry of Health of Colombia in 2012 [6] and its goal is to collect and analyze demographic, clinical, and administrative information on people with cancer across the country through the annual report of 134 variables. Taking into account that 98% of the Colombian population is insured to the national health system and must be reported to the NACR by its health insurers, it can provide reliable information about real-life patterns and trends of the most common cancer types in Colombia. Since the first measurement in 2015, 279,155 people have been reported with cancer. Unique identifiers have been created for identifying and protecting the personal information of the participants. Data on prevalent cases are updated every year, while for new cases, full registration is completed. There is a well-established data monitoring process to guarantee the quality of information, which is carried out in two steps: a prior identification of mistakes in the reporting process through a systematized algorithm. Then, the information reported is auditing and compared with health clinical records to ensure their accuracy for all new diagnoses reported.

Eligibility of participants

The analysis was performed with information from people with breast, prostate, or cervix uteri cancer reported during the study period. In case of breast cancer, we restricted the analysis to women.

Cancer incidence data

Incident cases were defined as people with a primary breast, prostate, or cervix uteri tumor, diagnosed within the analysis time frame and reported by the first time to the NAC*R. cancer* diagnosis could be clinical or histopathological. The diagnosis was confirmed in medical records through a data monitoring process. The anatomic site and histology were coded according to the International Classification of Diseases 10th edition (ICD-10) and the International Classification of Diseases for

Oncology third edition (ICD-O-3). For the types of cancer analyzed, codes were defined as follows: breast (ICD-10: C50 to D50; ICD-O-3: C50), cervix uteri (ICD-10: C53 to D06; ICD-O-3: C53), and prostate (ICD-10: C61; ICD-O-3: C61).

Cancer mortality data

Information about deaths was reported to the CAC by health insurers. It was verified with external sources provided by the Ministry of Health and the National Registry of Civil Status. Deaths for any cause were considered to estimate mortality rates.

Demographic and clinic data

Demographic information included age, sex, region, and the municipality of residence and health insurance. Regarding region, they were defined by the Department for National Statistics (DANE, by its acronym in Spanish), from Colombia's 32 departments according to the gross domestic product, identifying 6 regions: Bogotá D. C, Central, Eastern, Pacific, Caribbean and Other departments (Figure S1 of Supplementary Material). Municipalities were defined as autonomous territories, at a lower level than departments and their classification was also provided by the DANE. About health insurance, there are four regimes (contributory, subsidized, special, and exception) and a minimum proportion is uninsured. In respect of clinical data, invasive cancer was defined following IARC criteria based on ICD-10 [7]. The staging was determined depending on the type of cancer, as follows: for breast and prostate cancer the Tumor-Node-Metastasis (TNM) classification was used based on the eighth edition of the American Joint Committee on Cancer (AJCC) [8, 9] and for cervical cancer, the staging was based on the revised 2018 International Federation of Gynecology and Obstetrics (FIGO) system [10]. Patient care opportunity was calculated as the number of days between the clinical suspicion and the confirmed diagnosis (date of pathology report or clinical diagnosis) and, between the diagnosis and the first treatment (systemic therapy, radiotherapy, or surgery).

Statistical analysis

We summarized continuous variables as medians and interquartile range (IQR) and categorical variables as absolute values and percentages. Incidence and mortality rates were calculated using the mid-year population projected by the DANE (national, regional, or municipal) for the calendar year of interest. Rates by region or municipality were age-standardized (ASR) to the Colombian population estimated by the DANE with a cut-off date on June 30th, 2018 (n = 49,834,240). In the case of breast and cervix uteri cancer, we restricted the population to women only (n = 25,228,444) and, for prostate cancer we used the male population (n = 24,605,796). National estimations were standardized using the LAC population estimated by the United Nations for 2019 [11]. ASR were calculated including only invasive cases. Also, ASR and their 95% confidence intervals were estimated by region and municipalities and were expressed per 100,000 people. For each type of cancer, municipalities whose incidence and mortality were significantly higher than national estimations were highlighted in the maps. The statistical analyses were performed in Stata version 13 (StataCorp LP, College Station, Texas, USA), and QGIS version 3.12.2 was used to create the maps.

Results

National incidence and mortality rates for each type of cancer

Breast cancer was the most frequent type among all incident cases and deaths with 16.31% (n = 4506) and 13.82% (n = 2454), respectively. Age-standardized incidence and mortality rates for breast, prostate, and cervical cancer were, in their order: 18.69 (CI 95%: 18.15–19.25) and 10.48 (CI 95%: 10.07–10.91); 11.34 (CI 95%: 10.90–11.78) and 7.58 (CI 95%: 7.22–7.96); 5.93 (CI 95%: 5.62–6.25) and 4.31 (CI 95%: 4.05–4.58) per 100,000 people.

Demographic and clinic characteristics of incident cases (breast, prostate and cervical cancer)

Table 1 shows demographic and clinical information new cases of breast, cervical, and prostate cancer. Women diagnosed with cervical cancer were younger than those with breast cancer. The highest proportion of people diagnosed with invasive cancer was found in prostate cancer, while the lowest in cervical cancer. Regarding regions, Central and Bogotá D.C. had the greatest number of new cases. The contributory insurance had more than 67.00% of incident cases of breast and prostate cancer, while cervical cancer was more frequent in the subsidized. Most new cases of cervical cancer were in situ, while breast and prostate cancer were mainly diagnosed in stage II. Consistently with the above, surgery was more common in cervical cancer, while systemic therapy was the most indicated treatment in breast and prostate cancer. In terms of care opportunity, time to diagnosis was less for cervical cancer, whereas that, time until the first treatment was shorter for breast cancer.

Incidence and mortality rates by regions

Table 2 shows incidence and mortality rates of breast, prostate, and cervical cancer by regions. Compared with national estimations, the incidence of breast cancer was significantly higher in Bogotá D.C., and Central region, while Caribbean, Eastern and Other departments regions had incidence rates significantly lower. The incidence of prostate cancer was significantly higher in Bogotá D.C.

Table 1 Demographic and clinic characteristics of new cases of breast, prostate and cervical cancer in Colombia 2018[a]

Variables	Type of cancer		
	Breast (*n* = 4855)	**Prostate (*n* = 2617)**	**Cervical (*n* = 1930)**
Age, years[b]	57 (47–66)	68 (62–74)	47 (37–59)
Age categories, years			
0–9	0 (0.00)	1 (0.04)	0 (0.00)
10–19	1 (0.02)	0 (0.00)	1 (0.05)
20–29	75 (1.54)	0 (0.00)	125 (6.48)
30–39	389 (8.01)	0 (0.00)	497 (25.75)
40–49	1004 (20.68)	42 (1.60)	474 (24.56)
50–59	1349 (27.79)	355 (13.57)	377 (19.53)
60–69	1216 (25.05)	1074 (41.04)	257 (13.32)
70–79	592 (12.19)	876 (33.47)	141 (7.31)
80+	229 (4.72)	269 (10.28)	58 (3.01)
Region			
Central	1522 (31.35)	776 (29.65)	513 (26.58)
Bogotá D.C.	1104 (22.74)	654 (24.99)	400 (20.73)
Pacific	810 (16.68)	462 (17.65)	377 (19.53)
Caribbean	827 (17.03)	411 (15.71)	356 (18.45)
Eastern	544 (11.20)	295 (11.27)	217 (11.24)
Other departments	48 (0.99)	19 (0.73)	67 (3.47)
Health insurance			
Contributory	3265 (67.25)	1768 (67.56)	857 (44.40)
Subsidized	1351 (27.83)	663 (25.33)	1025 (53.11)
Exception	178 (3.67)	96 (3.67)	32 (1.66)
Special	52 (1.07)	88 (3.36)	12 (0.62)
Uninsured	9 (0.19)	2 (0.08)	4 (0.21)
Invasive cancer (yes)	4506 (92.81)	2593 (99.08)	1425 (73.83)
Staging (yes)	4503 (92.75)	1903 (72.72)	1814 (93.99)
Clinical stage			
In situ	419 (8.63)	42 (1.60)	535 (27.72)
Stage I	904 (18.62)	514 (19.64)	434 (22.49)
Stage II	1759 (36.23)	773 (29.54)	366 (18.96)
Stage III	1148 (23.65)	190 (7.26)	392 (20.31)
Stage IV	273 (5.62)	384 (14.67)	87 (4.51)
No data	352 (7.25)	714 (27.28)	116 (6.01)
Treatment			
Systemic therapy	3112 (64.10)	926 (35.38)	614 (31.81)
Radiotherapy	714 (14.71)	582 (22.24)	603 (31.24)
Surgery	2033 (41.87)	751 (28.70)	636 (32.95)
Care opportunity[b]			
Clinical suspicion to diagnosis	35 (18–68)	39 (20–90)	34 (15–76)
Diagnosis to treatment	59 (36–91)	71 (35–114)	71 (42–105)

[a]Includes invasive and in situ tumors. Data are presented as absolute values (proportions), unless otherwise specified
[b]Reported values are medians (interquartile ranges)

Table 2 Incidence and mortality rates for breast, prostate and cervical cancer by regions, Colombia 2018[a]

Region	Type of cancer					
	Breast		Prostate		Cervical	
	n	ASR (95% CI)	n	ASR (95% CI)	n	ASR (95% CI)
Incidence						
Bogotá, D.C.	1012	21.59 (20.28–22.97)*	648	15.56 (14.38–16.80)*	267	5.73 (5.06–6.46)
Caribbean	797	16.69 (15.55–17.89) ¥	404	8.38 (7.58–9.24) ¥	312	6.48 (5.78–7.24)
Central	1385	21.02 (19.93–22.16)*	768	11.73 (10.91–12.59)	382	5.95 (5.36–6.57)
Eastern	511	11.84 (10.84–12.91) ¥	293	6.66 (5.92–7.47) ¥	155	3.61 (3.07–4.23) ¥
Pacific	757	17.44 (16.22–18.72)	461	10.93 (9.96–11.98)	255	5.86 (5.17–6.63)
Other departments	44	8.27 (5.98–11.11) ¥	19	3.72 (2.23–5.76) ¥	54	9.99 (7.48–13.04)*
National	**4506**	**18.69 (18.15–19.25)**	**2593**	**11.34 (10.90–11.78)**	**1425**	**5.93 (5.62–6.25)**
Mortality						
Bogotá, D.C.	442	9.71 (8.83–10.67)	292	7.98 (7.09–8.95)	160	3.44 (2.93–4.02) ¥
Caribbean	494	10.49 (9.59–11.46)	329	6.70 (6.00–7.47) ¥	266	5.59 (4.94–6.30)*
Central	700	10.48 (9.72–11.29)	457	6.99 (6.36–7.66)	265	4.03 (3.56–4.54)
Eastern	332	7.59 (6.80–8.46) ¥	234	5.13 (4.49–5.83) ¥	130	2.99 (2.50–3.55) ¥
Pacific	466	10.64 (9.69–11.65)	318	7.29 (6.51–8.14)	176	4.02 (3.45–4.66)
Other departments	20	3.77 (2.28–5.82) ¥	11	2.18 (1.09–3.84) ¥	24	4.68 (2.98–6.96)
National	**2454**	**10.48 (10.07–10.91)**	**1641**	**7.58 (7.22–7.96)**	**1021**	**4.31 (4.05–4.58)**

[a]All rates are age-standardized per 100.000 population. They were estimated including only invasive cases
*ASR significantly higher than national estimations. *p*-value < 0,05 in a test of proportions
¥ASR significantly lower than national estimations. *p*-value < 0,05 in a test of proportions

but significantly lower in the Caribbean, Eastern, and Other departments regions. Finally, cervical cancer incidence was significantly higher in Other departments while it was lower in the Eastern region. Regarding mortality, its distribution across the regions was more heterogeneous than the incidence. Breast cancer mortality rates were significantly lower in Eastern, and Other departments, compared to national. In the case of prostate cancer, they were significantly lower in the Caribbean, Eastern and Other departments, whereas for cervical cancer, the lowest ASR were observed in Bogotá D.C. and Eastern region.

