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ARTÍCULO ORIGINAL

Spatiotemporal Analysis of Childhood Acute Lymphocytic Leukemia in Cali, Colombia, 2000-2015

Análisis espacio-temporal de leucemia linfoblástica aguda pediátrica en Cali, Colombia, 2000-2015

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Abstract

Introduction: Leukemia is the most common type of cancer in children both in the world and in Colombia. Childhood acute lymphocytic leukemia (C-ALL) represents 30% of pediatric cancers. The available evidence from studies on the presence of clusters of C-ALL is inconclusive.

Objective: To determine the spatiotemporal distribution of C-ALL in the city of Cali during 2000-2015.

Methods: Cases of C-ALL recorded between 2000-2015 in the city of Cali, Colombia, were included. Census sectors and the population projected by the DANE were used for spatial analyses. Adjusted rates, Moran's index and the Getis-Ord index were calculated. Census sectors-rate maps, heat maps, optimized hot-spot maps, kernel density maps, and Kulldorff's circular spatial scan maps were constructed.

Results: Kulldorff's spatial and spatiotemporal analysis and hot-spot analysis identified a stable cluster. The independent analysis yielded two clusters with statistical significance.

Conclusion: The results suggest the presence of two C-ALL clusters in the city of Cali.

Keywords: Cancer, childhood cancer, leukemia, acute lymphocytic leukemia, children, clusters, Colombia, spatial analysis, Moran's index

Resumen

Introducción: Las leucemias son los cánceres más comunes en niños, tanto en el mundo como en Colombia. El 30% del cáncer infantil corresponde a la leucemia linfoblástica aguda (LLA). La evidencia de estudios sobre la presencia de conglomerados espacio-temporales de las leucemias infantiles no es concluyente.

Objetivo: Determinar la distribución espacio-temporal de la LLA infantil en la ciudad de Cali, entre 2000 y 2015.

Métodos: Se incluyeron casos de LLA infantil registrados entre el año 2000-2015, en la ciudad de Cali, Colombia. Se usaron sectores censales y la población proyectada del DANE para los análisis espaciales. Se calcularon: tasas ajustadas, índice de Moran e índice de Getis-Ord. Se construyeron mapas de tasas-sectores censales, de calor, de puntos calientes optimizados, de densidad de Kernel y de escaneo circular de Kulldorff.

Resultados: Se encontró un conglomerado estable para los análisis espaciales por Kuldorff y de puntos calientes. El análisis independiente arrojó dos conglomerados con significancia estadística. Esto fue corroborado por el índice de Moran, que determinó un patrón general agregado de los casos de LLA infantil para casos y tasas.

Conclusión: Los resultados sugieren la presencia de dos conglomerados de LLA infantil en la ciudad de Cali.

Palabras clave: Medicina Nuclear, Neoplasia de la tiroides, Infraestructura, Instituciones de Salud, Radiofármacos.

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Introduction

ELeukemia is the most common childhood cancer (CC) worldwide (1). After leukemia, the most common types of cancer in children under 15 years of age are tumors of the central nervous system and lymphomas. The incidence rate of these three types of CC varies between regions and within regions by sex, age, and ethnic group (2). Leukemia is more frequent in males, the subgroup aged 0-4 years, and the Latino population. Globally, leukemias represent approximately 30% of all cancers in children under 15 (3).

In Colombia, leukemias are the most common cancer among children under 15 years of age, followed by lymphomas, malignant central nervous system tumors, neuroblastomas, and retinoblastomas (4). The most frequent childhood neoplasms in Colombia are similar to those worldwide (5), with an age-adjusted annual incidence rate of 149.6 per million for the 0-14 age group and 58.4 per million for leukemia between 1992 and 2013 (2); 32.9% of CCs in Colombia are acute lymphocytic leukemia (ALL), 15% are central nervous system tumors, and 8.9% are non-Hodgkin lymphomas (6). In Colombia, for 2015, the incidence rate of childhood ALL (C-ALL) was estimated at 57.9 per million, with a mortality rate of 17.3 per million in children under 18 years of age (7). For 2017, the estimated prevalence of CC was higher in eight of the country's 32 departments (national prevalence: 343.4, high-prevalence departments: 405.1-561.5), among which Valle del Cauca occupied the third place. For C-ALL, Valle del Cauca was the department with the highest prevalence (204.5 per million <18-year-old) (6).

The 5-year survival of childhood leukemia in Colombia was estimated at approximately 55% between 2005 and 2009, compared to 85% in the United States in the same period (8). In Cali, the 5-year overall survival for C-ALL ranged between 72% and 46% for children with private or public insurance (9). According to the Global Burden of Disease Study 2017, the age-standardized disability-adjusted life-years (DALY) rate for CC in Colombia belong to the higher quintile (81-100%), and one-fourth are due to ALL. This national indicator is comparable to some African and Southeast Asian countries and superior to countries in North America and some European countries, which are in the first and second quintiles, respectively (10). In Valle del Cauca, the adjusted mortality was 6.8 per million <18-year-old), which was the ninth place in Colombia (6). Considering its incidence and mortality in the country, C-ALL is considered an event of public health interest and has been under mandatory surveillance in Colombia since 2008 (6).

