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Factors associated with the latency to diagnosis of childhood cancer in Peru

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Abstract

Background: The latency to diagnosis is the time between the detection of a patient's first symptoms and the cancer diagnosis. The aim of this study was to identify the latency to the diagnosis of cancer in children in Peru and the clinical and sociodemographic factors associated with this latency.

Methods: All patients diagnosed with lymphoma and solid tumors between 2012 and 2014 at a social security referral hospital in Peru were retrospectively evaluated. Clinical and demographic variables were analyzed to assess their association with the latency to diagnosis.

Results: A total of 284 patients younger than 18 years of age were included in the study. The median time to diagnosis was 8.8 weeks, with a median patient interval of 2 weeks and diagnostic interval of 4.4 weeks. We found significant differences in the latency to diagnosis for different types of cancer (longer for Hodgkin lymphoma and shorter for Wilms tumor). Older children had significantly longer latencies to diagnosis ($P = 0.048$; OR: 1.05, 95% CI [1.0–1.1]), as did children who were first diagnosed by a general physician rather than by a pediatrician or surgeon ($P = 0.028$; OR: 2.1, 95% CI [1.1–4.2]). Parental age, level of education, marital status, metastatic disease, clinical stage, and gender did not significantly affect latency to diagnosis as analyzed by a multivariate analysis.

Conclusion: In Peru, median latency to diagnosis was comparable to that described in developing countries, where the index of suspicion for childhood cancer remains low. It is crucial to establish strategies to optimize early diagnoses using associated factors.

KEYWORDS

childhood cancer, lag time, latency to diagnosis

1 | INTRODUCTION

The worldwide incidence of childhood cancer is rising and has become the leading cause of disease-related mortality in developed countries.[1] Multidisciplinary approaches for treating cancer using chemotherapy, radiotherapy, and surgery have allowed for increased survival rates around the globe.[2] In developed countries, overall survival rates have improved to 80%; nevertheless, almost four of five cases occur in middle- and low-income countries, where reported survival rates are lower.[3] In our country, delayed presentation and advanced disease at diagnosis are common features in childhood cancer.[4]

Diagnosing cancer in children remains a complex process that includes related factors such as parental characteristics (knowledge of symptoms, parental level of education, attitudes, and beliefs), the healthcare system (trained personnel, referrals, and geographical accessibility), and the clinical presentation (age, histological type, symptoms, primary tumor site, clinical stage, and first medical specialist consulted).[5]

Authors divide the latency to diagnosis (also known as the *wait time* or *lag time*) into the *patient interval* (length of time between noticing the first cancer-related symptoms and the first visit to a physician or healthcare professional) and the *diagnostic-interval* (length of time from the first medical visit to a definitive cancer diagnosis).[6] These definitions have replaced terms such as *delay*. In spite of being broadly used in medical articles about the latency to diagnose cancer, such terms often imply a negative and unclear connotation, as there is no established reference point for the *delay* in diagnosis, which leads to an arbitrary and individual reference point for every study.[7] In some

studies, early diagnosis of cancer has been associated with a reduced risk of mortality,[8,9] which is of particular interest in pathologies such as retinoblastoma, and possibly leukemia, Wilms tumor, and rhabdomyosarcoma. However, studies on most types of brain tumors, bone sarcomas, and Hodgkin lymphoma reported an adverse association and even a paradoxical positive relation, with the biological nature and aggressiveness possibly being more relevant for prognosis.[5,8]

Existing literature is scarce regarding the latency to diagnose childhood cancer in developing countries. Two systematic reviews have focused mainly on data published from developed countries.[7,8] In Peru there are no previous studies related to the association between sociocultural factors and diagnostic intervals for childhood cancer. The aim of our study was to determine the latency to diagnosis, and the clinical and sociodemographic factors associated with it, in children diagnosed with cancer at the Edgardo Rebagliati Hospital in Lima, Peru, a national referral center for pediatric cancer.

