RESEARCH ARTICLE

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Factors associated with abandonment of therapy by children diagnosed with solid tumors in Peru

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Abstract

Background: Abandonment of treatment is a major cause of treatment failure and poor survival in children with cancer in low- and middle-income countries. The incidence of treatment abandonment in Peru has not been reported. The aim of this study was to examine the prevalence of and factors associated with treatment abandonment by pediatric patients with solid tumors in Peru.

Methods: We retrospectively reviewed the sociodemographic and clinical data of children referred between January 2012 and December 2014 to the two main tertiary centers for childhood cancer in Peru. The definition of treatment abandonment followed the International Society of Paediatric Oncology, Paediatric Oncology in Developing Countries, Abandonment of Treatment recommendation.

Results: Data from 1135 children diagnosed with malignant solid tumors were analyzed, of which 209 (18.4%) abandoned treatment. Bivariate logistic regression analysis showed significantly higher abandonment rates in children living outside the capital city, Lima (forest; odds ratio [OR] 3.25; $P < 0.001$), those living in a rural setting (OR 3.44; $P < 0.001$), and those whose parent(s) lacked formal employment (OR 4.39; $P = 0.001$). According to cancer diagnosis, children with retinoblastoma were more likely to abandon treatment compared to children with other solid tumors (OR 1.79; $P = 0.02$). In multivariate regression analyses, rural origin (OR 2.02; $P = 0.001$) and lack of formal parental employment (OR 2.88; $P = 0.001$) were independently predictive of abandonment.

Conclusion: Treatment abandonment prevalence of solid tumors in Peru is high and closely related to sociodemographical factors. Treatment outcomes could be substantially improved by strategies that help prevent abandonment of therapy based on these results.

KEYWORDS
abandonment, childhood cancer, low- and middle-income countries

1 | INTRODUCTION

Pediatric cancer survival rates have significantly improved in recent decades in high-income countries (HIC), reaching a global cure rate greater than 80%.[1] In low- and middle-income countries (LMIC),

several factors such as delayed diagnosis, treatment-related toxicity, and abandonment of treatment contribute to higher rates of advanced disease at onset, cancer progression, and mortality, leading to worse prognoses and outcomes.[2–4] In Peru, a long latency of diagnosis, a higher percentage of initial metastatic disease, and poor survival rates have been described as common features of childhood cancers.[5,6]

Treatment abandonment in children with cancer has been defined as the failure to start or complete potentially curative therapy.[2] Abandonment rates are highly variable among reports from LMIC,[7] and multifactorial reasons include socio-economic pitfalls, the perceived incurability of cancer, the adverse effects of chemotherapy,

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Abbreviations: AWD, alive with disease; DOD/DOC, dead of disease/other cause; HIC, high-income countries; INEN, Instituto Nacional de Enfermedades Neoplásicas (National Institute of Neoplastic Diseases); IQR, interquartile ratio; LFU, lost to follow-up; LMIC, low- and middle-income countries; NED, no evidence of disease; OR, odds ratio; RH, Rebagliati Hospital

religious beliefs, magical thinking, and a low level of satisfaction with health system personnel.[8,9]

Several studies in Latin America have focused on treatment abandonment by children with cancer,[10–15] especially in leukemias. Abandonment reports in pediatric cancer studies are crucial as abandonment not only contributes to treatment failure but also increases the possibility of unnecessary suffering, rescue therapy, mutilating surgeries, and wasted healthcare resources.[16]

The aim of this study was to determine the prevalence of and factors associated with treatment abandonment by children with malignant solid tumors in Peru.

2 | MATERIAL AND METHODS

2.1 | Study population and setting

Peru is a Latin American upper middle-income country[17] with 31.7 million inhabitants, of which 28% are children aged 0–14 years. The biggest urban area is Lima, the capital city, with almost 10 million inhabitants.[18] The rural population represents 21% of the total population in Peru,[19] most commonly living in the Andean and forest provinces. According to data from the International Incidence of Childhood Cancer (IICC3),[20] 525 newly diagnosed cases of childhood cancer are reported yearly, with patients cared for at public and private facilities. In Lima, there are two main tertiary referral centers for the treatment (not exclusively) of childhood cancer: the National Institute of Neoplastic Diseases (INEN is its acronym in Spanish) and the Rebagliati Hospital (RH). This study was conducted in those two centers.

The INEN is financially supported by the Peruvian government, which pays for cancer treatment for all children.[21] However, the lack of available beds and delayed medical appointments are common problems resulting from a patient demand that exceeds capacity. For parents who cannot afford accommodations near the hospital, a nonprofit organization provides shelter and food expenses during the length of the hospitalization.