Spatial analysis in cancer study is used to describe and understand the geographic patterns of its incidence, keeping in mind that each type of cancer corresponds to an etiologically different event. The study of conglomerates or geographic clusters is a type of spatial analysis that uses the specific location of cases or their density in a specific area to determine whether there is an agglomeration of cases that exceeds the expected rate by chance (11). Spatial cluster studies are important to characterize risk according to geographic conditions. They are helpful as an exploratory analysis to establish hypotheses of possible causal relationships, but by themselves, they do not determine causality. Controlling for other variables at the same temporal and spatial scales is usually done as an attempt to isolate the effect of space and time. Evidence from studies on the presence of spatiotemporal clusters of childhood leukemia is inconclusive. In a systematic review and meta-analysis on this topic, Kreis et al. (12) reported that one in nine studies showed significant evidence of the presence of clusters. In children under 5 years of age, clusters were present when the place of residence at the time of diagnosis was used, but not when using the place of residence on the date of birth. For children older than 5, the presence of clusters was very weak. Several studies have identified clusters of C-ALL among the total population, and one out of seven found clusters among children younger than 5, but no evidence was found for children older than this age. None of the studies that provided information for this evidence were from Latin American countries, given the limited information available on these types of studies in the region.

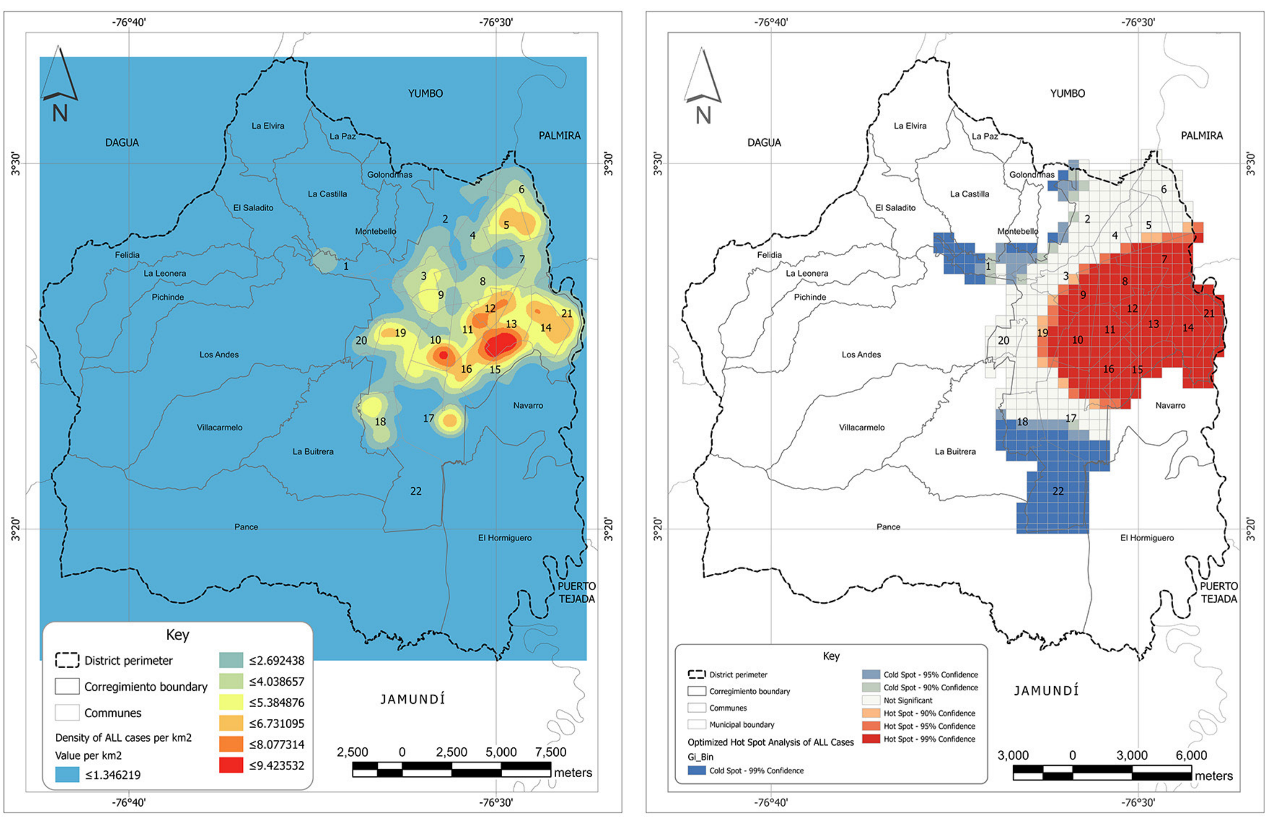
A study analyzed the presence of C-ALL clusters in Colombia between 2009 and 2017, using information from the public health surveillance system for CC and municipalities as a unit of spatial analysis (13). Five cluster zones were identified in the country, one of which was located around the city of Cali. This finding highlighted the need to examine the distribution of C-ALL at a smaller spatial scale in Cali to provide health authorities with specific details on locations and potential explanations for clusters of incident cases that might help guide preventive CC programs. Thus, this study aimed to determine the spatial distribution and explore the presence of C-ALL clusters in the municipality of Cali in the period 2000-2015, seeking to provide exploratory information as a starting point for a better characterization of the risk of developing ALL, related to geographic conditions, in the pediatric population of the city of Cali.