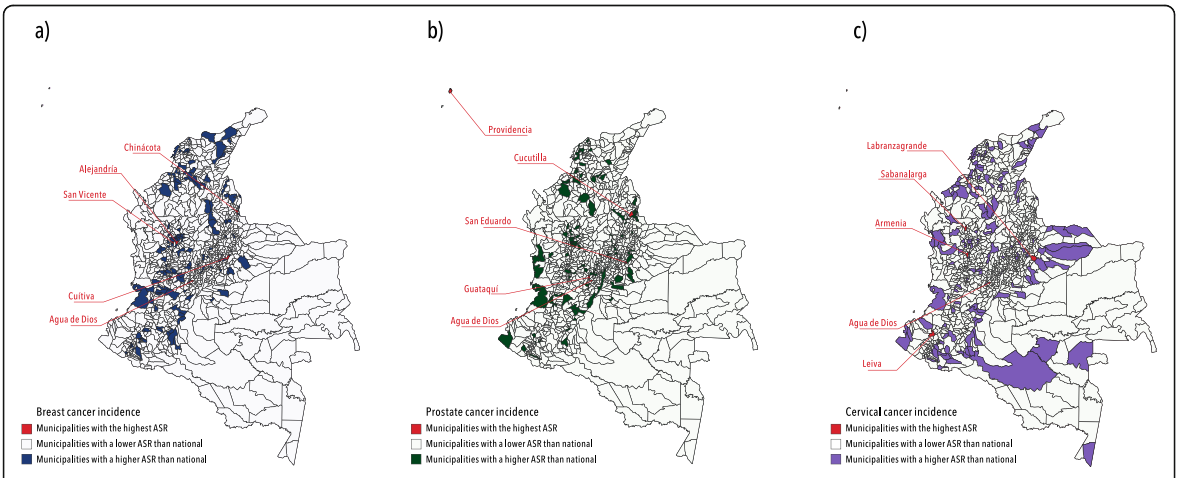

Fig. 1 Age-standardized incidence rates of breast, prostate and cervical cancer by municipalities, Colombia 2018. Figure 1 shows the age-standardized incidence rates for each cancer by municipalities (**a**) Age-standardized incidence rates of breast cancer (**b**) Age-standardized incidence rates of prostate cancer (**c**) Age-standardized incidence rates of cervical cancer. ASR: Age-Standardized Rates. Data source: new cases of cancer reported to the National Administrative Cancer Registry during 2018

Incidence and mortality rates by municipalities

Figure 1 shows the municipalities with the highest incidence rates. We identified a heterogeneous pattern depending on the type of cancer. Nearly one-half of new cases occurred in five capital cities (Bogotá D.C., Medellín, Cali, Cartagena, and Barranquilla). Agua de Dios, a municipality in Cundinamarca had the highest incidence rate for breast cancer (1502.12; CI 95%: 655.84–2716.23) and were in the top 3 for prostate (218.42; CI 95%: 71.43–470.35) and cervical (364.16; CI 95%: 167.78–657.83) cancer. The highest incidence rates for prostate (364.02; CI 95%: 9.22–1407.09) and cervical (665.88; CI 95%: 16.86–2545.84) cancer were observed in Cucutilla (Norte de Santander) and Labranzagrande (Boyacá).

On the other hand, the highest mortality rates across the municipalities are presented in Fig. 2. Close to 50.00% of the cancer deaths occurred in the same capital cities in the top for incidence (Bogotá D.C., Cali, Medellín, Barranquilla, and Cartagena). Agua de Dios, Socha (Boyacá) and El Peñol (Nariño) had the highest ASR for breast (191.63; CI 95%: 48.94–458.07), prostate (782.39; CI 95%: 19.81–2987.81) and cervical cancer (2086.38; CI 95%: 253.70–5918.24), respectively. See Tables S1 and S2 of Supplementary Material for complete information about incidence and mortality rates by municipalities.

Discussion

During 2018, breast cancer was the leading cause of incidence and mortality in Colombia. Most new cancer cases (~ 50.00%) occurred in Central and Bogotá D.C. regions as well as in the contributory insurance, conversely, cervical cancer was more frequent in the subsidized. Regards incidence by region, there was a homogeneous pattern for breast and prostate cancer. Some regions showed significantly higher incidence rates than national, varying by type of cancer, as follows: Bogotá D.C. and Central for breast cancer, Bogotá D.C. for prostate cancer and "other departments" for cervical cancer. Consistently, Eastern region had both, incidence and mortality rates, significantly lower than national for all types of cancer. By municipalities, Agua de Dios in Cundinamarca was among the highest incidence rates for breast and cervical cancer and they were significantly higher than national. Mortality patterns by municipality were highly heterogeneous.

There are differences in ASR for all types of cancer between CAC and GLOBOCAN estimations. Generally, GLOBOCAN rates overestimate both, incidence and mortality rates reported by CAC. In 2018, the biggest difference was observed for prostate cancer (CAC: 11.34 vs. GLOBOCAN: 49.80), followed by breast (CAC: 18.69 vs. GLOBOCAN: 44.10) and cervical cancer (CAC: 5.93 vs. GLOBOCAN: 12.70). The same pattern was found for mortality in prostate (CAC: 7.58 vs. GLOBOCAN: 12.00), breast (CAC: 10.48 vs. GLOBOCAN: 11.90) and cervical cancer (CAC: 4.31 vs. GLOBOCAN: 5.70). Differences are consistent with a previous study conducted by the CAC and could be explained by the data sources and methodology used. In the case of GLOBOCAN, data on incidence come from four Colombian city-based registries that have been classified as high quality and the calculation is based on projections, whereas CAC information provided by health insurers is updated yearly [12].

In both sexes combined, the leading causes of new cases of cancer and deaths in Colombia are different from global trends. While in the world, lung cancer was the most commonly diagnosed and the leading cause of

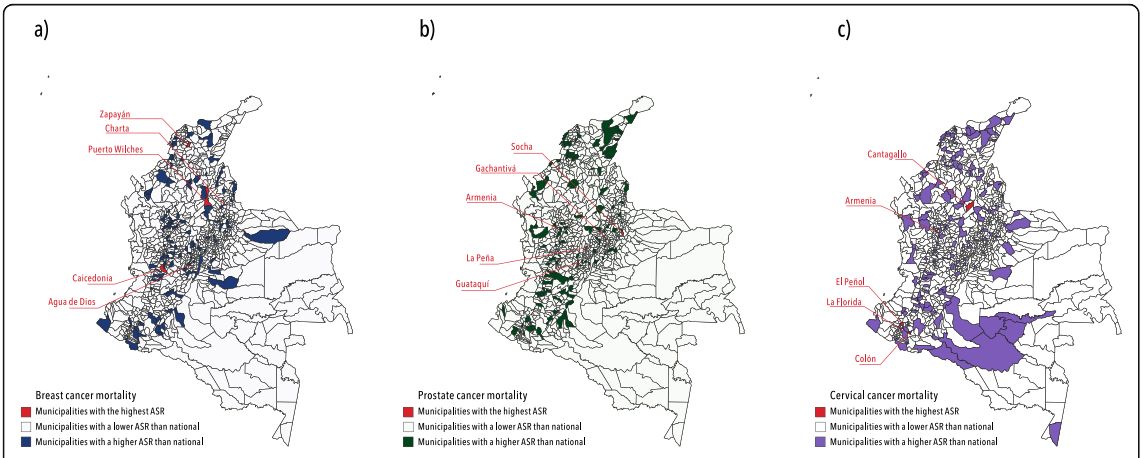

Fig. 2 Age-standardized mortality rates of breast, prostate and cervical cancer by municipalities, Colombia 2018. Figure 2 shows the age-standardized mortality rates for each cancer by municipalities (**a**) Age-standardized mortality rates of breast cancer (**b**) Age-standardized mortality rates of prostate cancer (**c**) Age-standardized mortality rates of cervical cancer. ASR: Age-Standardized Rates. Data source: cancer deaths reported to the National Administrative Cancer Registry during 2018

death [2], in Colombia was breast cancer. Compared with LAC, breast cancer was also the leading type among new cases and unlike Colombia, mortality trend was similar to the world [2].

Differences in cancer distribution between Colombia and the world reflect the ongoing social, economic, and health care changes in LAC. Such remarkable geographical contrast can be explained by differences in exposure to risk factors (reproductive, dietary, hormonal and environmental) and serious inequalities in timely access to screening and effective cancer treatment [5, 13].

Discrepancies in the distribution of incidence and mortality worldwide were also reflected in Colombia's regions. In terms of incidence, there was a homogeneous trend in breast and prostate cancer, with the highest ASR in Bogotá D.C., Central and Pacific regions, being significantly higher than the national in Bogotá D.C. This pattern could be explained by geographical proximity and similar social and economic development, which from a broad epidemiological perspective, implies a comparative distribution of risk background and access to quality care. Furthermore, domestic differences on prostate cancer incidence could also be explained by the distribution of ethnic or genetic variations across the country that have been linked with a higher risk of this type of cancer [14–16]. Indeed, regions with the highest incidence coincide with a high proportion of Afro-Colombian population [17]. Otherwise, prostate cancer screening coverage has also been associated with incidence rates and more than other cancer, screening with the prostate-specific antigen (PSA) increases the probability of being diagnosed [18]. In fact, countries with a high PSA screening coverage also have higher incidence rates, early diagnosis and lower mortality rates [19]. In Colombia, an organized population screening is not recommended. Early detection is focused on men aged > 50 years or those aged < 50 years with known risk factors and screening interval should not be inferior to 5 years [20, 21]. According to the national health survey, conducted in 2015, coverage of PSA screening in men older than 50 years was 44.60% and it varied by insurance, geographic location, education and socioeconomic level, being higher in Bogotá D. C while the lowest was identified in "other departments" [22]. This coverage corresponds to the magnitude of prostate cancer incidence in those regions.

On the other hand, the incidence pattern for cervical cancer was different, showing a significantly higher ASR in "other departments" region, mainly composed of nonmetropolitan and rural areas. It has been reported that women in rural areas may experience barriers to optimal cervical cancer prevention, screening, and treatment, as well as, a higher frequency of risky sexual behaviors [23, 24].

Regarding mortality, its distribution varied widely between regions, being the Eastern region the one that had lower ASR than national for all types of cancer. According to previous studies, disparities in mortality can be explained by diagnosis in advanced stages, limited access to quality health services, and treatment opportunity [25–27]. However, in our study population, there were no differences between the proportion of people diagnosed with invasive neoplasms or the first treatment initiation.

As the trend is evaluated at a lower level, such as municipalities, there is more variability in patterns for both, incidence and mortality. Nevertheless, Agua de Dios in Cundinamarca was among the significantly higher incidence rates than the national for all types of cancer. The above may suggest a high prevalence of known risk factors in the municipality, as well as, limited access to screening, early diagnosis, and quality treatment.

Although there is a national policy for cancer attention [28], differences in incidence and mortality trends can be related to local approaches for implementing health programs and emerging social and economic changes typical of each region, department or municipality.

Finally, some studies have documented similar results and remarkable findings. According to the analysis of the cancer situation in 2015 performed by the Colombian Cancer Institute, in the city of Pasto, its population-based cancer registry showed how types of cancer, such as breast and prostate cancer had a higher incidence in urban areas while cervical cancer was commonly diagnosed in rural areas [22]. Likewise, a report prepared by the National Health Observatory showed that there was a high health inequality across the country for these type of cancer. For example, in breast cancer, a higher concentration of cases and deaths was observed in regions with the highest wealth per capita, in women belonging to the contributory insurance and with increased access to mammography and specialized centers [29, 30].

Regarding cervical and prostate cancer, their findings suggest that higher mortality rates were reported in regions with noteworthy socioeconomic inequality. They found that the lowest cervical cancer mortality rates were observed in the richest municipalities and at departmental/regional settings, they found a correlation between a higher income inequality (measured by the GINI index) and higher death rates. In the case of prostate cancer, the lowest rates were also reported in the richest municipalities, however, there was no evidence of a gradient consistent with municipal poverty levels. Surprisingly, at the departmental/regional level findings were contradictory, with a directly proportional correlation between income per capita and prostate cancer mortality rates, but and an inversely proportional association with the GINI inequality index [30].

Strengths and limitations

This analysis has important strengths, including the large completeness of the NACR, which guarantees the

external validity and utility of our findings in the evidence-informed health policymaking process at the national and regional levels. Furthermore, the accuracy and quality of the information of all new cases were verified by a data monitoring process.

On the other hand, some limitations should be discussed. First, the passive case reporting by the health insurers could lead to under-reporting. In any case, it would be a small proportion because the reporting process is mandatory [12]. The cross-sectional nature of the analysis does not allow establishing consistency in the trends we observed. Moreover, information bias cannot be ruled out because clinical records are the primary data source and they may be subject to error.

Conclusions

We observed clear differences in cancer incidence and mortality across regions and municipalities, depending on each type of cancer. Our findings are important to improve the policy response from governments and health insurers regarding screening coverage, early detection, and access to treatment. Prioritization of health resources to geographical areas with incidence and mortality rates higher than national is crucial in a developing country, especially in breast, prostate, and cervical cancer, for which a better diagnosis and treatment can make a major difference in terms of survival, quality of life and economic burden of disease.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-020-07611-9.