2 | MATERIALS AND METHODS

2.1 | Research design and setting

We carried out a retrospective cohort study, following the guidelines from the STROBE checklist for observational studies in epidemiology (www.strobe-statement.org). All patients included in the study were younger than 18 years of age and diagnosed with solid malignant tumors and lymphomas between January 2012 and December 2014 in the Edgardo Rebagliati Hospital. The Pediatric Oncology Unit at the hospital was founded 11 years ago, has 17 hospital beds, and is the main tertiary referral center for treating childhood cancers nationwide, along with the National Institute of Neoplastic Diseases (INEN, for its acronym in Spanish). Cancer diagnoses were established using the International Classification of Childhood Cancer (ICCC) standards based on the ICD-O-3/WHO 2008 codes.

2.2 | Study procedures

Data were collected from medical records (diagnosis, clinical stage, demographic data, and diagnostic intervals in days and weeks) and via telephone interviews with patients' relatives (marital status, age, and education level of the parents at the time of the diagnosis). Data obtained were recorded in a data collection form, specifically designed for the current study. Two medical authors (L.V. and M.T.) recorded the information and called each patient's mother, father, or guardian.

2.3 | Operational definitions

The term *patient interval* referred to the interval of time measured in days that elapsed between the onset of cancer-related symptoms and the patient's first visit to a physician. The term *diagnostic interval* was defined as the interval of time that elapsed between the patient's first contact with a physician and the cancer diagnosis. *Latency to diagnosis* is the sum of the patient interval and the diagnostic interval. The term *time of referral* was defined as the time it took to complete the administrative paperwork for a patient's transfer from a primary or secondary care center to our hospital.

2.4 | Statistical analysis

All statistical analyses were carried out using Stata v12 (StataCorp. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP; 2011). Descriptive statistics included measurements of the central tendency and dispersion for latency to diagnosis, patient interval, and diagnostic interval in days and weeks. Univariate and multivariate analyses were carried out using a linear regression with the latency to diagnosis as the dependent variable. In addition, median diagnosis latencies for every histological subtype were established and the latency to diagnosis for each patient was categorized as "longer" or "shorter" compared to the median for their specific cancer type. Multiple linear regression and logistic regression analyses were performed in reverse. The analyses started with a saturated model and then the variables with lower strengths of association were consecutively removed. Variables that were significant in the bivariate analysis, and relevant for the analyses, were included. Statistical significance was established at 5% for a two-dimensional test.

2.5 | Ethical considerations

Our study was endorsed by the Institutional Review Board (IRB) of our hospital. Confidentiality safeguards were in place to protect patients' names, medical record numbers, and diagnoses, and safeguards against their identification by a third party were implemented. Telephone calls to parents were made by the patients' attending doctors in the context of daily patient care.

3 | RESULTS

A total of 314 children and adolescents under 18 years of age were diagnosed with childhood cancer from January 2012 to December 2014 at our hospital; of those, we included 284 patients (90.4%). Reasons for exclusion included rejection of telephone communication and incomplete medical records (Fig. 1). The median age of subjects was 9 years (interquartile range [IQR], 3–13), and 160 of the subjects were males (56.3%) while 124 were females (43.7%); the male:female ratio was 1.28. Metastatic disease was present in 65 cases (22.9%). There was no sex difference between the excluded (43.7% female) and included patients ($P = 0.7$). Excluded patients were younger (median, 4 years; IQR, 2–8) than those who were included. Baseline characteristics are shown in Table 1.

The median diagnosis latency was 8.8 weeks or 62 days (IQR, 30–129) as detailed in Table 2. The diagnostic intervals were significantly longer ($P < 0.01$) than the patient intervals. Median latency to diagnosis varied according to the histological type of cancer, with the shortest intervals in patients with Wilms tumor (median, 4 weeks) and hepatoblastoma (median, 4.4 weeks), and the longest intervals in Hodgkin lymphoma (median, 31 weeks) and osteosarcoma (median, 14.3 weeks) ($P < 0.01$) (Fig. 2).