Materials and methods

Study location and population

The city of Cali is the capital of the department of Valle del Cauca, located in the southwest of Colombia (3°27′26″ N and 76°31′42″ W), near the Pacific coast, with an area of 564 km2 and a total population close to 2.5 million people and a pediatric population of 543,416 children under 14 years of age. It has an average altitude of 1,070 m and an average temperature of 24°C. The political-administrative distribution of the municipality of Cali consists of 22 communes in the urban area and 15 sectors in the rural area (14). The socioeconomic stratum in some communes is heterogeneous, which means that it is possible to find stratum one to six in the same commune.

The department of Valle del Cauca is among the five departments with the least monetary poverty in the country (15), with a multidimensional poverty index of 14.1-10.8 for 2018-2019 (16), occupying the fourth place in Colombia (17). The city of Cali, however, presents an important level of segregation of zones in conditions of poverty and marginality (18), particularly in the east and northwest zones of the city, with a tendency to worsen over time (19) (Figure 1).



The study population was a pediatric population, defined as children under 15 who habitually reside in the city of Cali. The pediatric population used as the denominator for the analyses corresponded to the population projected by the National Administrative Department of Statistics (DANE), based on the 2005 census (559,457; population estimated at the middle of the study period) (20). The unit of spatial analysis for clusters was census sectors defined by the DANE (21). Therefore, the population under 15 years of age for each census sector was estimated from the projected population of Cali between 2000 and 2015, using as the base population distribution by census sectors reported in the DANE 2005 census. The national 2018 census was not used because the study period spans more closely to the 2005 census (almost a mid-period year) and its annual projections; additionally, at the time of the study analysis, there were still several inconsistencies in terms of the estimated population by the 2019 census in Valle del Cauca, particularly in the city of Cali (22).

Cases of childhood acute lymphocytic leukemia

Information on confirmed C-ALL cases was obtained from the population-based Cancer Registry of Cali (RPC-Cali). All registered cases with a diagnosis date between January 1, 2000, and December 31, 2015, were included. The RPC-Cali is the oldest population-based cancer registry in Latin America, with standardized methods for information collection, analysis, storage, validation, and dissemination, which ensures data and procedure quality (23). Additionally, the RPC-Cali is validated by the International Agency for Research on Cancer.

From each C-ALL case, information was collected on sex, age, date of birth, date of diagnosis, and the census sector to which the patient belonged, based on the address or neighborhood of residence at the time of diagnosis recorded by the RPC-Cali. The socioeconomic stratum of the residence was assigned according to the predominant stratum in the census sector to which it belonged, using data provided by the Planning Department of the city of Cali.

The C-ALL cases were geocoded with latitude and longitude coordinates using an automated tool complemented by the Google Earth® tool. When an address was provided, a point was placed in the exact place on the map. When the address was not precise, the point was placed in the center of the block. Once the point of residence was identified, the corresponding census sector was assigned using DANE's cartography, the projection for Colombia in Custom Azimuth Equidistant mode, and the Datum WGS 1984 in ArcGIS 10.6.1 software developed by ESRI. This software's licensing was temporarily free of charge due to the worldwide emergency caused by COVID-19.

Spatiotemporal analysis

A descriptive exploratory analysis of incident cases of C-ALL was conducted that included the dimensions of space and time. C-ALL cases were described by year (time) and location (space). For the spatial exploratory study, an analysis of areas (incidence rate by census sectors) and points (cases) was carried out. The Moran's index (Moran's I) was calculated as a measure of spatial autocorrelation in the data, where the index values ranged from -1.0 to +1.0, with value 0 representing completely random patterns in the spatial distribution. For the spatial analysis by points, a "hot spot analysis was used, and for the spatial analysis by area, hypothesis tests of clustering were performed to assess the presence and location of clusters in the city.