Additional file 1: Figure S1. Socioeconomic distribution of regions in Colombia, 2018[1]. **Table S1.** Incidence rates for breast, prostate and cervical cancer by municipalities, Colombia 2018[1]. **Table S2**. Mortality rates for breast. Prostate and cervical cancer by municipalities. Colombia 2018[1].

Abbreviations

GLOBOCAN: Global Cancer Observatory; LAC: Latin American and the Caribbean; DALYs: Disability-Adjusted Life-Years; YLLs: Disability-Adjusted Life-Years; YLDs: Years Lived with Disability; NACR: National Administrative Cancer Registry; CAC: Cuenta de Alto Costo (High Cost Diseases Fund); DANE: Departamento Administrativo Nacional de Estadística (Department for National Statistics); IQR: Interquartile range; ASR: Age-standardized rate; PSA: Prostate-specific antigen

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Not applicable.

Authors' contributions

LA and AMV had the research idea. Analyses were performed by JAHV and maps were created by PXRB. The first draft of the manuscript was written by JAHV and PXRB. JAG wrote about the clinical aspects to support the discussion. AMGQ prepared the supplementary material. AMV reviewed and adjusted the methodology. LA reviewed the results and the discussion. All authors reviewed the final version. This article is an original research work and all authors have seen and approved the final version of the manuscript. We declare that it hasn't been published before, as well as not being considered for publication in a different journal

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due they are owned and managed by the Colombian health system but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Conforming to the information nature, this study has no risk for participants and informed consent or ethics approval was not required. Information was collected and analyzed following international standards (The Declaration of Helsinki, The Belmont Report and The International Guidelines prepared by the Council for International Organizations of Medical Sciences (CIOMS)), as well as national regulations (Resolution 8430 of 1993, stated by The Colombian Health Ministry) for conducting human research which stated that due the nature of the NACR and its direct regulation by the state, an ethics approval was not necessary. Confidentiality was guaranteed throughout the information processing (reporting, managing, analysis and publication). All records were anonymized before the analysis. Furthermore, access to data was restricted to the research team and the results only can be used for approved research or academic purposes.
The consent to participate was not applicable, the data were obtained from administrative health databases, therefore, no administrative permits and/or licenses were required to access and use patient clinical/personal data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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Publisher's Note

HEMOFILIA

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HEMOFILIA

National registry of haemophilia and other coagulopathies: A multisector initiative in the Colombian Health System

Autores: Luisa Fernanda Alvis, Patricia Sánchez, Lizbeth Acuña, Germán Escobar, Adriana Linares, María Helena Solano, Sergio Robledo

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Trabajo colaborativo con la Asociación Colombiana de Hematología y Oncología (ACHO) y la Asociación Colombiana de Hematología y Oncología Pediátrica (ACHOP) como actores de interés

Objetivo:

Describir la construcción e implementación de del registro nacional de hemofilia y otras coagulopatías de la CAC.

Principales hallazgos

- Se describe la estructura del registro, su metodología, resultados y alcance.

Relevancia de los hallazgos

- Visibilidad internacional del registro.
- Posicionamiento del registro de la CAC como fuente de información válida y confiable.
- Definición del registro como pionero en la región. La publicación de los métodos permite que otros contextos latinoamericanos integren sistemas similares y fortalece el trabajo en red.

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ORIGINAL ARTICLE

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National registry of haemophilia and other coagulopathies: A multisector initiative in the Colombian Health System

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Abstract

Introduction: Haemophilia is an orphan and high-cost disease worldwide and, especially in middle-income countries as Colombia. Given its burden of disease, in 2014, a national administrative registry was created to centralize demographic, clinical and economic information regarding to haemophilia and other coagulopathies.

Objective: To describe the building and implementation processes of the Colombian registry of haemophilia and other coagulopathies.

Methods: The 'consensus conference' methodology was used to design the registry. It was a multisector process, which included different actors of the health system (healthcare payers and providers, government institutions, academic and scientific organizations and patients).

Results: Colombia's national registry includes 95 variables, grouped in four sections: (1) sociodemographic data, (2) clinical condition, (3) economic costs, and (4) administrative updates. According to a resolution, stated by the Ministry of Health, payers and providers of healthcare must report annually to the registry the information of new and existing patients with coagulopathies.

Conclusions: A national registry serves as an organized and interactive system for monitoring morbidity and mortality, assessing healthcare access and its impact on disease complications, as well as associated costs to medical assistance. Furthermore, registry information can guide a rational making decision process to use economic resources efficiently. On the other hand, data about orphan diseases can encourage health research and evidence-based care to improve quality of life and reduce associated disability.

KEYWORDS

blood coagulation disorders, decision-making, haemophilia, inherited, rare diseases, registries

1 | INTRODUCTION

In Colombia, orphan diseases are defined as chronic and life-threatening conditions with a low prevalence (<1 cases per 5000 people).[1] They were recognized as a crucial public health issue because of their highly specialized care process, which increase the economic costs associated with health assistance.[1]

Since 2012, the first steps in planning a nationwide registry focused on orphan diseases were given.[1,2] The initial phase included a survey, performed by the High Cost Diseases Fund (CAC, by its

acronym in Spanish), from which, haemophilia was identified as the most frequent orphan disease with a prevalence of haemophilia A and B of 4.7 and 1.1 cases per 100 000 males, respectively.[3]

According to the above, the national prevalence of haemophilia (A and B) was estimated by 5.25 cases per 100 000 inhabitants in the country.[2] Under this context, haemophilia was identified as a priority disease. Therefore, it was necessary to establish a registry for monitoring demographic, clinical and economic situation of haemophilia in Colombia, in order to manage the associated risk in an efficient way and improve the quality of care.

To the best of our knowledge, in Latin America, there are eight national registries in Brazil, Chile, Colombia, Costa Rica, Dominican Republic, El Salvador, Mexico and Venezuela.[4]

The Colombian health system is funded by public and private sources and its coverage is closer to 96% of total population. The remaining 4% is grouped under special insurance. There are two insurance regimes: the contributory and subsidized and each citizen must be affiliated in one of those. The employed population is included in the contributory regime where both, employer and employee, make an economic contribution to pay for health services. Otherwise, in the subsidized regime, only unemployed and low-income people are affiliated and the healthcare assistance is paying by employed population and government resources.[5] The healthcare plan includes the same services, procedures, medicines and interventions for both regimes. However, there are different health payers who are responsible for managing the resources and paying the healthcare providers.

Health-related costs in patients with haemophilia are higher than in general population because of pharmacological treatment (prophylaxis or 'on-demand'), and medical follow-up in case of complications such as inhibitors, recurrent bleeding, musculoskeletal problems (chronic haemophilic arthropathy and joint replacements) and infectious diseases is expensive. Additionally, there are indirect costs associated with productive years lost due to disability.[6,7] In terms of costs associated with factor replacement, Colombia had the highest per capita consumption of factor VIII (4.6 units) and IX (0.7 units) in the Americas region, comparing with similar income countries.[8]

According to the high disease and economic burden of haemophilia and other coagulopathies, a national patient registry is imperative, especially in middle-income countries where access to health is heterogeneous. Therefore, the aim of this article is to describe the creation and implementation of the Colombian registry of haemophilia and other coagulopathies.

2 | MATERIALS AND METHODS

The 'consensus conference' methodology was used to define the operation, structure and confidentiality of the registry.[9] The CAC led the process, and two groups were created: clinic experts and bibliographic reviewers. Most stakeholders of the health system were invited to participate: healthcare payers and providers, the Ministry of Health, control and surveillance government institutions (Superintendence of Health and the Ombudsman), the Health Technology and Evaluation Institute, scientific associations (The Colombian Society of Hematology and Oncology and The Colombian Society of Pediatric Hematology and Oncology), patient organizations (The Colombian League of Hemophilia and other Blood Deficiencies-ColHemofilicos) and universities (National University of Colombia and Foundation University of Health Sciences). In coordination with the actors, a 10-step methodology was used by the CAC to define the structure and functioning of the registry (Table 1).

In stage 1, a systematic search for clinical practice guidelines (CPG) was performed in the main databases (PubMed, Trip Database, Cochrane, Scielo and National Guideline Clearinghouse), as well as in The World Federation of Hemophilia and The National Hemophilia Foundation—USA websites. Search algorithm was built with MeSH/DeCS terms and the following filters: published in the last 10 years, human research and language (English and Spanish).

In stage 2, the CPG which met the inclusion criteria were evaluated with the Appraisal of Guidelines Research and Evaluation (AGREE) tool[10] and those rated as 'not recommended' were excluded. Then, after a full-text review of the CPG included, a board of clinical experts selected the relevant variables and outcomes to measure in the registry (stage 3). After that, conceptual and operational definitions for relevant variables were proposed (stage 4), and the first draft of the registry structure was prepared (stage 5).

A pilot study was performed to determinate validity and feasibility of the variables previously included (stage 6). It was carried out for 3 months, and 541 patients from six health payers were included. Sample was selected randomly in two stages: in the first one, six health payers were included and the selection probability was proportional to the number of patients managed. In the second step, we used random sampling for selecting the patients from each health payer.

After adjustment for the pilot test results, a preliminary proposal of the variables and their definitions were voted by a panel of stakeholders with wide knowledge in bleeding disorders and the functioning of the health system (stage 7). Those variables with greater than 50% approval were included in the final proposal (stage 8) and sent to the Ministry of Health for reviewing and editing (stage 9). Finally, the structure and functioning of the registry was published by the Ministry of Health (stage 10).

3 | RESULTS

As a result of stage 1, 1300 documents were found, and after a title and abstract review, editorials, non-systematic reviews and off-topic articles were excluded. Finally, 44 documents were reviewed in full text, identifying 15 CPG which were evaluated with the AGREE tool. After evaluation, 6 CPG were classified as 'Highly recommended', 5 'Conditioned recommended' and 4 'Not recommended'. Finally, 11 CPG were included (stage 2).

TABLE 1 Registry developing process

Stage	Description	2014 Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	2015 Dec	Jan
1	Systematic search for CPG												
2	Evaluation of CPG												
3	Identification of objectives and outcomes related to clinical management												
4	Selection of variables to measure, objectives and outcomes												
5	Preparation of the first draft with registry structure												
6	Conducting a pilot study												
7	Discussion and consensus about registry structure												
8	Final proposal design												
9	Reviewing and editing by the Ministry of Health												
10	Stating and publishing by the Ministry of Health												

Abbreviation: CPG, Clinical Practice Guidelines.

The results of stage 2 allowed to identify the objectives and expected outcomes regarding clinical management of patients with haemophilia. Then, they were evaluated by a board of clinical experts who selected 91 variables related to diagnosis, severity, treatment regimen and complications such as bleeding, chronic haemophilic arthropathy, infections and inhibitors (stages 3 and 4).

According to the results of the pilot study, from the proposed 91 variables, 87.0% were available on clinical records and 4.5% of them required some adjustments related to the response scale, mainly focused on a better definition of categories. We identified some difficulties to collect data in 7.5% (variables such as first bleeding date, first clinical symptom of bleeding, first bleeding aetiology, comorbidities (diabetes, hypertension, obesity), needing help or a device for improving mobility).

Once the pertinent adjustments were made, 4 additional variables were added, so we obtained a total of 95 variables, which were voted by the stakeholders, and all of them were included in the final proposal (stage 8). They were grouped in four sections: sociodemographic data, clinical condition, health-related costs and administrative updates (Table S1).

3.1 | Sociodemographic data

This section includes 16 variables, which are crucial for a cross-checking with other official sources of information in order to verify the reliability of vital statistics, mainly. Furthermore, their descriptive analysis provides valuable information for epidemiological and governance goals.[6]

3.2 | Clinical condition

A total of 72 variables are grouped in this section. Diagnosis process information includes the following: age at diagnosis, diagnosis test indication, diagnosis date, the healthcare provider where the diagnosis was confirmed, deficiency classification and its severity. Otherwise, treatment regimen is divided into two categories: (1) initial treatment, initial scheme, factor replacement and starting date; and (2) current treatment, scheme and factor, patient's weight, dose and frequency of prophylaxis, prescribed units in lasts 12 months (only for on-demand treatment), and the medication brand name and presentation.

Regards to complications, there are variables as the number of hemarthrosis and extra joint bleeds in the last 12 months as well as the bleeding aetiology (spontaneous or traumatic) and localization. Furthermore, information related to inhibitors (immune tolerance induction in the last 12 months and its length), chronic haemophilic arthropathy, infectious complications (hepatitis C virus (HCV), hepatitis B virus (HBV) or human immunodeficiency virus (HIV)) and other complications (pseudotumors, fractures and anaphylaxis) is collected.

Some variables in this section seek to describe medical assistance, including information about the health professional who leads the care process, as well as the number of clinical appointments with haematologist, orthopaedist, dentist, nursing, nutritionist, psychology, among others.