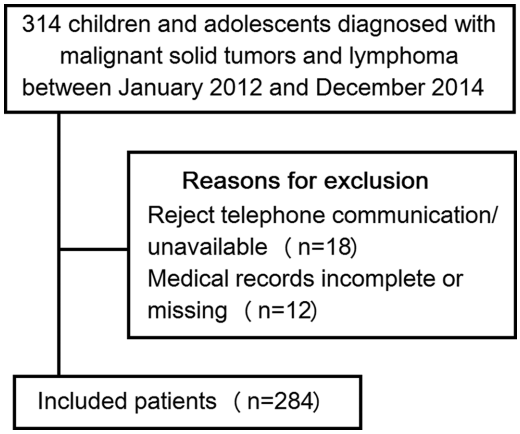

FIGURE 1 Flow chart of the study population.

In univariate analysis using linear regression, factors associated with a significantly longer latency to diagnosis were the age at presentation (the youngest patients had shorter times to diagnosis, $P < 0.01$), parental age ($P < 0.01$), marital status of the parents ($P = 0.017$), histological type ($P < 0.01$), and the type of first attending physician ($P = 0.001$). Children first seen by a general physician ($P = 0.008$) and older children ($P = 0.023$) had significantly longer latencies to diagnosis according to the multivariate analysis (Table 3). There was no statistically significant association between the latency to diagnosis and the presence of initial metastasis, the clinical stage at diagnosis, geographical residency, or sex.

Univariate logistic regression of the latency to diagnosis (categorized as longer as or shorter than the median for all histological types) showed a significant association with age ($P = 0.04$), mother´s level of education ($P = 0.042$), and the type of first attending physician ($P = 0.009$). Multivariate analysis was significant for associations between the age at presentation ($P = 0.048$; odds ratio [OR]: 1.05, 95% CI [1.0–1.1]) and being seen first by a general physician and a longer diagnosis latency ($P = 0.028$; OR: 2.1, 95% CI [1.1–4.2]). Two patients were initially treated by an alternative medicine practitioner (bonesetter or *huesero*), nine patients followed instructions from nonmedical personnel at a public drugstore, and 13 patients self-medicated at onset.

Of the 284 cases, we have referral information regarding 231 patients. Most of the patients (69.3%) did not follow a standard administrative referral and were brought directly to our hospital by the emergency department. Seventy-one patients were referred to our hospital from a primary or secondary care center, with a median latency to diagnosis of 20 days (IQR, 15–30.5) (Table 2). Twenty-one patients (29.6%) were referred in less than 2 weeks, and 11 patients (15.5%) in less than a week from their hospitalization in another medical care center. The median number of doctors visited prior to being evaluated in our institution was 3 (range, 1–8).

4 | DISCUSSION

The median latency to diagnosis in our population was longer than has been reported in developed countries such as Canada,[10]

TABLE 1 Baseline characteristics

Characteristic	Total (N = 284), n (%)
Sex	
Male	160 (56.3)
Female	124 (43.7)
Age (years), median (IQR)	9 (3–13)
Age group (years)	
<2	34 (11.9)
2 to <5	59 (20.8)
5 to <10	62 (21.8)
10 to <14	69 (24.3)
>14	60 (21.1)
Diagnosis	
CNS and intraspinal neoplasms	49 (17.3)
Non-Hodgkin lymphoma	35 (12.3)
Osteosarcoma	34 (11.9)
Wilms tumor	25 (8.8)
Rhabdomyosarcoma	22 (7.8)
Bone/soft-tissue Ewing tumor	21 (7.4)
Hodgkin lymphoma	17 (5.9)
Retinoblastoma	14 (4.9)
Langerhans cell histiocytosis	14 (4.9)
Hepatoblastoma	11 (3.9)
Gonadal germ cell tumors, testes	10 (3.5)
Neuroblastoma	8 (2.8)
Gonadal germ cell tumors, ovarian	7 (2.5)
Other specified soft tissue sarcomas	6 (2.1)
Hepatic carcinoma	5 (1.9)
Other diagnosis	6 (2.1)
Clinical stage[a]	
I	20 (7.5)
II	62 (23.2)
III	89 (33.3)
IV and V	96 (36.0)
Place of residence[b]	
Lima/Callao	148 (53.6)
Coast	59 (21.4)
Andean	52 (18.8)
Forest	17 (6.2)
First attending physician	
Pediatrician	136 (47.9)
Surgeon	34 (11.9)
General practitioner	65 (22.9)
Other	49 (17.3)
Mother´s education level[b]	
Elementary school	23 (8.6)
Secondary school	106 (39.6)
Higher education	139 (51.9)