For the spatial analysis by points, a kernel density map (or heat map) was constructed, where the density of C-ALL cases per km2 was estimated with a search radius of 1,226.5 m, which was automatically estimated by the algorithm of the ArcGIS Software (24). The Getis-Ord index and the optimized hot spot analysis (OHSA) were also estimated as indicators of the grouping of high and low values. The resulting z-scores and p-values indicate where high- or low-value features cluster spatially. For positive z-scores that are statistically significant, the larger the z-score, the more intense the clustering of high values (hot spot). For negative z-scores that are statistically significant, the smaller the z-score, the more intense the clustering of low values (cold spot). For the latter, a cell size of 524 m and an optimal distance band of 4,717 m were used. For the analysis of points (cases) and areas (rates), the ArcGIS software was used under temporary free licensing due to the worldwide emergency caused by COVID-19 (April-August 2020).

For the spatial analysis by area, the cumulative specific and direct age-standardized incidence rates of C-ALL were calculated by census sectors, using as "standard" population the projected population of Cali for 2008, corresponding to the mid-point year of the study period. The EPIDAT 4.2 program was used to calculate standardized rates. In this analysis, five census sectors were excluded because they had only one case and a very low estimated population, presenting therefore unstable rates. The standardized rates were used to construct a map with the distribution of rates classified into five categories, using a geometric interval classification method, due to the asymmetric distribution of census sector rates.

Kulldorff's circular spatial scan hypothesis test was used to detect spatial and spatiotemporal clusters. The geographic coordinates of the centroids of the 404 census sectors of Cali were calculated and weighted by population using census population data available on the DANE Geoportal (25). Kulldorff's circular spatial scan (26) evaluates the null hypothesis of the nonexistence of geographic clusters, that is, a random distribution of C-ALL cases (27), and from the centroid of each census sector, systematically evaluates whether the C-ALL risk is equal inside and outside the scanned circle (28). The parameters used were retrospective spatial and spatiotemporal analysis, Poisson probability modeling, and scanning for areas with high rates. Three population risk scenarios (10%, 25%, and 50%) were used to determine cluster stability. For all spatial analyses, data on patient age and residence at the time of C-ALL diagnosis were input into the free software SaTScan (https://www.satscan.org/).

Ethical aspects

Given that secondary databases obtained from the RPC-Cali records were used, the risk was classified as a minimum-risk investigation according to Article 11 of Resolution No. 008430 of 1993 of the Ministry of Health. The study was authorized by the RPC-Cali for use of information. The framework project titled "Identification of CC clusters and their relationship with fixed sources of air pollution in Colombia" was approved by the Ethics Committee of the Universidad Industrial de Santander, and this project had the approval of the Ethics Committee of the Universidad del Valle.

Results

During the years 2000-2015, 1,322 records of CC were identified in the population residing in the municipality of Cali, of which 469 (35.5%) corresponded to acute leukemia and 390 (83.1%) were confirmed cases of ALL. During the 16 years of the study, on average, 83 CC cases/year and 23 C-ALL cases/year were registered. The average specific annual incidence rate of C-ALL in Cali between 2000 and 2015 was 43.58 per million in children under 15 years. For the geographical analysis, 19 cases of C-ALL were discarded because they did not have an address or neighborhood that allowed georeferencing the case. Thus, for the geographical analysis, 371 cases of C-ALL were analyzed.

Characterization of the pediatric population

The average age was 6.1 ±4.1 years, with a median of 5 (interquartile range: 7). The data by age did not follow a normal distribution (asymmetry: 0.391, standard error: 0.124; and kurtosis: -1.008, standard error: 0.247). The data showed two peaks of cancer incidence by age, the highest at approximately 2-4 years (10.7%, 10.4%, and 11.5% for 2, 3, and 4 years, respectively), where the cumulative percentage reached 43.8%. The proportion of cases was slightly higher for males (52.5%) compared to females. The predominant socioeconomic stratum was 3, but the cumulative frequency of cases in strata 1, 2, and 3 was 85.6%, while stratum 6 corresponded to less than 1%.

Spatial analysis of C-ALL cases

A total of 98.7% of C-ALL cases were distributed in the urban area of Cali (Figure 1). In the heat map, 10 foci were observed. The most representative foci were those covering the south-east part of the city, including the communes 10, 13, and 16, with a density of ≤9.4 cases/km2, and the communes 11, 12, and 14, with a density of ≤8.1 cases/km2 (Figure 1A). The highest concentration of cases occurred in the eastern part of the city (red color in Figure 1a). The analysis of hot spots using OHSA corroborated this assessment and simultaneously identified several aggregates (Figure 1B). A strong grouping pattern of high values was shown (confidence level of 99%) in the eastern central part of Cali, which encompasses communes 7 (east) to 16 (south-east) and 21 (east). In the same figure, two additional and significant groups of low values are observed on the south part of the city in commune 22 and parts of communes 17 and 18, and in the hillside area on the north-west of the city in communes 1 and 2.