Finally, there are two variables to describe the number of hospitalizations and emergency admissions associated with haemophilia care during in the last year.

3.3 | Healthcare-related costs

Four variables were included: two of them related to clotting factor costs over the last year, one more to place the total cost of disease management (including treatment, medical appointments, therapies, laboratory test and other interventions) and the last one is linked to disability costs caused by the disease.

3.4 | Administrative updates

Variables in this section define patient current administrative situation in the Colombian health system. Therefore, they allow to identify number, cause and date of deaths, changes in health payers affiliation, number of new cases and treatment dropouts, particularly.

Further, the stakeholders of the health system decided to exclude acquired disorders and include information about 12 inherited bleeding disorders, with special emphasis in haemophilia A or B, and a sociodemographic characterization of other disorders such as haemophilia carriers, von Willebrand disease and low frequency deficiencies (fibrinogen, prothrombin, factor V, combined factor V and VIII, factor VII, factor X, factor XI and finally factor XIII).

Regarding the registry operation, it was stated that every year, health payers in cooperation with their healthcare providers must collect data from their affiliates to update registry information on a web platform, which was designed to validate the structure, coherence and consistency of provided information. The above was necessary taking into account that in Colombia, there are no standardized medical records, in fact, each healthcare provider has its own software, or even paper medical records are still used in the most remote areas in the country.

Once information is uploaded in the interface, the CAC performs a data monitoring process to ensure its quality. It is accomplished by health professionals specialized in auditing, who compare the information on the registry against the one available in electronic/paper medical records, and if any inconsistency is identified, the relevant adjustments are made.

It is important to mention that the registry is classified as administrative.[11] Figure 1 describes registry's information flow defined to guide the process.

The last aspect we considered in the functioning of the registry was data confidentiality. In order to achieve it, a triangulation process was established with the official database of affiliates to the health system across the country managed by the Ministry of Health and the creation of a unique identifier number which was assigned to ensure data anonymization and the follow-up. The CAC was the institution in charge of the responsibility to guarantee personal and clinical data protection according to national regulations.

Finally, the updated draft was sent to the Ministry of Health, in order to check its consistency with national health regulations (stage 9). Registry operation started in 2015, through an administrative measurement of the Colombian government (stage 10), which stated that annual report is mandatory for all actors in the Colombian health system.

3.5 | Registry evolution (2015-2019)

The registry is operating since 2015. In the first year, 3501 cases of coagulopathies were reported, and from those, 1,834 were prevalent cases of haemophilia. By 2018, a total of 4,395 people living with congenital blood disorders were identified and 2237 of them had haemophilia. A book with the current situation of the reported blood diseases is published annually.[12] Also, risk management indicators (eg proportion of patients who developed inhibitors, spontaneous and traumatic bleeding rate and access to haematologist/dentist consultations) are calculated every year to evaluate and compare access to health services between the health payers and healthcare providers, and according to their evolution, the Ministry of Health and other actors of the health system adjust national and local regulations, as well as clinical practice protocols for improving quality of care.

4 | DISCUSSION

Colombia is a Latin American country, and its current population is 50.4 million people. According to the latest World Bank classification, it is an upper middle-income country. Between 2014 and 2018, average annual health expenditure was 7.2% of gross domestic product (GDP), which is lower than in the United States (16.9%) or the European Union (over 10.0%) but similar to other countries in the region.[13]

According to the above, in a health system with limited funds, haemophilia care represents an important economic burden to the system, despite its low prevalence.

Before the registry, prevalence of haemophilia was estimated with data provided by the National Census of Orphan Diseases conducted by the National Institute of Health, the Ministry of Health and the CAC in 2008. By 2019, there were 2331 people living with haemophilia (A or B) and the age-adjusted prevalence was 4.6 cases per 100 000 people.[12]

Direct costs associated with treatment are especially higher. For example, in 2010, clotting factor replacement costs over 74 million USD to the Colombian health system.[14] Additionally, the need to make haemophilia a visible disease and standardize its care was the basis for the development of the 10 Principles of Haemophilia Care for Europe (PCHE), published in 2008, and one of them was focused on the creation of national patient registries.[15]

Since that, a better quality of care in rare blood diseases has become a relevant topic on a global scale. Therefore, the Colombian registry was built for improving outcomes related to healthcare and managing resources efficiently in the Colombian health system. A multisector approach was used to determine its structure and scope, and because of that, it is a useful tool for public health making

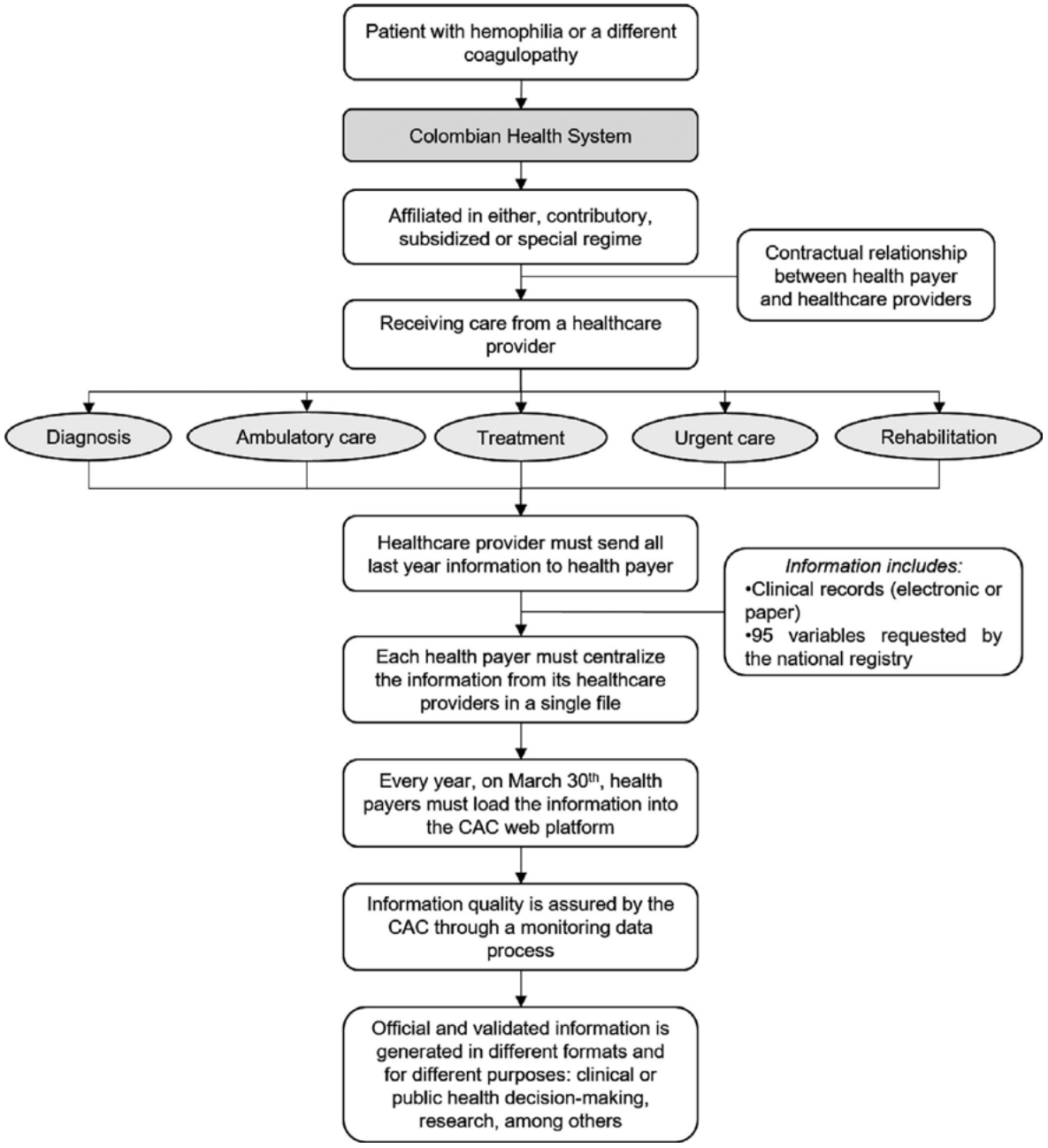

FIGURE 1 Functioning of the Colombian registry of haemophilia and other coagulopathies. *CAC: High Cost Diseases Fund (CAC, by its acronym in Spanish)

decision process. It was classified as administrative, because it contains some variables related to the Colombian health system dynamic and its updating process was stated by the Ministry of Health with an active participation of healthcare payers and providers.

Opposing to Brazil,[16,17] Italy[18] and Switzerland,[19] where the registries information comes from haemophilia care centres, in Colombia, healthcare payers and providers must update the registry. The information is not collected directly from the healthcare providers because there is not a single health records system in the country.

The registry collects valuable information for health services planning because variables about affiliation regime, healthcare

payers and providers, and municipality or department burden of disease are useful to determinate tendencies over the time. Also, from that information public health decision makers can lead an equitable distribution of resources.

Another strength of the registry is the inclusion of some variables related to pregnant status and access to contraception and genetic counselling in women carriers of haemophilia and those with a different coagulopathy. This is particularly important for focusing prevention, early detection and childbirth care programs on high-risk population.[20,21]

Despite its important role helping people with inherited blood disorders to make more informed choices, genetic counselling is novel in developing countries.[22] Thus, data monitoring in this field is necessary and could be a cost-effective intervention.

The registry most extensive part is focused on clinical condition (75.8% of variables), and it is a common feature with other registries worldwide.

It is well known that haemophilia has a strong relationship with heritage. However, recent evidence has reported that around 30% of cases are attributed to new mutations[15]; in fact, family history and clinical indication for diagnostic test were included.

Regards to clinical course, evidence has shown that severity of haemophilia and other coagulopathies is directly associated with incidence of complications.[15] This effect becomes stronger with increasing age; for example, in people with severe haemophilia A or B, joint bleeding prevalence increases from 21% in children aged 1-6 years, to 50% in those aged 10-17 years and 60% or more in patients aged 18-65 years.[23,24] Previous evidence justified the inclusion of variables related to severity and age at diagnosis because of their clinical and predictive value.

Furthermore, taking into account that the characteristic phenotype in haemophilia is the bleeding tendency,[22] variables for characterizing its frequency, location and origin were included. Also, clinical characteristics of bleeding are associated with inhibitors, especially in mild and moderate haemophilia. In severe haemophilia A, cumulative incidence of inhibitors ranged between 20% and 30%.[25] When inhibitors are present, treatment options and dosage must be modified and those changes increase costs notably.[26-28] In consequence, inhibitors are the most serious complication in patients with haemophilia, reason why there are some variables in the registry for predicting its impact on health-related outcomes.[29]

In terms of therapeutic regime, clotting factor replacement is the gold standard.[22] The scheme choice depends on treatment objectives, severity and history of complications, and it could be 'on-demand' (indicated for acute bleeding) or prophylaxis (a regular infusion of factor concentrate in order to prevent haemorrhages, including hemarthrosis).[30,31] About prophylaxis benefits, it has demonstrated a significant decreased in bleeding frequency and preservation of joint function.[32]

Inclusion of treatment variables will allow developing indicators and nested research studies about access, cost-efficiency to prevent complications and management by healthcare payers and providers.

It is recognized that care by a multidisciplinary team of trained professionals within a comprehensive care environment is important to maximize outcomes.[33,34] Indeed, the registry includes information about healthcare provider and team in charge of clinical assistance and follow-up.

Despite there are a lot of authorized clotting factor options, quality information about their doses, frequency and costs is limited. It justifies the inclusion of information about the prescribed factor (recombinant or plasma-derived).

In the same line, healthcare-related costs are higher in haemophilia, and because of that, its follow-up is priory over other orphan diseases in the country. Although it is recognized that high costs are mostly related to direct costs (factor concentrate, complications, hospitalizations and procedures), indirect costs (reduced productivity at work or school) and intangible costs (quality of life and disability) also have a considerable impact.[35,36] In fact, the registry includes information regards to all types of health costs, except for quality of life which is difficult to measure in a population context.

Cost variables will be useful to establish an accurate social and economic burden of blood orphan diseases. Also, from those findings, public policies and attention processes can be adjusted according to needs and improvement opportunities.

4.1 | Confidentiality

In countries like Italy[18] and Germany,[37] a consent or authorization form signed by patients or parents is required for including epidemiological and sociodemographic data. In Colombia, the legislation allows the use of clinical data for the registry's purposes because the CAC is a technical organization (CAC) of the health system. In fact, the CAC has authorization for auditing data in order to guarantee the quality, reliability and veracity of the reported information.

The Colombian registry was a multisector initiative, led by the national government, in which healthcare payers' and provider's participation was decisive for focusing on orphan blood diseases and keeping the registry update.