(*Continued*)

TABLE 1 *(Continued)*

Characteristic	Total (N = 284), n (%)
Father´s education level[b]	
Elementary school	6 (2.3)
Secondary school	88 (32.9)
Higher education	173 (64.8)
Mother's age (years), median (IQR)[b]	36 (32–41)
Father's age (years), median (IQR)[b]	39 (34–44.5)
Marital status[b]	
Married	213 (80.9)
Separated/divorced	50 (19.1)

[a]Data on clinical stage were missing in 17 cases, due to lack of standard staging system (i.e., histiocytosis).
[b]Data were missing in place of residence in 8 cases, level of education of the mother in 16 cases, level of education of the father in 17 cases, parental age in 28 cases and marital status in 21 cases.

TABLE 2 Latency to diagnosis and referral time (days) for pediatric cancer, Hospital Nacional Edgardo Rebagliati Martins, 2012–2014

	Median	IQR	Mean	SD	Range
Latency to diagnosis (N = 284)	61.5	30–127.9	107.1	127.7	4–1098
Patient interval	14	6.5–61	39.9	62.1	0–548
Diagnostic interval	30.5	17–76.3	66.4	100.2	0–1,006.5
Referral time (N = 74)	20	15–30.5	26.0	19.8	2–122

IQR, interquartile range; SD, standard deviation.

United Kingdom,[11] United States,[12] and Israel[13]; and comparable to published data from low- and middle-income countries.[14,15]

Age is an important factor in diagnosing cancer in children. Older patients have a significantly higher risk for a delay of diagnosis than younger patients.[11,12,16–18] A Mexican study found that children between ages 10 and 14 had 1.8 times higher risk for delay of diagnosis than children under 1 year of age.[19] In children with retinoblastoma, those under 2 years of age had a lower risk of a delay in diagnosis.[20] In two Canadian cohorts, younger children had shorter latencies to diagnosis than older children.[10,21] In our study, we found a positive correlation between age and the latency to diagnosis as a continuous and categorical variable. This finding could be because younger children usually receive more care and attention so that a body asymmetry or increase in volume might be observed earlier and more easily.

The association between sex and latency of diagnosis was also evaluated in several studies. Pollock et al. described longer lag times in girls for a diagnosis of non-Hodgkin lymphoma.[12] In contrast, one study showed that male sex mildly increased the risk of a delay in the diagnosis of childhood cancer.[19] Most studies do not find a correlation between sex and the latency to diagnosis,[13,17,22,23] which is what we also found in the current study.

Parental level of education has been shown to be a relevant factor for the latency to diagnose cancer.[13] Chantada et al. reported that patients with retinoblastoma in Argentina had a higher risk for a delayed diagnosis when their parents had only elementary or primary education level.[20] In Mexico, a lower education status (of <11 years) was significantly correlated with a longer diagnostic interval.[19] We could not establish a significant association in our study. Nevertheless, in our country, the association might not be as strong because it is common for parents with a higher of level of education to seek medical attention in private centers instead of in public tertiary hospitals. In our study, we did not find an association between parental age and the latency to diagnosis, which has been previously described.[2] Our sample size could have affected our findings; however, the effect in the univariate analysis is large enough that it seems unlikely to have occurred solely by chance.

The type of disease is a relevant factor for the latency to diagnosis. In a systematic review of studies performed in developed countries,[8] diagnosis latencies were shorter in patients with leukemia, Wilms tumor, and non-Hodgkin lymphoma, and longer in patients with brain tumors (low-grade astrocytomas and gangliogliomas), osteosarcoma, and Ewing sarcoma. These findings were similar to those described in another systematic review that included developing countries.[7] In other studies from developing countries, the diagnosis latency is usually longer for Hodgkin lymphoma, osteosarcoma, and retinoblastoma.[14,15,19,20] In our study, Hodgkin lymphoma had the significantly longest latency to diagnosis, possibly because of the usual presentation of asymptomatic cervical lymphadenopathy, where careful observation is sometimes needed.[13]