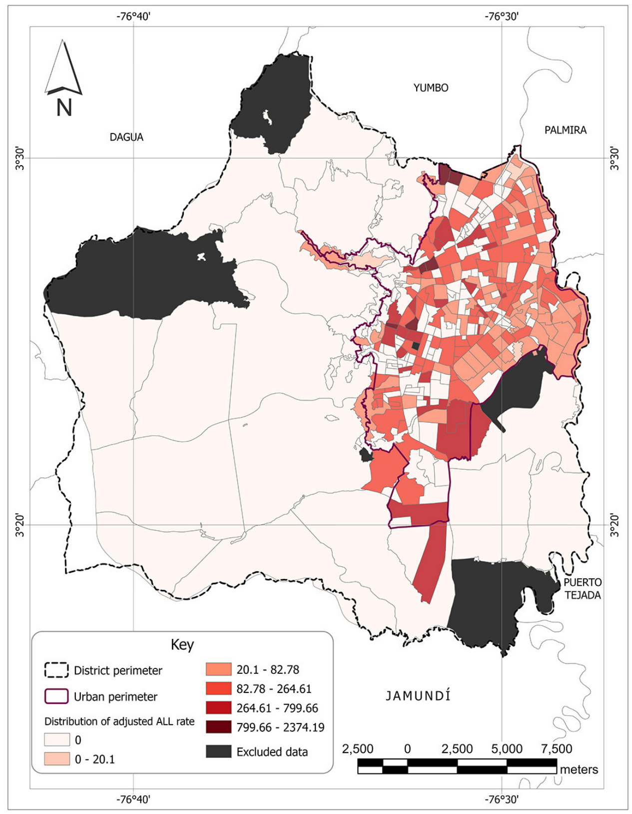
C-ALL cases showed an aggregated distribution pattern according to Moran's I (I=0.12 and p<0.001). A positive value of the index means that the spatial distribution of high and low values is more grouped than expected (nonrandom). The analysis of high/low clusters (Getis-Ord General G) showed that there were clusters with high values (G=0.0031 and p<0.01).

Spatial analysis of C-ALL by census sectors in Cali

As a complement to the point analysis (cases), an area analysis (census sectors) was carried out, which considered the population risk. Figure 2 shows the incidence rates of C-ALL in the census sectors adjusted for age and sex. There was a heterogeneity of rates in the city and four sectors with very high rates located in the northwestern region of Cali. Other census sectors with high rates were also observed, mainly towards the south end of the city. Most of the sectors with low rates were in the eastern zone. Fifty-four percent of the census sectors had no cases in the period evaluated, 0.74% had rates of 0.1-20.1, 17.1% had rates of 20.2-82.9, 18.8% had rates of 82.9-264.7, 6.4% had rates of 264.8-799.7, 1.5% had rates of 799.8-2,374.2, and 1.5% had rates of >2,374.3 (Figure 2).

Moran's I was 0.012 (p<0.001), which indicates a spatial autocorrelation in the distribution of rates. A similar result was obtained with the Getis-Ord general G-test for high values (G=0.004 and p<0.001).

Table 1 shows the results of the spatial analysis with Kulldorff's circular scan test using values of 10%, 25%, and 50% as the maximum limit. In all three scenarios, two clusters with statistical significance (Figure 3A in red) were identified. The first, in the central-western area of the city, had 17 observed cases distributed in a radius of 0.96 km with a relative risk (RR) of 7.27. This cluster is located at south of commune 19, including the neighborhoods of Tequendama, El Lido, and San Fernando (Figure 3A). The second cluster was in the southeastern zone, with 16 observed cases distributed in a radius of 7.27 km and an RR of 4.8. This area includes the Navarro garbage dump, and the south zone of the Aguablanca district (a socioeconomic deprivation area), and the development area of commune 17.