Multidisciplinary approach allowed to obtain quality and opportunity data, which have led to a sustainable follow-up with major improvements in health care and patient outcomes. Another strength is that nationwide accurate information grants feasible comparison with orphan blood diseases situation worldwide. Regarding to limitations, the registry has a limited clinical information about other coagulopathies, because it was initially focused on haemophilia. Additionally, there is no patient interface to allow the patients to directly report their treatments, bleedings and quality of life measures.

5 | CONCLUSIONS

The Colombian registry was created to achieve several purposes: to determinate frequency and distribution of congenital coagulopathies

across the country, along with the quality of their healthcare and cost-effectiveness and risk indicators to manage the burden of disease and encourage standardized clinical practice.

Construction and managing of the Colombian haemophilia and other coagulopathies registry through a standardized methodology and participation of health system actors can assure decision-making processes based on evidence and national needs, as well as a more efficient resource management and health research focusing on epidemiologic distribution of disease and its complications, cost-effectiveness of treatments and impact on disability.

DISCLOSURES

All authors stated that they had no competing interests which can lead to biased results.

AUTHOR CONTRIBUTIONS

LFA and PS wrote the first draft of the manuscript. AL and MHS wrote about the clinical aspects to support the discussion, and they reviewed all the document. LA and GE wrote the discussion and conclusions. SR wrote the introduction and reviewed the results. All authors approved the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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HEMOFILIA

Primary prophylaxis was associated with lower arthropathy in Colombian men with haemophilia B: A longitudinal analysis (2015-2019)

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Alcance: internacional

Trabajo colaborativo con la Asociación Colombiana de Hematología y Oncología (ACHO) y la Asociación Colombiana de Hematología y Oncología Pediátrica (ACHOP) como actores de interés

Objetivo:

Evaluar la asociación entre la profilaxis primaria (PP) y la prevalencia de artropatía hemofílica crónica (AHC) en hombres colombianos con hemofilia B durante el periodo 2015-2019

Principales hallazgos

- La prevalencia de AHC en la línea de base fue de 36,84%%.
- La PP fue prescrita al 37,85%.
- Las personas con PP tuvieron mejor frecuencia de AHC, hemartrosis, complicaciones infecciosas e inhibidores de título alto en comparación con el grupo que recibió profilaxis secundaria o terciaria.
- La PP se asoció con una disminución del 89,70% en la posibilidad de presentar AHC.

Relevancia de los hallazgos

- Visibilidad de la alta cobertura de profilaxis en Colombia, posicionándose como uno de los pocos países que la garantiza a la población adulta.
- Los hallazgos confirman los beneficios clínicos de la prescripción de la PP, apoyando los algoritmos de tratamientos que se siguen en el país.
- Los resultados apoyan la necesidad de incrementar la cobertura de la profilaxis en el país debido a su impacto positivo en la mitigación de desenlaces clínicos de interés como la AHC, disminuyendo además su alto impacto social y económico.

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ORIGINAL ARTICLE

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Primary prophylaxis was associated with lower arthropathy in Colombian men with haemophilia B: A longitudinal analysis (2015-2019)

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Abstract

Introduction: The risk of chronic haemophilic arthropathy (CHA) is related to severity. Evidence suggests that primary prophylaxis (PPr) could reduce CHA incidence and its impact on quality of life.

Aim: To evaluate the association between PPr and CHA in Colombian males with haemophilia B (HB) during 2015 to 2019.

Methods: A panel-time analysis was performed with data provided by the National Health System to update a nationwide open cohort of people with congenital coagulopathies. The association was evaluated in a logistic random-effect regression model (LRERM), adjusted by age at diagnosis, prophylaxis dose and frequency, severity, haemarthrosis and high-titre inhibitors.

Results: During 2015-2019, a total of 362 men with HB and treated with either, primary, secondary or tertiary prophylaxis were identified. At baseline, CHA prevalence in the cohort was 36.84% (n = 133), median age was 19.0 years (IQR: 10.0-27.0), and median age at diagnosis was 1.0 year (IQR: 0.0-4.0). PPr was prescribed in 37.85% (n = 137), and median dose (IU/Kg/dose) was almost the same for primary vs. secondary/tertiary prophylaxis. Patients in PPr had a lower frequency of severe HB, CHA, haemarthrosis, infectious complications and high-titre inhibitors than those in secondary or tertiary prophylaxis (STPr). In the LRERM, PPr was associated with a significant reduction of 89.70% in the odds of CHA (aOR = 0.103, IC 95%: 0.040, 0.270; $P < .001$), compared with STPr.

Conclusions: PPr decreased the odds of CHA by 89.70% in males with HB in Colombia. Our findings are consistent with previous studies and support the strategy to prescribe PPr to our patients.

KEYWORDS

haemophilia B, haemophilic arthropathy, men, prophylaxis, registries

1 | INTRODUCTION

Haemophilia B (HB) is a X-linked bleeding disorder characterized by a deficiency or complete absence of the coagulation factor IX.[1] HB incidence is not well known, but estimated to be 1 in 30 000 male live births.[2,3] According to the Annual Global Survey (2018), there are 34 289 people living with HB, who represent a 17.0% of people with haemophilia worldwide.[4] In Colombia, 9.27% of people with coagulopathies had HB. By 2018, the overall and men age-standardized prevalence were 0.8 and 1.6 cases per 100 000 inhabitants, respectively.[5] Prevalence is expected to continue increasing due to better and timely diagnosis, improved access to haemophilia care and more efficient surveillance systems through population-based registries.[6]

HB-related complications are directly associated with severity.[7] Despite the improvements in early diagnosis and treatment, long-term complications remain a public health issue because they impact on burden of disease and health-related costs. One of those is the chronic haemophilic arthropathy (CHA), end stage of recurrent and inadequate treated joint bleeding, among other factors.[1]

Chronic haemophilic arthropathy is a disabling condition, often starting at an early age, defined by chronic pain, joint impairment[8,9] and poor quality of life.[10-12] Information about its frequency is limited. CHA prevalence ranges from 20.9% in Sweden[13] to 42.8% in Taiwan.[14] On the other hand, Sweden patients treated with high-dose prophylaxis regimen had lower CHA (31.0%), compared to Dutch patients under intermediate dose (68.0%).[15] In Colombia, it has been estimated in 33.60% among HB patients, regardless of prophylaxis.[5] Age, severity, bleeding rate, treatment scheme and complications, such as inhibitors, have been proposed as CHA-related factors.[14,16,17]

In respect of treatment, some evidence suggests a lower frequency of CHA-associated factors (joint bleeding, Pettersson score and limited joint range of motion) and CHA as the end point of joint damage in patients with primary or even secondary prophylaxis compared to on-demand.[17-20] However, most studies have included mixed populations or restricted their samples only to haemophilia A but also in HB the burden of CHA is considerable and frequently underestimated.

Furthermore, results from haemophilia population registries are limited despite its relevant role in supporting evidence-informed decision-making, particularly in low- and middle-income countries, where effectiveness measurements are extremely relevant. Also, in Latin America there are no studies to evaluate the effect of prophylaxis over CHA frequency, using a population-based approach.

According to the above, our aim was to evaluate the association between primary prophylaxis (PPr) and CHA in men with HB reported to the Colombian Registry of Haemophilia and other Coagulopathies from 2015 to 2019.

2 | MATERIAL AND METHODS

2.1 | Data sources

A panel-time analysis was performed on data provided by the Colombian Registry of Haemophilia and other Coagulopathies (CRHOC). The CRHOC was created by the Colombian Health Ministry in 2014 for centralizing demographic, clinical and health costs information regarding to bleeding disorders nationwide.[21] CRHOC coverage is almost universal, taking into account that 96% of total population is affiliated to the Colombian Health System and all of them must be reported annually by the insurance companies.[22] Since its beginning, a total of 4349 people with coagulopathies have been reported. Each patient is identified with a unique study ID, which was used to link the datasets. Every year, information is updated for prevalent cases and for incidents, a complete registration is performed. Data quality is guaranteed by a complex data monitoring process, achieved in two steps: an initial cross-check through a systematized validation mesh which identifies mistakes in the reporting process by the insurance providers. Once, those mistakes are detected and solved, information is compared with health clinical records to verify its authenticity.

2.2 | Eligibility of participants

Males with HB reported to the CRHOC from 1 February 2014 to 31 January 2019 and treated with either, primary, secondary or tertiary prophylaxis were included.

2.3 | Dependent and independent variables

CHA was the dependent variable and it was defined by a dichotomous variable, which answers the question: 'Was the patient diagnosed with CHA during the period?' Diagnosis was validated against clinical records looking for the ICD-10: M36.2. CHA was determined on each clinical centre by a multidisciplinary team, led by experienced haematologists and orthopaedists in collaboration with physical rehabilitation services. CHA diagnosis was performed following the international criteria, which include a combination of physical, functional and radiographic tools. During the data monitoring process, CHA diagnosis was validated if there was evidence on clinical records (medical notes, images or radiographic scales). Also, there have been established some specific filters to discard misclassification with haemarthrosis. The independent variable was type of prophylaxis (primary versus secondary/tertiary), prescribed during the follow-up and confirmed in medical records. In the CRHOC, prophylaxis type was defined according to the disease stage, in which it was initiated as follows: PPr was a regular and continuous clotting factor IX replacement in absence of documented joint disease and administering before age 3 years and the second clinically evident joint bleed. Finally, to be considered as a secondary/tertiary prophylaxis (STPr), replacement therapy must be initiated after two or more large joint bleeds but before the clinical onset of joint disease.[1,7]

2.4 | Comorbidities and adjustment variables

We used ICD-10 codes for identifying comorbidities associated with HB; these included human immunodeficiency virus (HIV)

infection (ICD: B20-B24), hepatitis B virus (HBV) infection (ICD: B16.0, B16.1, B18.0, B18.1) and hepatitis C virus (HCV) infection (ICD: B17.1, B18.2). In the same way, age at diagnosis, prophylaxis dose and frequency, and haemophilia family history, severity, presence of haemarthrosis and high-titre inhibitors were validated with healthcare records. Age at diagnosis was reported in years. Severity was classified according to clotting factor activity in severe (<1%), moderate (1%-5%) and mild (>5-<40%). Clinically evident haemarthrosis (yes/no), and the general and joint bleeding rate (number of bleeds per year) and their aetiology (spontaneous or traumatic) during the follow-up were recorded. Finally, from inhibitors, their presence and classification (low or high-titre) were reported.

2.5 | Statistical analysis

A descriptive analysis was performed. Means and standard deviations (SD) or medians and interquartile range (IQR) were reported for numeric variables, according to their distribution. Absolute numbers and relative frequencies were informed for categorical variables. The differences in demographics and clinical variables at baseline were evaluated using *t* test or its non-parametric equivalent Mann-Whitney *U* test and chi-square for categorical variables.

We estimated age at diagnosis-adjusted and multivariable logistic random-effect regression models (LRERM) for evaluating the association between PPr and CHA. Multivariable models were adjusted by age at diagnosis, prophylaxis dose and frequency, severity, haemarthrosis (clinically evident) and high-titre inhibitors. Confounders were selected using the directed-acyclic graph method. We selected a random-effect model because is the most suitable due to the study aim. In fact, this kind of model allows adjustment on non-observed individual characteristics and a better understanding of the underlying mechanism of the interest association.[23] Robust standard errors were used. Adequacy and specification of random-effect model were tested using the Breusch-Pagan and Hausman test, respectively.

Moreover, some stratified analyses by haemarthrosis, presence of high-titre inhibitors and HB severity were conducted. Additionally, we assessed whether the main association was modified by the presence of haemarthrosis in an effect modification model and the significance level was set at 0.10. We performed sensitivity analyses, including some recognized clinical associated factors of CHA (haemarthrosis and joint bleeding rate) as dependent variables in adjusted models in order to verify consistency of the interest association. Finally, we evaluated the effect of clinically evident haemarthrosis in CHA, restricting analysis to PPr group.

Since we found missing data over 10% in age at diagnosis, we conducted a multiple imputation by chained equations and re-estimated overall, stratified and interaction models. Due to effect sizes did not change substantially, all results are based on a complete case analysis.

P values < .05 (two-tailed) were considered statistically significant, except for the effect modification model. All statistical analyses were performed in Stata (version 13.0; StataCorp LP, College Station, Texas, USA).