Clinical staging has failed as a significant factor for latency to diagnosis in our study, as previously reported.[11] Although it may seem logical for a longer diagnosis latency to be correlated with a higher stage, we confirmed that very aggressive tumors might have a rapid presentation with an advanced disease. Interestingly, 65.2% of our patients were diagnosed at stages III, IV, and V, which has also been reported in Mexico, where at least 50% of children with solid tumors were diagnosed at stages III and IV.[19] It could be hypothesized that the difference in diagnosis latencies between developed and developing countries correlates with the increased stage at presentation in the developing countries. Further studies are needed to clarify this point.

The type of physician who was first seen was associated with the latency to diagnosis in our cohort. Similarly, some authors have reported longer intervals in children who were first seen by a general physician rather than a pediatrician [13] or an emergency physician.[9,10] Additionally, the total number of doctors visited before determination of a definitive diagnosis of cancer is also an important variable. In a study involving children who were diagnosed with brain tumors, parents visited an average of five physicians before a diagnosis was made.[24] In our study, patients had a median of three visits to other physicians prior to visiting our hospital. In our country, suspicion levels for cancers are low among general physicians and pediatricians who are not familiar with these diseases due to their low incidence and frequent association with death. Geographic distance from a healthcare center has also been studied, with some studies finding prognostic value,[13,19] but not others,[10] including ours, as we found that location of residence played no part in our patients' diagnosis latencies.

Most studies[10,11,13] find that the diagnostic interval is significantly longer than the patient interval. Some factors that could contribute