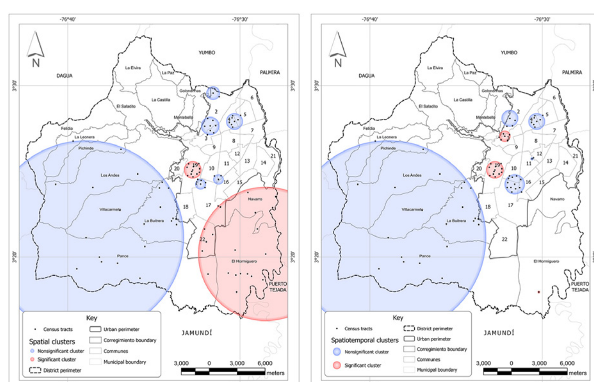


Table 1. Analysis of spatial clusters of C-ALL, Cali, 2000-2015

Population risk (%)	Clusters	Census areas	Radius (km)	Estimated population	Number of cases	Expected cases	RR	Likelihood ratio	*p*-value
10	1	12	0.96	3794	17	2.44	7.27	18.7653	0.0000019
	2	21	7.27	5285	16	3.46	4.80	12.1940	0.00092
	3	8	1.00	4305	11	2.76	4.07	7.0545	0.115
	4	22	10.53	110	2	0.07	28.47	4.7631	0.618
	5	7	0.60	4524	9	2.90	3.15	4.1356	0.819
	6	3	0.58	8471	13	5.44	2.44	3.8488	0.889
	7	2	0.75	184	2	0.12	17.00	3.7789	0.917
	8	8	0.92	6267	10	4.02	2.53	3.1789	0.949
25	1	12	0.96	3794	17	2.44	7.27	18.7653	0.0000027
	2	21	7.27	5385	16	3.46	4.80	12.1940	0.0012
	3	8	1.00	4305	11	2.76	4.07	7.0545	0.133
	4	22	10.53	110	2	0.07	28.47	4.7631	0.662
	5	7	0.60	4524	9	2.90	3.15	4.1356	0.845
	6	3	0.58	8471	13	5.44	2.44	3.8489	0.904
	7	2	0.75	184	2	0.12	17.00	3.7789	0.917
	8	8	0.92	6267	10	4.02	2.53	3.1789	0.987
50	1	12	0.96	3794	17	2.44	7.27	18.7653	0.000035
	2	21	7.27	5385	16	3.46	4.80	112.1940	0.0013
	3	8	1.00	4305	11	2.76	4.07	7.0545	0.145
	4	22	10.53	110	2	0.07	28.47	4.7631	0.674
	5	7	0.60	4524	9	2.90	3.15	4.1356	0.856
	6	2	0.75	184	2	0.12	17.00	3,7789	0.925
	7	8	0.92	6267	10	4.02	2.53	3.1789	0.987

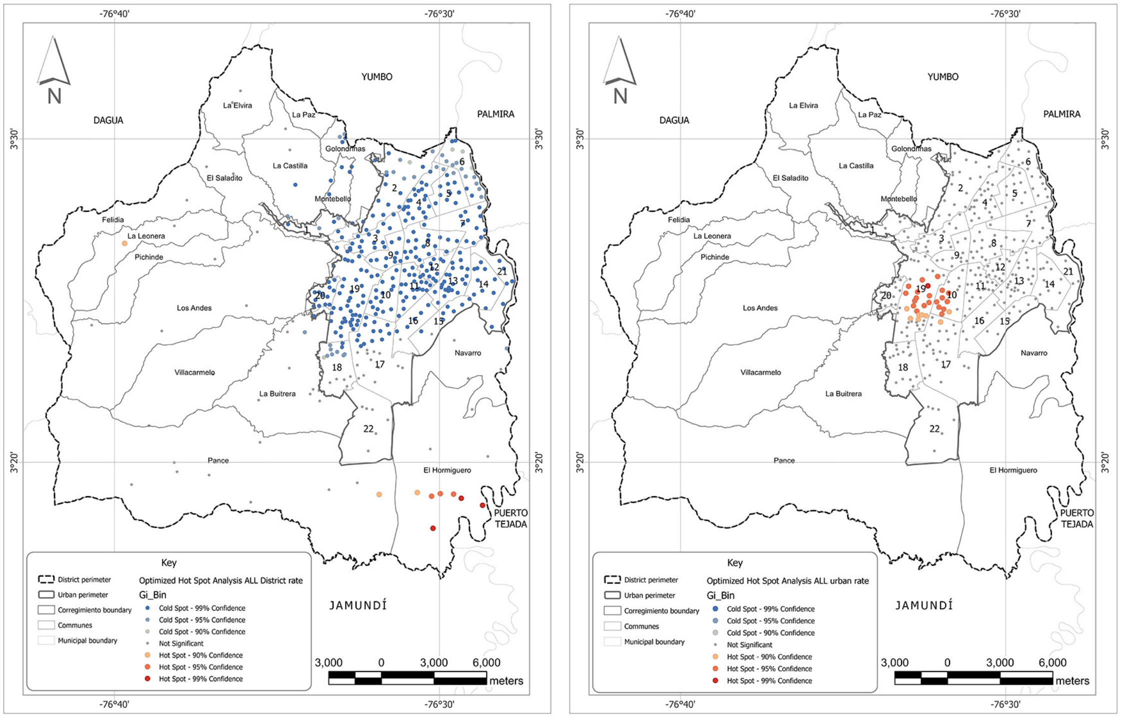
The spatiotemporal analysis detected the presence of two clusters for the three population risk scenarios (Table 2). Figure 3B shows the clusters with statistical significance when the population risk was set at 25%. Cluster one coincided with the first cluster identified in the spatial analysis, in the western part of the city and occurred over a sustained period (2001-2008). Cluster two was significant and had an extremely high relative risk; therefore, we consider it an artifact of having two cases and a very low population, resulting in an unstable calculated rate (Figure 3B, red dot to the southeast). Cluster three, which occurred between 2009 and 2010, was statistically significant and located on the northwest part of Cali, influenced by areas such as downtown, San Antonio, El Peñón, and Centenario in the exit to the “sea route” (Table 2, Figure 3B).