3 | RESULTS

3.1 | Sociodemographic and clinical characteristics of participants at baseline

Over 630 males with HB were reported to the CRHOC between 2015 and 2019. From them, 362 met the inclusion criteria and were analysed. At baseline, the overall prevalence of CHA was 36.84% (n = 133) and PPr was prescribed in 37.85% (n = 137). Median age was 19.0 years (RIQ: 10.0-27.0), median age at diagnosis was 1.0 year (IQR: 0.0-4.0), and haemophilia family history was reported by 44.72% (n = 161). Related to clinical variables, 61.73% (n = 221) and 35.75% (n = 128) were classified as severe and moderate HB, respectively. Otherwise, haemarthrosis was reported by 45.43% (n = 164), high-titre inhibitors by 3.31% (n = 12), any infectious complication (HIV, HBV or HCV) by 2.49% (n = 9), and general and joint bleeding rates were 1.0 (IQR: 0.0-3.0; min = 0.0, max = 26.0) and 0.0 (IQR: 0.0-1.0; min = 0.0, max = 11.0), respectively.

3.2 | Sociodemographic and clinical characteristics of participants at baseline, comparing by prophylaxis type

Table 1 shows the differences in demographic and clinical variables between people receiving PPr and STPr at baseline. Median of prophylaxis dose was almost the same in both groups, while proportion of patients who received prophylaxis once or twice a week was higher in PPr. Median age and family history of haemophilia were significantly lower in men with PPr. Prevalence of haemarthrosis, joint bleeding rate and infectious complications was also significantly lower in PPr. Other complications, such as pseudotumours, anaphylaxis, fractures and high-titre inhibitors, were slightly low in men treated with PPr.

3.3 | Trends of CHA during the follow-up

Figure 1 shows predicted probabilities of CHA from 2015 to 2019. As expected, frequency of CHA was lower in PPr than in STPr during the entire follow-up. In PPr group, CHA increased between 2015 and 2017, followed by a slight decrease and finally, a further increase by the end of the follow-up.

3.4 | Association between PPr and CHA

Age at diagnosis-adjusted model showed an inverse and statistically significant association between PPr and CHA (Table 2). When

TABLE 1 Sociodemographic and clinical characteristics of the study population between primary and secondary/tertiary prophylaxis at baseline

Variables[a]	Primary prophylaxis (n = 137)	Secondary/tertiary prophylaxis (n = 225)	*P*-value[b]
Prophylaxis dose, IU/Kg/dose[c]	30.0 (23.5-40.0)	30.0 (23.0-38.0)	.777
Prophylaxis frequency, %			
Once a week	11 (8.73)	15 (6.94)	.078
Twice a week	98 (77.78)	148 (65.52)	
Three times a week	17 (13.49)	50 (23.15)	
More than four times a week	0 (0.00)	3 (1.39)	
Age at baseline, y[c]	12.0 (9.0-20.0)	20.0 (14.0-32.0)	**.0001**
Age at diagnosis, y[c]	1.0 (0.0-3.0)	1.0 (0.0-6.0)	.242
Haemophilia family history, %			
Yes	43 (31.39)	118 (52.91)	**.0001**
No	94 (68.61)	105 (47.09)	
Severity, %[d]			
Severe	81 (59.56)	140 (63.06)	.730
Moderate	52 (38.24)	76 (34.23)	
Mild	3 (2.21)	6 (2.70)	
Hemarthrosis, %[d]			
Yes	47 (34.31)	117 (52.23)	**.001**
No	90 (65.69)	107 (47.77)	
General bleeding rate[e,f]	1.0 (0.0-14.0)	1.0 (0.0-26.0)	.120
Joint bleeding rate[e,g]	0.0 (0.0-8.0)	0.0 (0.0-11.0)	**.003**
High-titre inhibitors, %			
Yes	3 (2.19)	9 (4.00)	.351
No	134 (97.81)	216 (96.00)	
Other bleeds, %[h]			
Yes	50 (36.50)	85 (37.78)	.807
No	87 (63.50)	140 (62.22)	
Infectious complications, %[i]			
Yes	0 (0.00)	9 (4.00)	**.018**
No	137 (100.00)	216 (96.60)	
Other complications, %[j]			
Yes	11 (8.03)	19 (8.44)	.889
No	126 (91.97)	206 (91.56)	

[a]Data are presented as absolute values (proportions), unless otherwise specified.
[b]Differences were evaluated with Mann-Whitney U test for continuous variables and chi-square test for categorical variables.
[c]Reported values are medians (interquartile ranges).
[d]Less than 5% missing values.
[e]Reported values are medians (minimum and maximum values).
[f]Includes any aetiology (spontaneous and traumatic) and location (haemarthrosis and others).
[g]Includes only traumatic or spontaneous joint bleeds.
[h]Include traumatic or spontaneous iliopsoas and other muscles haemorrhages, and intracranial, oral, neck and throat bleeds.
[i]Infectious complications include HIV, HBV or HCV.
[j]Other complications include (pseudotumours, anaphylaxis and fractures).

adjusting for confounders, direction, magnitude and statistical significance were remained. Indeed, in men who received PPr the odds of CHA was 89.70% (CI 95%: 73.48%, 96.00%; $P < .001$) lower, compared with those treated with STPr.

In all stratified analysis, direction of associations did not change. We observed a strong inverse and statistically significant association between PPr and CHA in men without clinically evident haemarthrosis. The multivariate-adjusted odds of CHA in men without haemarthrosis

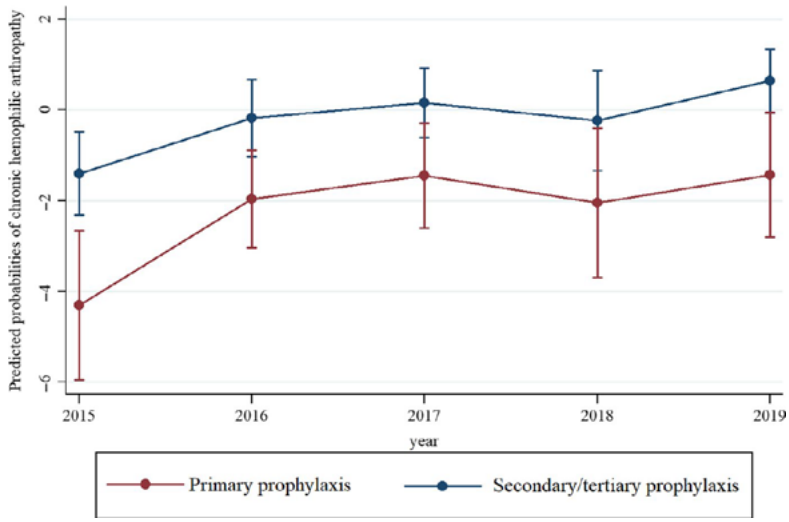

FIGURE 1 Trend of chronic haemophilic arthropathy during the follow-up in Colombian males with HB, comparing by prophylaxis type. The predicted probabilities of haemophilic arthropathy and their 95% confidence intervals for each year, comparing men who were treated with primary vs. secondary/tertiary prophylaxis are shown

TABLE 2 Multivariate-adjusted odds of chronic haemophilic arthropathy by prophylaxis treatment and stratified by haemarthrosis and severity in Colombian men with HB[a]

Model	Secondary/tertiary Prophylaxis (n = 225)	Primary Prophylaxis (n = 137)	*P*-value
Prophylaxis dose (IU/Kg/dose)[b]	30.0 (23.0-38.0)	30.0 (23.5-40.0)	–
Overall			
Age-adjusted[c]	Reference	0.125 (0.051, 0.310)	<.001
Multivariable[d]	Reference	0.103 (0.040, 0.270)	<.001
Stratified[e]			
Haemarthrosis	Reference	0.017 (0.010, 3.530)	.778
Non-Haemarthrosis	Reference	0.022 (0.003, 0.141)	<.001
Severe HB	Reference	0.044 (0.008, 0.248)	<.001
Mild/Moderate HB	Reference	0.074 (0.020, 0.280)	<.001

[a]Values are odds ratios (95% CI) obtaining from logistic random-effect regression models, unless otherwise specified.

[b]Reported values are medians and interquartile ranges.

[c]Adjusted by age at diagnosis of HB.

[d]Multivariable models were adjusted by age at diagnosis (y), prophylaxis dose (continuous), prophylaxis frequency (more than three times/week vs. once/twice a week), severity (severe vs. mild/moderate), clinically evident haemarthrosis (yes vs. no) and high-titre inhibitors (yes vs. no).

[e]All stratified models are multivariable.

and treated with PPr was 97.84% lower than in STPr (CI 95%: 85.88%, 99.67%; $P < .001$). In contrast, in men with haemarthrosis, the relation between PPr and CHA went to the null (OR = 0.017; CI 95%: 0.010, 3.530; $P = .778$). The same pattern of a strong inverse association was found according to severity. The magnitude was higher in men with severe HB (OR = 0.044; CI 95%: 0.008, 0.248; $P < .001$) than in those with mild or moderate HB (OR = 0.074; CI 95%: 0.020, 0.280; $P = < .001$).

3.5 | Modification of the effect of PPr on CHA by haemarthrosis

A statistically significant effect modification was found between prophylaxis and clinically evident haemarthrosis ($P = .097$). In haemophilic men without haemarthrosis and receiving PPr, the multivariate-adjusted odds of CHA was 94.43% (OR = 0.056; CI 95%: 0.015, 0.214; $P < .001$) lower than in men treated with STPr. Otherwise, in men with haemarthrosis, the possibility of CHA was 77.94% (OR = 0.221; CI 95%: 0.070,0.714; $P = .012$) lower among those treated with PPr, compared with STPr. Figure 2 shows the predicted probabilities of CHA according to the effect modification found between prophylaxis and haemarthrosis status.

3.6 | Sensitivity and additional analyses

When comparing our interest association with models using haemarthrosis and annual joint bleeding rate as depending variables we

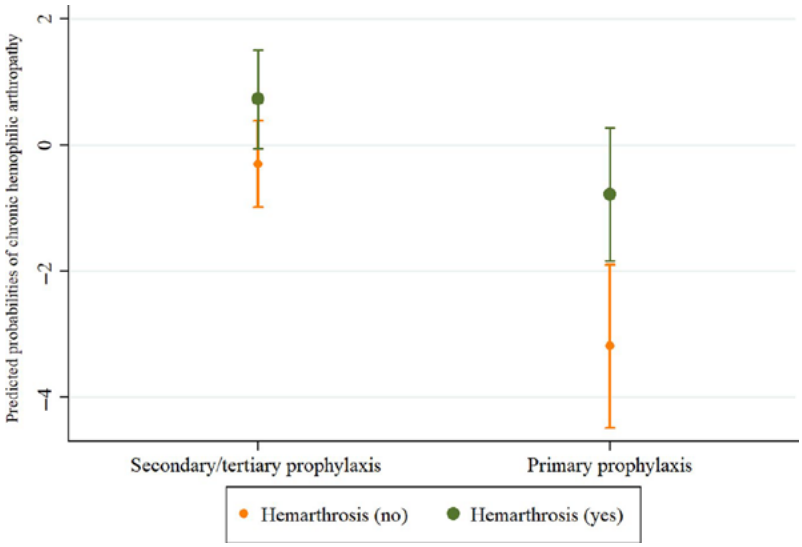

FIGURE 2 Effect modification of the association between primary prophylaxis and chronic haemophilic arthropathy by haemarthrosis status in Colombian males with HB. The predicted probabilities of haemophilic arthropathy and their 95% confidence intervals as a result of the interaction model are shown. We evaluated the effect of prophylaxis (primary vs. secondary/tertiary) in people with and without clinically evident haemarthrosis

found consistency. Specifically, for haemarthrosis, association was inverse, but magnitude decreased importantly (OR = 0.703; CI 95%: 0.444, 1.114; *P* = .133). In the case of joint bleeding rate, we performed a log-transformed random-effect linear regression model in which, PPr was inversely associated with the number of joint bleed episodes although it was no longer significant (Coef= −5.980%; CI 95%: −22.440, 10.613; *P* = .103). On the other hand, when the analysis was restricted to men in PPr, we found a strong, direct and statistically significant association between presence of clinically evident haemarthrosis and CHA (OR = 20.780; CI 95%: 2.737, 157.727; *P* = .003).

4 | DISCUSSION

In Colombia, men with HB who received PPr have decreased the odds of CHA by 89.70%, compared with those under STPr. Furthermore, this strong effect was modified by the haemarthrosis status, finding a stronger decrease in CHA in men with PPr and without haemarthrosis than in those with haemarthrosis (94.43% vs. 77.94%, respectively). In terms of complications associated with HB, descriptive analysis showed that haemarthrosis and infectious complications were significantly lower in PPr group than in STPr. Although frequency of high-titre inhibitors was lower in PPr, differences were no statistically significant.