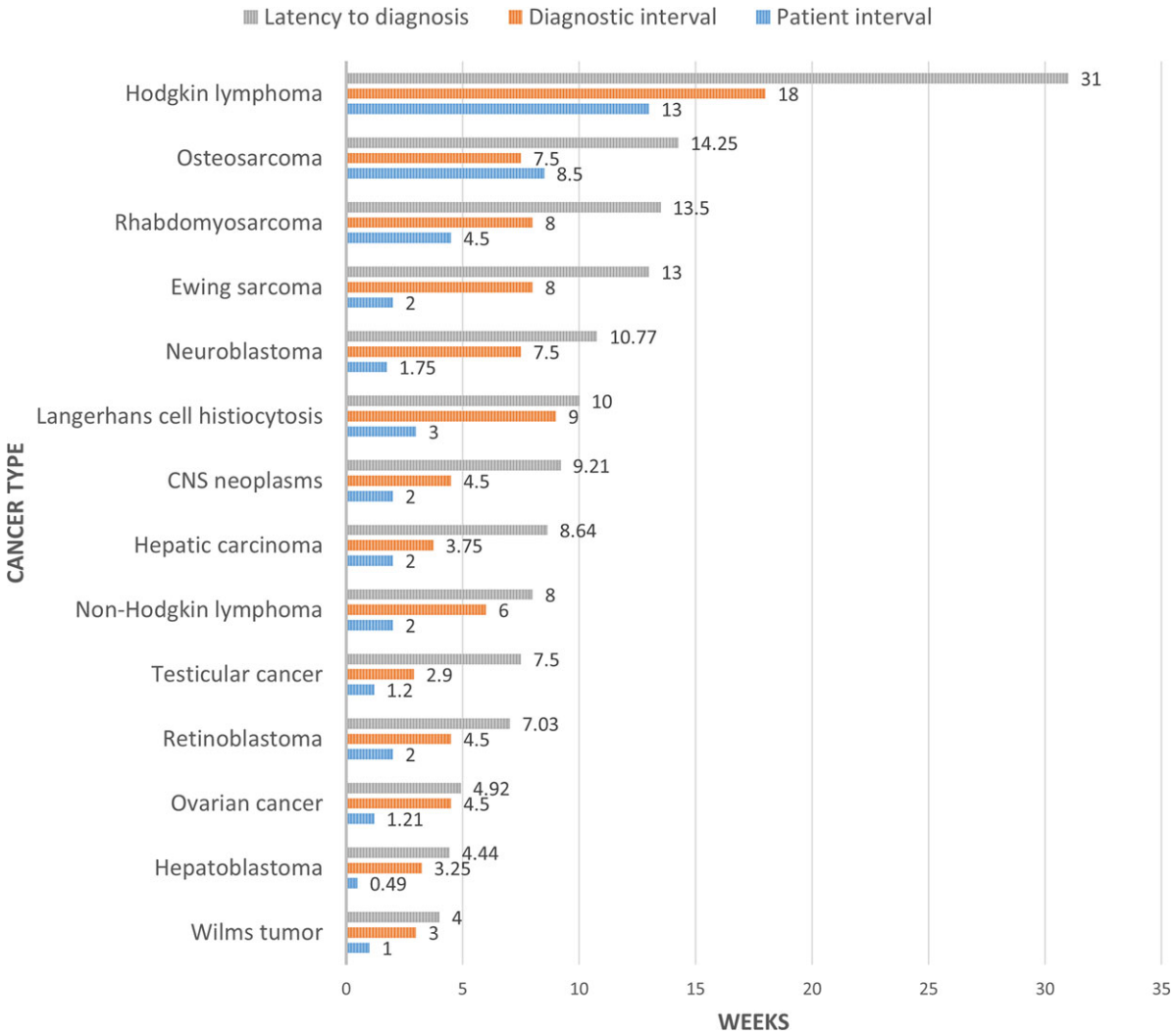

FIGURE 2 The median latency to diagnosis in children with cancer (weeks).

to a longer patient interval are the use of symptomatic medication (prescribed by nonmedical personnel), financial factors, and consults with alternative medicine practitioners. Delays in diagnosis due to a longer diagnostic interval could be due to the problems with geographical access, including difficulties traveling to Lima, the country's capital; financial and family restrictions (families with several children or with other sick children); and administrative delays with patient referrals. Our patients were referred in an average of 26 days, but the longest delay time was 4 months (122 days). Also, 11 patients visited personnel offering alternative sources of treatment, which reflects their lack of trust in the healthcare system.

Because this is a retrospective study, it has certain limitations. First, medical records were not always complete, which made it necessary to use information from telephone conversations with patients' relatives in almost all cases. This could limit the reliability of the information because of recall bias (especially concerning the time of onset of the cancer symptoms). Nevertheless, this potential bias should be equal among the groups. Second, leukemia patients were not included in the study because our team only treats children with solid tumors, so the data quality could be low as there is no cancer registry in our institution. Also, our population involved children from families with social security health insurance coverage and whose parents' education levels and work statuses are higher than most people in Peru. These factors could affect generalization and external validity of our findings.

However, there are also many strengths of this study. This study provides a regional approach to the epidemiology of childhood cancer diagnosis in our country and represents a reliable report on the diagnostic time intervals associated with clinical and sociodemographic factors. In addition, our institution is currently in the process of implementing a childhood cancer registry and most of the findings described in this study could contribute to the establishment of useful variables for data collection in future research studies. Moreover, this study could serve as a baseline model for the current status of childhood cancer diagnosis in our country, and allow for the design of a future prospective multicenter study with the aim of establishing a potential association between the latency to diagnosis and mortality due to childhood malignancies. The main objective would be to determine which pathologies would benefit from national policies regarding early cancer diagnosis and achieve effective intervention programs.

TABLE 3 Results from univariate and multivariate linear regressions for factors associated with the latency to diagnosis of childhood cancer, Hospital Nacional Edgardo Rebagliati Martins, 2012–2014