Table 2. Spatiotemporal cluster analysis of C-ALL, Cali, 2000-2015

Population risk (%)	Clusters	Census areas	Radius (km)	Estimated population	Number of cases	Expected cases	RR	Likelihood ratio	*p*-value	Time
10	1	12	0.96	3794	13	1.23	10.96	19.119603	0.00011	2001-2008
	2	1	0	5	2	0.0004	5,009.10	15.03291	0.0036	2004-2005
	3	6	0.63	2102	5	0.17	29.97	12.134681	0.041	2009-2010
	4	2	0.19	1827	4	0.22	18.64	7.896737	0.781	2000-2002
	5	8	0.92	6267	7	1.02	6.99	7.559828	0.869	2003-2006
	6	4	0.92	2251	5	0.45	11.26	7.52092	0.877	2000-2004
	7	13	1.11	19376	12	3.08	3.99	7.497572	0.880	2012-2015
	8	22	10.53	110	2	0.018	113.92	7.483056	0.881	2006-2009
25	1	12	0.96	3794	13	1.23	10.96	19.119603	0.00015	2001-2008
	2	1	0	5	2	0.0004	5,009.10	15.03291	0.0044	2004-2004
	3	6	0.63	2102	5	0.17	29.97	12.134681	0.048	2009-2010
	4	2	0.19	1827	4	0.22	18.64	7.896737	0.807	2000-2002
	5	8	0.92	6267	7	1.02	6.99	7.559828	0.884	2003-2006
	6	4	0.92	2251	5	0.45	11.26	7.52092	0.891	2000-2004
	7	13	1.11	19376	12	3.08	3.99	7.497572	0.893	2012-2015
	8	22	10.53	110	2	0.018	113.92	7.483056	0.894	2006-2009
50	1	15	0.96	3794	13	1.23	10.61	19.119603	0.00018	2001-2008
	2	1	0	5	2	0.0004	5,009.10	15.03291	0.005	2004-2005
	3	6	0.63	2102	5	0.17	29.97	12.134681	0.053	2009-2010
	4	100	2.75	181740	20	7.13	2.91	7.994545	0.803	2000-2000
	5	8	0.92	6267	7	1.02	6.99	7.559828	0.890	2003-2006
	6	4	0.92	2251	5	0.45	11.26	7.52092	0.896	2000-2004
	7	22	10.53	110	2	0.018	113.92	7.483056	0.899	2006-2009

The results of OHSA for the urban and rural census sectors (using rates) are presented in Figure 4A. When rural census sectors were included, clusters were evident in the Pance-Hormiguero (south) and La Leonera sectors (north-west), where high C-ALL rates were found (Figure 4A). A grouping pattern was observed in the centroids of census sectors (points in Figure 4B) located mainly at south-east in communes 10 and 19, which coincided with the clusters found using Kulldorff's test (Figure 3A). No grouping of low-rate values (cold spots) was observed (Figure 4B). The first cluster also coincided with a cluster found with Kulldorff's test. In Figure 4A, census sectors were observed as cold spots (blue) because the rates in the rural area were very high (unstable) due to their low-risk population.

Discussion



Between 2000 and 2015, C-ALL cases accounted for 29% of all CC cases in the city of Cali. The results of this study suggest the presence of C-ALL clusters in the city during that period. Using spatial analysis of areas with census sectors as the unit of analysis, two spatial clusters of C-ALL were identified, the first in the urban area on the west of the city (commune 19) and the second in the rural area on the south-east side (Hormiguero). The spatiotemporal analysis showed that the cluster of the urban area occurred over an extended period between 2001 and 2008.

The spatial analysis of C-ALL in Cali differs in terms of the location of potential clusters when using points or areas (rates) as unit of analysis. The spatial analysis based on points (location of cases) reflects the density of the general and children population across the city with higher density of points located in the eastern area (Figure 1). This analysis provides information about the location of cases and might be useful for health care organizations. The spatial point analysis, however, does not consider the baseline population and therefore cannot be interpreted as indication of population at higher risk of C-ALL. In contrast, the spatial analysis using areas (census sectors) include the baseline population at risk during the study period and provides information in terms of zones with a higher risk of C-ALL incidence (Figures 3 and 4). This spatial analysis by areas (rates) provides useful information to identify zones in the city with incident rates higher than expected at random (11,26). Therefore, the clusters identified in the spatial analysis based on areas might be used to focus future studies on ecological and individual levels to assess specific environmental, occupational, or other individual exposures during pregnancy or early childhood that might be causal contributors to C-ALL (29).