The effect of prophylaxis on joint damaged has been widely studied in haemophilia A, especially in paediatric population[20] and recently in adolescents and adults with consistent protective results.[16,24,25] However, the effect of prophylaxis in haemophilia B has been less evaluated, despite being the second most frequent form of haemophilia, most evidence comes from a small number of patients with HB, enrolled in studies conducted predominantly in haemophilia A. Another aspect to consider is the outcome definition due to most studies have used some predictors of CHA such as haemarthrosis or limited joint range of motion.[6]

Considering the above, comparison of our findings is limited. The inverse association between PPr and CHA was also reported in a systematic review where prophylaxis was associated with fewer joint bleeding episodes in people with haemophilia A or B, and therefore with better joint function, compared to on-demand treatment.[26] A retrospective cohort also found that both short-term (joint bleeds/year) and long-term (CHA prevalence) outcomes were significantly lower in patients under prophylaxis, compared with on-demand treatment.[27]

Evidence from clinical trials also supports the superiority of any prophylaxis type for preventing joint bleeds and damage in people with HB, with dramatic reductions ranging between 83% and 91% administering long-acting clotting factor IX, mainly (28-30). These findings are especially relevant in developing countries such as Colombia, where most therapies are standard-acting.

Protective effect of PPr can be explained by different mechanisms. From a biological perspective, administration of PPr, following the goal proposed by international treatment guidelines based on personalized medicine[1] prevents CHA through the control of its most important predictor: haemarthrosis. It is well established that recurrent joint bleeds increase haemoglobin release which leads to iron depositions in the joint[8,31]; even a single joint bleed can have devastating effects on joint structure and functioning.[32] Vascular changes are irreversible, even after the first bleed; in fact, susceptibility to new bleedings increases. Indeed the role of PPr is crucial for stopping their progression, promoting tissue recovering and improving joint movement which result in a more active lifestyle and a significant reduction of irreversible damage.[6,9,33]

Biological mechanisms place haemarthrosis both, as a precursor and as an intermediate event that speeds up the joint damage. In fact, this assumption was evident in our results because presence

of haemarthrosis itself increased the odds of CHA and also it was identified as an effect modifier in the interest association.

Despite PPr is considered as the preferred therapeutic approach in people with severe HB for maintaining a moderate phenotype and the prevention of joint bleeds,[6] we found a no statistically significant lower frequency of PPr in men with severe HB. This could be explained because the use of PPr in the country started around 2010 as the standard of care for patients with severe haemophilia, before it was not available mainly due to administrative barriers from payers. In order to that, the prescription of PPr is expected to increase with a longer follow-up, taking into account that PPr is currently covered by the health system.

Regarding to clinical manifestations and other complications, in descriptive analyses we found a lower prevalence of haemarthrosis and infectious diseases in PPr related to STPr. Clinical trials have compared annualized joint bleeding rates according to replacement treatments, founding dramatic reductions ranging from 13.6 to 28.7 with on-demand to 0.0 to 3.5 in patients with prophylaxis.[28-30] Biological mechanism for explaining those differences is basically the same as for CHA. Association between prophylaxis and infectious diseases has not been studied. However, results from an observational study in a Chinese haemophilia centre, where almost 100% of patients were under on-demand treatment, showed a higher seroprevalence of HBV (3.0%) and HCV (7.0%) than in our study. Nevertheless, we classified HBV and HCV based on medical records and it should be underestimated.

The effect of prophylaxis on inhibitor development is one of the most concerning aspects in haemophilia therapy.[6,34] This association is still unknown in HB, but recent studies suggest that inhibitors susceptibility is more given by genetic factors which confer a personal risk profile.[35] Despite we found a comparable prevalence of inhibitors among men treated with PPr or STPr, further studies are required to establish a robust epidemiological association.

4.1 | Strengths and limitations

The current analysis has important strengths, including the high completeness of the CRHOC (almost 96% of Colombian population affiliated to the health system), which provides the closest approach to the total of men living with HB nationwide and it is the most efficient method to explore associations in rare diseases such as HB in a real-world setting. It also limits selection bias and increases external validity of our findings. Prospective information recording and analysis guarantee temporality of association.

Otherwise, there were several limitations that should be considered when interpreting the results of our study. The major limitation is the dichotomizing of the CHA due to the nature of the information reported to the registry for that variable, which only allowed to establish its clinical presence or absence, reason why the outcome of this study was defined as a dichotomous variable. Therefore, it was not possible to identify differences in the association by severity, which is important taking into account that CHA is a degenerative and highly variable status. Since register data only allow the adjustment for some variables, unmeasured confounding at the expense of non-available characteristics such as socio-economic status, education level, physical activity, diet and body mass index cannot be ruled out. Despite the CRHOC has implemented a rigorous data monitoring process, there is heterogeneity in variable measurement process that can lead to non-differential misclassification of both, exposition and outcome, in which case, the association goes towards the null value. Regards to analysis, although it was an unbalanced panel, we can assume that missing data were randomly distributed, because data recording process was independent of the research question. Besides, effect measures obtained from regression models using multiple imputed data did not change significantly, including stratified and interaction models.

Finally, it is important to recognize that CRHOC participants with prophylaxis are young and age could play an important role to explain our results and limit the external validity.

5 | CONCLUSIONS

We found an inverse, strong and statistically significant association between PPr and CHA in Colombian men living with HB. Comparing with STPr, in men treated with PPr the odds of CHA decreased by 89.70%. This relation was consistent in stratified analyses by haemarthrosis status and severity. Furthermore, we observed a significant effect modification by haemarthrosis status, identifying a stronger inverse association among men without haemarthrosis. We also found an inverse association between PPr and some CHA predictors such as haemarthrosis and joint bleeding rate. Our findings are consistent with prior evidence, mostly provided by clinical trials and demonstrate that PPr also has a protective effect in a real care setting, which supports the need of policy planning actions focused on increasing prophylaxis coverage and individualizing prescription, especially in people with early joint damage, in order to enhance prophylaxis benefits. Further population-based studies are required for a better understanding of differential effect of PPr according to its dosage and frequency in people with HB. Also, it is important to explore the association taking into account the variability of CHA, expressed by its severity.

DISCLOSURES

All authors declare no conflict of interest. This article is an original research work, and all authors have seen and approved the final version of the submitted manuscript. We declare that it has not been published before and not being considered for publication in a different journal.

AUTHOR CONTRIBUTIONS

The analyses were performed by JAHV and supervised by AMV. The first draft of the manuscript was written by JAHV and reviewed by

AMV and LA. AL and MHS wrote about the clinical aspects to support the discussion, and they reviewed all the document. All authors approved the final version.

ETHICAL APPROVAL

Conforming to the information nature, this study has no risk for participants. Information was collected and analysed following the international standards, and national regulations (Resolution 8430 of 1993, stated by the Colombian Health Ministry) for conducting human research. Confidentiality was guaranteed throughout the information processing (reporting, managing, analysis and publication). In order to achieve the above and in compliance with the Law 1581 of 2012, which stated conditions for protecting personal data in Colombia, all records were anonymized before the analysis. Furthermore, access to data was restricted to the research team and the results only can be used for approved research or academic purposes.

INFORMED CONSENT

Conforming to the information nature, this study has no risk for participants and informed consent or ethics approval was not required according to the national regulations (Resolution 8430 of 1993, stated by The Colombian Health Ministry) for conducting human research.

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PARTICIPACIÓN EN EVENTOS CIENTÍFICOS – PRESENTACIÓN DE POSTERS Y PONENCIAS ORALES

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PARTICIPACIÓN EN EVENTOS CIENTÍFICOS – PRESENTACIÓN DE POSTERS Y PONENCIAS ORALES

ERC y precursoras

Título del poster	Autores	Evento	Ámbito	Tipo	Objetivo	Principales hallazgos	Enlace para consultar el iPoster
El control de los factores de riesgo en pacientes con hipertensión arterial y diabetes mellitus tipo 2 en la región Pacífica colombiana	Adalberto Quintero, Miguel Urina-Triana, Ana Maria Valbuena-García, Alejandro Bryon, Luis Alberto Soler, Lizbeth Acuña-Merchán	XXVIII Congreso Colombiano de Cardiología y XVII Congreso SISIAC	Nacional	Póster	Describir el control y el logro de metas de los factores de riesgo en la población hipertensa y diabética de la región Pacífica durante el periodo de reporte 2019.	· Las prevalencias de hipertensión y diabetes fueron de 8,36% y 2,79%, respectivamente. · El 30,10% de los hipertensos tuvo cifras tensionales <130/80 mmHg. · El 34,90% de los diabéticos tuvo HbA1C <7%. · El IMC promedio fue de 27,72 (DE±5,17). · El 67,61% no cumplieron la meta de LDL. · Las concentraciones de LDL más elevadas se observaron en Chocó y las más bajas en el Valle del Cauca. · Existe una alta variabilidad de la HbA1C en los departamentos que componen la región, según la edad, principalmente marcada antes de los 50 años. · Valle del Cauca fue el departamento con la mayor proporción de hipertensos con cifras tensionales normales.	Link CAC
El control de los factores de riesgo en pacientes con hipertensión arterial y diabetes mellitus tipo 2 en la región Caribe colombiana	Adalberto Quintero, Miguel Urina-Triana, Ana Maria Valbuena-García, Alejandro Bryon, Luis Alberto Soler, Lizbeth Acuña-Merchán	XXVIII Congreso Colombiano de Cardiología y XVII Congreso SISIAC	Nacional	Póster	Describir el control y el logro de metas de los factores de riesgo en la población hipertensa y diabética de la región Caribe durante el periodo de reporte 2019.	· Las prevalencias de hipertensión y diabetes fueron de 7,82% y 2,21%, respectivamente. · El 31,14% de los hipertensos tuvo cifras tensionales <130/80 mmHg. · El 35,14% de los diabéticos tuvo HbA1C <7%. · El IMC promedio fue de 27,11 (DE±5,66). · El 63,98% no cumplieron la meta de LDL. · Las concentraciones de LDL más elevadas se observaron en La Guajira y las más bajas en Atlántico y Sucre. · El promedio de HbA1C fue significativamente mayor en Córdoba en comparación con la región y los demás departamentos. · Sucre fue el departamento con la menor proporción de hipertensos con cifras tensionales normales.	Link CAC
El control de los factores de riesgo en pacientes con hipertensión arterial y diabetes mellitus tipo 2 en Bogotá, D.C.	Adalberto Quintero, Miguel Urina-Triana, Ana Maria Valbuena-García, Alejandro Bryon, Luis Alberto Soler, Lizbeth Acuña-Merchán	XXVIII Congreso Colombiano de Cardiología y XVII Congreso SISIAC	Nacional	Póster	Describir el control y el logro de metas de los factores de riesgo en la población hipertensa y diabética en Bogotá, D.C. durante el periodo de reporte 2019.	· Las prevalencias de hipertensión y diabetes fueron de 9,47% y 2,92%, respectivamente. · El 38,10% de los hipertensos tuvo cifras tensionales <130/80 mmHg. · El 40,24% de los diabéticos tuvo HbA1C <7%. · El IMC promedio fue de 27,94 (DE±5,11). · El 69,15% no cumplieron la meta de LDL. · El promedio de HbA1C según la edad fue similar en los hombres y las mujeres. · No se observaron diferencias en las cifras de presión arterial según el sexo.	Link CAC

PARTICIPACIÓN EN EVENTOS CIENTÍFICOS – PRESENTACIÓN DE POSTERS Y PONENCIAS ORALES

ERC y precursoras (continuación)