	Univariate analysis		Multivariate analysis	
	β-Coefficient (95% CI)	*P*-value	*β*-Coefficient (95% CI)	*P*-value
Gender (male/female)	19.8 (−11.4 to 49.0)	0.222		
Age	5.8 (3.1–8.5)	<0.001	4.8 (0.7 –8.9)	0.023
Diagnosis				
Wilms tumor	1		1	
Bone/soft-tissue Ewing tumor	114.6 (44.7–189.2)	0.002	94.4 (12.1–76.6)	0.025
Non-Hodgkin lymphoma	56.9 (−6.9 to 120.9)	0.08	31.9 (−41.8 to 105.5)	0.395
Hodgkin lymphoma	157.1 (89.2–245.5)	<0.0001	128.9 (33.9–223.9)	0.008
Gonadal germ cell tumors, testes	52.0 (−39.3 to 143.4)	0.263	48.5(−49.3 to 146.3)	0.329
Gonadal germ cell tumors, ovarian	20.7 (−83.7 to 125.1)	0.697	3.3 (−114.5 to 121.1)	0.956
Langerhans cell histiocytosis	89.5 (8.0–171.0)	0.031	113.3 (22.8–203.8)	0.014
Osteosarcoma	76.0 (10.7–139.3)	0.023	31.1 (−48.8 to 110.9)	0.445
CNS and intraspinal neoplasms	51.5 (−7.2 to 112.8)	0.084	39.9 (−29.4 to 109.3)	0.258
Retinoblastoma	72.8 (−8.7 to 154.3)	0.08	103.9 (13.7–194.1)	0.024
Rhabdomyosarcoma	68.6 (−3.7 to 140.9)	0.063	58.7 (−24.6 to 141.9)	0.166
Other soft tissue sarcomas	149.3 (38.3–260.3)	0.009	107.7 (−15.5 to 230.9)	0.086
Neuroblastoma	46.7 (−52.4 to 145.9)	0.354	66.9 (−36.7 to 170.6)	0.204
Hepatoblastoma	−9.4 (−98.2 to 78.5)	0.826	9.7 (−88.9 to 108.2)	0.847
Hepatic carcinoma	134.4 (14.8–354.0)	0.028	112.1 (−27.3 to 251.5)	0.114
Other diagnosis	118.4 (7.4–229.4)	0.037	85.1 (−45.9 to 216.2)	0.202
Initial metastases (present/absent)	−27.9 (−63.4 to 7.7)	0.124		
Mother´s education level				
Elementary school	1		1	
Secondary school	−57.1 (−116.3 to 1.4)	0.056	−19.4 (−81.6 to 42.8)	0.5
Higher education	−43.3 (−100.6 to 14.6)	0.143	−0.1 (−60.5 to 60.4)	0.9
Father's education level				
Elementary school	1			
Secondary school	−10.7 (−119.8 to 97.6)	0.841		
Higher education	−25.0 (−131.7 to 82.2)	0.649		
Mother's age	3.6 (1.4–5.8)	0.002		
Father´s age	2.9 (0.91–4.9)	0.005		
Marital status				
Married	1		1	
Separated/divorced	48.2 (8.8–89.3)	0.017	14.5 (−26.9 to 55.9)	0.492
Place of residence				
Lima/Callao	1			
Coast	7.6 (−32.3 to 46.3)	0.736		
Andean	25.9 (−14.2 to 68.6)	0.197		
Forest	16.9 (−48.9 to 81.7)	0.621		
First attending physician				
Pediatrician	1		1	
Surgeon	38.9 (−8.6 to 86.6)	0.108	29.8 (−23.5 to 83.2)	0.54
General practitioner	62.7 (25.2–100.2)	0.001	56.9 (14.9–98.9)	0.008
Other	7.3 (−32.1 to 48.6)	0.730	−15.9 (−64.8 to 60.4)	0.519

CI, confidence interval.

5 | CONCLUSIONS

In Peru, the median latency to diagnosis was comparable with that described in developing countries, where the index of suspicion for childhood cancers remains low. According to our findings, interventions such as educational tools are needed, including general population campaigns (to raise awareness of clinical symptoms of cancer and of the need for regular physical examinations in children and adolescents) and continued medical education for family doctors and pediatricians. Also, it is critical to improve communication flow between first-, second-, and third-level healthcare centers to achieve faster referrals.

It is vital to understand the factors that influence interval times in childhood cancer diagnoses so that policies and programs can be implemented to improve medical care for children with cancer. Future studies must examine the role of the latency to diagnosis in the prognosis and survival rates in children with cancer, and then, strategies to reduce interval time based on prognostic factors must be designed and implemented.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

IQR interquartile range
OR odds ratio

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