Studies of clusters of childhood leukemia in different parts of the world show different results. In Britain, preliminary evidence was found of the presence of spatial clusters of childhood leukemia cases by date of diagnosis since the 1990s (29), similar to that found in this study. In the same country, spatial and spatiotemporal clusters were identified in age groups of 0-14 and 1-4 years but not for the group 5-14 years (30). In a meta-analysis, strong evidence was found for childhood leukemia clusters between 0 and 5 years related to the address at the time of diagnosis, while the evidence was weak for the 0-15-year age group (12). In Spain, clusters were associated with the home address at the time of pregnancy, but there was no correlation with the address at the time of diagnosis (31). Other studies have not found any evidence of such clusters (32,33). Specifically, for ALL, a significant spatial autocorrelation was found in Hungary for incident cases in children under 5 years of age, with a higher differential risk in males (34).

The presence of C-ALL clusters has been explained by several factors. Spatial clusters in Spain, for example, have been related to proximity to industrial sources of pollution (35,36), while the detection of spatiotemporal clusters in other European countries has been explained by a potential exposure to viral infectious agents not yet defined (37-39). In some studies, spatial clusters have been associated with the occupational exposure of parents to smoking, alcohol, solvents, or paints (40). Other studies failed to find a relationship between an infectious or environmental etiology and cancer (41).

The heterogeneity in the findings of clusters of childhood leukemia is probably related to the specific conditions of the study region. The conditions of infectious, occupational, and environmental exposures can differ between places even within the same country. Additionally, exposure times or windows can change and therefore differentially influence the incidence of childhood leukemia (42). The ethnic composition of the population, known as population mixture, has been correlated with the incidence of leukemia and the presence of clusters that were indirectly related to a potential infectious etiology (37,43). In the case of Cali and Colombia, the population has little population mixture, so the possible factors related to the finding of C-ALL clusters may be due to socioeconomic conditions or exposure to infectious or environmental agents.

Childhood cancer and C-ALL have shown variation in incidence related to socioeconomic conditions, with low- and middle-income countries having the highest incidence rates (44). Poverty with limitations for healthy lifestyles, higher exposure to environmental hazards, and limited access to healthcare services are probably the most probable mechanisms explaining these disparities. In Cali, the higher density of C-ALL cases is in areas with socioeconomic deprivation on the east side of the city, which is also the most densely populated area. In the cluster analysis, however, the consistent urban cluster is located on the west part, in commune 19. This finding might suggest that conditions other than socioeconomic factors can be contributing to the high cumulative incidence rate in these zones, although disparities in access cannot be ruled out with this exploratory analysis. Disparities in CC survival in Cali have been reported in terms of health insurance: 5-year overall survival rates for CC were 62% for private insurance, 43% for public insurance, and 23% for uninsured children (9). These findings support the inequity in the access to healthcare for CC patients by socioeconomic conditions.

Cluster studies that suggest an infectious etiology are based on findings of spatiotemporal clusters of acute leukemias that are well defined over time (12). This study identified the presence of two spatial clusters, one urban and one rural. In the first, the spatiotemporal analysis revealed long-term involvement over a period of eight years (2001-2008), while in the second cluster, there was no evidence of temporal grouping. Considering the above, the results of the analysis of C-ALL clusters in Cali suggest an etiology related to environmental or occupational exposures during pregnancy or early childhood. This hypothesis generated from the results of the present study can be explored using geographic methods. A recent study of CC in the metropolitan area of Bucaramanga found an association between the presence of a CC cluster and proximity to an industrial area (45). However, this type of association should be confirmed using other epidemiological designs that allow establishing causal associations.

Strengths and limitations

The main strength of this study is the data quality of C-ALL cases obtained from the population-based cancer registry of Cali over a period of 16 years. The RPC-Cali is recognized by the International Agency for Research on Cancer for the quality of its processes, which guarantees that the information used in the geographic analyses is of high quality. Furthermore, the use of diverse geographic analyses, including point and area analyses, allows demonstrating difference between case clusters (points) and risk clusters (areas). For the analysis of area clusters, the results are presented consistently using different measures of spatial clustering and circular scan hypothesis testing, which allows greater reliability of the findings.

The main limitation of this study is the lack of information on the place of residence before diagnosis. We used the place of residence of C-ALL patients at the time of diagnosis, which is the address available in the RPC-Cali; therefore, it was not possible to explore the effects of the latency periods of C-ALL or the changes in address between pregnancy and the time of diagnosis. Due to the limited number of ALL cases during the study period, it was not possible to perform subanalysis by age group or sex to identify differences due to these conditions. Finally, due to its ecological exploratory nature, the findings of this study do not allow relating C-ALL incidence to specific individual childhood exposures.

Conclusions

The results of this study indicate the presence of C-ALL clusters in the city of Cali between 2000 and 2015. Two spatial clusters of C-ALL were identified, the first in the urban area on the west part of the city (commune 19) and the second in the rural area on the south side (Hormiguero). The spatiotemporal analysis showed that the urban cluster was long-lasting, from 2001 to 2008. The results of the spatiotemporal analysis of C-ALL clusters in Cali suggest an etiology related to occupational or environmental exposures during pregnancy or early childhood that should be addressed in future studies.

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