Título del poster	Autores	Evento	Ámbito	Tipo	Objetivo	Principales hallazgos	Enlace para consultar el iPoster
El control de los factores de riesgo en pacientes con hipertensión arterial y diabetes mellitus tipo 2 en la región Central de Colombia	Adalberto Quintero, Miguel Urina-Triana, Ana Maria Valbuena-García, Alejandro Bryon, Luis Alberto Soler, Lizbeth Acuña-Merchán .	XXVIII Congreso Colombiano de Cardiología y XVII Congreso SISIAC	Nacional	Póster	Describir el control y el logro de metas de los factores de riesgo en la población hipertensa y diabética en la región Central durante el periodo de reporte 2019.	· Las prevalencias de hipertensión y diabetes fueron de 9,71% y 2,99%, respectivamente. · El 35,83% de los hipertensos tuvo cifras tensionales <130/80 mmHg. · El 37,91% de los diabéticos tuvo HbA1C <7%. · El IMC promedio fue de 28,00 (DE±5,86). · El 61,20% no cumplieron la meta de LDL. · Las concentraciones de LDL más elevadas se observaron en Caquetá y las más bajas en Antioquia. · El promedio de HbA1C fue significativamente mayor en Caquetá. · Caquetá fue el departamento con la menor proporción de hipertensos con cifras tensionales normales.	Link CAC
El control de los factores de riesgo en pacientes con hipertensión arterial y diabetes mellitus tipo 2 en la región Oriental de Colombia	Adalberto Quintero, Miguel Urina-Triana, Ana Maria Valbuena-García, Alejandro Bryon, Luis Alberto Soler, Lizbeth Acuña-Merchán	XXVIII Congreso Colombiano de Cardiología y XVII Congreso SISIAC	Nacional	Póster	Describir el control y el logro de metas de los factores de riesgo en la población hipertensa y diabética en la región Oriental durante el periodo de reporte 2019.	· Las prevalencias de hipertensión y diabetes fueron de 6,94% y 2,22%, respectivamente. · El 35,83% de los hipertensos tuvo cifras tensionales <130/80 mmHg. · El 32,60% de los diabéticos tuvo HbA1C <7%. · El IMC promedio fue de 28,00 (DE±5,86). · El 68,12% no cumplieron la meta de LDL. · Las concentraciones de LDL más elevadas se observaron en Meta y las más bajas en Santander. · El promedio de HbA1C fue significativamente mayor en Meta. · Cundinamarca fue el departamento con la mayor proporción de hipertensos con cifras tensionales normales.	Link CAC
El control de los factores de riesgo en pacientes con hipertensión arterial y diabetes mellitus tipo 2 en la región "Otros departamentos" de Colombia	Adalberto Quintero, Miguel Urina-Triana, Ana Maria Valbuena-García, Alejandro Bryon, Luis Alberto Soler, Lizbeth Acuña-Merchán .	XXVIII Congreso Colombiano de Cardiología y XVII Congreso SISIAC	Nacional	Póster	Describir el control y el logro de metas de los factores de riesgo en la población hipertensa y diabética en la región "Otros departamentos" durante el periodo de reporte 2019.	· Las prevalencias de hipertensión y diabetes fueron de 3,18% y 1,08%, respectivamente. · El 40,76% de los hipertensos tuvo cifras tensionales <130/80 mmHg. · El 21,40% de los diabéticos tuvo HbA1C <7%. · El IMC promedio fue de 28,50 (DE±7,97). · El 71,05% no cumplieron la meta de LDL. · Las concentraciones de LDL más elevadas se observaron en Guaviare y las más bajas en Vaupés. · El promedio de HbA1C fue significativamente mayor en Guainía. · Guainía fue el departamento con la menor proporción de hipertensos con cifras tensionales normales.	Link CAC

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ERC y precursoras (continuación)

Título del poster	Autores	Evento	Ámbito	Tipo	Objetivo	Principales hallazgos	Enlace para consultar el iPoster
Variabilidad regional del nivel de hemoglobina glicosilada en la población diabética, Colombia 2018	Adalberto Quintero, Miguel Urina-Triana, Ana Maria Valbuena-García, Alejandro Bryon, Luis Alberto Soler, Lizbeth Acuña-Merchán	XXVIII Congreso Colombiano de Cardiología y XVII Congreso SISIAC	Nacional	Ponencia oral	Describir la variabilidad regional de la hemoglobina glicosilada en la población diabética colombiana durante el 2018.	· En el 62,19% de las personas con diabetes, informadas al registro de la CAC se han reportado los niveles de HbA1C. · La media de HbA1C fue de 7,35% (DE±1,91). · El objetivo de la ADA para el control glicémico fue cumplido en el 54,25% de las mujeres y el 53,04% de los hombres. · En la región "Otros departamentos" se observó la mediana de HbA1C más elevada; la más baja se estimó en la región Central, donde más del 70% estaban afiliados al régimen contributivo. · En Amazonas y Guainía se observaron las medianas más altas de HbA1C. · En general, los niveles de HbA1C fueron mayores en los hombres, los afiliados al régimen subsidiado y, residentes en la región "Otros departamentos".	Link CAC
Risk Management Assessment of Provider-Insurer Binomial in Hemodialysis Patients, Colombia 2019	Ana Maria Valbuena-García, Alejandro Bryon, Andrés García-Sierra, Lizbeth Acuña-Merchán, Nathaly Ramírez	ISPOR EUROPE 2020	Internacional	Póster	Evaluar los resultados de los indicadores de gestión del riesgo en el binomio asegurador-prestador en las personas con hemodiálisis.	· A nivel nacional, los prestadores atienden un promedio de 4.393 pacientes con hemodiálisis. · En los cinco indicadores de gestión del riesgo seleccionados, el promedio de cumplimiento en los prestadores fue del 76,52%, con una alta variabilidad entre ellos. · La probabilidad de alcanzar las metas establecidas en los indicadores de gestión del riesgo depende del número de pacientes gestionados por el binomio asegurador-prestador. · El rendimiento del prestador es fundamental para garantizar el cumplimiento de los indicadores de gestión del riesgo a nivel del asegurador.	Link CAC

VIH

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VIH

Título del poster	Autores	Evento	Ámbito	Tipo	Objetivo	Principales hallazgos	Enlace para consultar el iPoster
Cost-effectiveness study of the use of Dolutegravir compared with Efavirenz in combination with Tenofovir and Emtricitabine, as the first line for the care of patients newly diagnosed with HIV or who have not started antiretroviral therapy in Colombia	Julieth Carolina Castillo, Ana Maria Valbuena-García, M Romero, G Acero, Lizbeth Acuña-Merchán	ISPOR EUROPE 2020	Internacional	Póster	Determinar la costo-efectividad del Dolutegravir en comparación con el Efavirenz en combinación con Tenofovir y Emtricitabina en los casos nuevos con VIH/sida.	· El costo total del tratamiento fue de US$2,71 millones para el Dolutegravir y de US$3,32 millones para el Efavirenz. · El ahorro estimado fue de US$616 mil. · Para el resultado de supresión viral, la razón de costo-efectividad fue mayor para el Dolutegravir en comparación con el Efavirenz. · La razón de costo efectividad por años de vida salvados fue de US$2,59 millones y de US$491 mil por discontinuidad.	Link CAC

CÁNCER

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Cáncer

Título del poster	Autores	Evento	Ámbito	Tipo	Objetivo	Principales hallazgos	Enlace para consultar el iPoster
Delays in time to treatment initiation and its associated factors in Colombian women with cervical cancer: A cross-sectional analysis	Juliana Hernández Vargas, Paula Ramírez, Ana Maria Valbuena-García, Lizbeth Acuña-Merchán, Jaime A. González	ISPOR EUROPE 2020	Internacional	Póster	Evaluar los factores asociados a las demoras para iniciar el tratamiento en los casos nuevos de cáncer de cérvix durante el periodo de reporte 2019.	· De las 1.249 mujeres incluidas, el 26,98% fueron diagnosticadas in situ y el 40,11% con enfermedad localmente avanzada. associated factors in Colombian women with cervical cancer: A cross-sectional analysis · Las demoras fueron significativamente mayores en la región Pacífica en comparación con Bogotá. · Las mujeres afiliadas al régimen subsidiado tuvieron un tiempo de espera mayor que las del contributivo.	Link CAC
Incidence and distribution of tumor STAGE of melanoma in adults by sex. Colombia, 2019.	Ana Milena Gil, Juliana Hernández Vargas, Paula Ramírez, Ana Maria Valbuena-García, Lizbeth Acuña-Merchán	ISPOR EUROPE 2020	Internacional	Póster	Evaluar las diferencias en la proporción de casos nuevos reportados y el estadio al diagnóstico en el melanoma según el sexo.	· La PCNR ajustada por la edad de melanoma fue de 2,69 casos (IC 95%: 2,42-2,97) por 100.000 adultos. · No se observaron diferencias significativas en la PCNR según el sexo. · El 35,02% y el 24,42% de los casos nuevos se diagnosticaron in situ y en estadios tempranos, respectivamente.	Link CAC
Concordancia de registros nacionales de cáncer infantil y su uso en la identificación de clústeres espacio-temporales en Colombia en el periodo 2009-2017	Lizbeth Acuña-Merchán, Marcela Rojas, Paula Ramírez, Laura Rodríguez-Villamizar		Nacional	Póster	Evaluar la concordancia de la información del sistema de vigilancia en salud pública (SIVIGILA) para cáncer y el Registro Nacional de Cáncer (RNC) que gestiona la cuenta de alto costo (CAC) y usar esta información para la identificación de clústeres de cáncer infantil (CI) en Colombia en el periodo 2009-2017	· Se identificaron 1.394 casos incidentes de CI en menores de 15 años en 2016, de los cuales 1.206 fueron reportados al SIVIGILA (86,50%). · Del total, se confirmaron 1.039 casos (74,5%) como incidentes. · Por parte de la CAC y las EAPB, del total de casos de SIVIGILA, 54 casos (3,80%) fueron descartados, 119 casos (8,50%) no fueron encontrados en las aseguradoras reportadas y 62 casos (4,40%) eran no asegurados por lo cual no pudieron ser confirmados por las entidades. · Se identificaron 684 casos reportados al SIVIGILA 2016 que no estaban en el RNC. · Usando la información ajustada del SIVIGILA 2009-2017, la prueba espacial de Kuldorff identificó cinco clústeres de CI en el periodo 2014-2017 y siete clústeres de leucemias agudas en el periodo 2009-2017.	Publicado como suplemento en la Revista Colombiana de Cancerología: Link CAC

HEMOFILIA

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Hemofilia

Título del poster	Autores	Evento	Ámbito	Tipo	Objetivo	Principales hallazgos	Enlace para consultar el iPoster
Morbidity, mortality and risk management indicators in hemophilia: Third payer in Colombia	Andrés García-Sierra, Lizbeth Acuña-Merchán, Ana Maria Valbuena-García	Presentado en dos eventos: "ISPOR EUROPE 2020" y "Sixth Global Symposium on Health Systems Research 2020"	Internacional	Póster	Analizar la relación entre los indicadores de gestión del riesgo en hemofilia y la morbimortalidad en las personas con hemofilia según el régimen de afiliación	· La prevalencia y la mortalidad de la hemofilia fueron 5,00 casos por 100.000 afiliados y 3,50 casos por 1.000.000 de afiliados, respectivamente. · La proporción de personas en profilaxis con artropatía hemofílica crónica fue directamente proporcional al número de afiliados, la prevalencia y la mortalidad. · La proporción de pacientes atendidos por equipo multidisciplinario se asoció inversamente con la mortalidad. · La tasa de sangrados se asoció con un aumento significativo de la mortalidad.	Link CAC
Primary prophylaxis was associated with lower arthropathy in Colombian men with hemophilia B: A Longitudinal analysis (2015-2019)	Adriana Linares, Maria Helena Solano, Juliana Hernández Vargas, Ana Maria Valbuena-García, Lizbeth Acuña-Merchán	WFH Virtual Summit 2020	Internacional	Póster	Evaluar la asociación entre la profilaxis primaria (PP) y la artropatía hemofílica crónica (AHC) en hombres con hemofilia B en Colombia durante el periodo 2015-2019.	· La prevalencia de AHC en la línea basal fue del 36,84%. · La PP fue prescrita al 37,85%, con una mediana de la dosis similar a la profilaxis secundaria y terciaria. · La PP disminuyó significativamente la posibilidad de presentar AHC en 89,70%, en comparación con la profilaxis secundaria o terciaria. · Esta reducción fue mayor en la hemofilia B leve o moderada.	Link CAC

TRANSVERSAL - ENFERMEDADES DE ALTO COSTO

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Transversal Enfermedades de alto costo

Título del poster	Autores	Evento	Ámbito	Tipo	Objetivo	Principales hallazgos	Enlace para consultar el iPoster
Healthcare System IMPACT of High-Cost Diseases Metrics in Colombia	Andrés García Sierra, Lizbeth Acuña Merchán, Ana Maria Valbuena García, Nathaly Ramírez	ISPOR EUROPE 2020	Internacional	Póster	Describir la selección y adopción de los indicadores de gestión del riesgo en las enfermedades de alto costo en Colombia.	· Entre 2010 y 2020, se han desarrollado 15 consensos basados en la evidencia. · Más de 280 indicadores han sido propuestos para evaluar la gestión del riesgo que realizan los aseguradores y prestadores en el país. · El porcentaje de personas con diabetes controladas ha incrementado de 33,40% en el 2015 a 56,00% en el 2019. · La proporción de personas con artropatía hemofílica crónica en profilaxis aumentó de 46,20% en el 2015 a 60,30% en el 2020. · El estudio de transmisión materno-fetal en los niños menores de 6 meses ha incrementado de 23,50% en el 2012 a 98,10% en el 2019. · El promedio de espera para acceder al primer tratamiento disminuyó de 42 días en el 2016 a 29 días en el 2018. · La proporción de pacientes con artritis recibiendo simultáneamente metotrexate y ácido fólico aumentó de 43,90% en el 2016 a 90,80% en el 2019.	Link CAC

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