RH is the largest hospital participating in a public-private partnership with the social security system of Peru (Essalud), and is financially dependent on the mandatory contributions of the insured population with formal employment (approximately 35% of the total population of Peru).[22] Therefore, the socio-economic characteristics of families attending both institutions may differ widely. Treatment for children with cancer is free of charge at both institutions.

For this study, the data from all patients aged 0–14 years and diagnosed with lymphoma or malignant solid tumors between January 2012 and December 2014 in INEN and RH were included. Data from patients with leukemia were excluded because their diagnoses and treatment were managed by a different medical team (pediatric hematology) in RH, and the data could not be collected.

2.2 | Data collection

Data regarding sociodemographic factors, clinical variables, and abandonment status were retrospectively collected from clinical records and hospital-based databases. Known predictor factors including age, gender, cancer diagnosis, treatment protocol length, time to travel to a tertiary facility, household origin (rural/urban), place of household origin, and parental employment (formal/informal) were extracted. Cases were matched to national databases such as the National Death Registry to verify their vital status.

2.3 | Operational definitions

As recommended in the position statement of the International Society of Paediatric Oncology–Paediatric Oncology in Developing Countries Abandonment of Treatment Working Group, treatment abandonment was defined as failing to complete therapy or missing treatment for a prolong period of 4 consecutive weeks.[2] This definition included upfront abandonment (refusal of treatment), defined as abandonment before initiating the medically indicated treatment regimen.[23]

Forgone curative treatment was defined as the discontinuation of disease-directed therapy with curative intent when the providers and the parents agree that the potential for cure or definitive control are too low to justify continuation.[23] This definition includes cases with only palliative intent and differs from treatment abandonment.

In the socio-economic variables, type of residence was defined as urban for those who live in capital cities of provinces and rural for those who live in the capital city suburbs, rural villages, and towns. Formal employment was defined as a formal working arrangement for one or both parents that could be full time or part time, with benefits such as social security health insurance (and a fixed monthly salary). According to place of residence, we divided Peru into three main regions: Coast, which is bounded by the Pacific Ocean; Andean, which is located on the Andean highlands, and the Forest, which is located on the Amazonian Jungle.

Outcome status was categorized as alive with disease (AWD), no evidence of disease (NED), lost to follow-up (LFU), and dead of disease/other cause (DOD/DOC). LFU was defined as completing therapy but missing subsequent appointments for at least 6 months.

2.4 | Statistical analysis

All statistical analyses were performed using Stata v14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Descriptive statistics included percentages and measurements of the central tendency (median and interquartile ratio, IQR) for age and protocol length.

Bivariate and multivariate analyses were carried out using a logistic regression model. Variables that were significant ($P < 0.05$) 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

This study was endorsed by the Institutional Review Boards of RH and INEN. Confidentiality safeguards were in place to protect patients' identification and diagnoses, and safeguards against their identification by a third party were implemented.

TABLE 1 Baseline characteristics of children diagnosed with lymphoma and solid tumors in Peru (2012–2014)

Variable	Total (N = 1135)
Gender, n (%)	
Male	624 (55%)
Age (years), n (%)	
0–5	508 (44.8%)
5–9	288 (25.4%)
10–14	339 (29.8%)
Median age, IQR (years)	6, 3–8
Type of cancer, n (%)	
Lymphoma	221 (19.5%)
Brain tumor	203 (17.9%)
Bone and soft tissue sarcoma	194 (17.1%)
Retinoblastoma	158 (13.9%)
Others	359 (31.6%)
Median protocol length, IQR (weeks)[a]	34, 24–37
Type of household, n (%)[a]	
Urban	878 (77.4%)
Rural	216 (19%)
Place of residence, n (%)[a]	
Lima/Callao	485 (42.7%)
Coast	218 (19.2%)
Andean	291 (25.6%)
Forest	102 (8.9%)
Time to travel to hospital (hr), n (%)[a]	
Less than 2	484 (42.6%)
2–5	288 (25.4%)
More than 5	322 (28.4%)
Type of parental employment, n (%)	
Informal	885 (77.9%)
Formal	250 (22.1%)

IQR, interquartile ratio.

[a]Data were missing for protocol length in 46 cases, type of household/time to travel to hospital in 41 cases, and place of residence in 39 cases.

3 | RESULTS

In total, 1135 children were diagnosed with malignant solid tumors and lymphomas during the study period; 77.9% were treated at INEN and 22.1% at RH. Total prevalence of abandonment was 18.4% (209 cases); of these, 27 (33%) refused treatment upfront. Of the total number of cases who abandoned treatment, 194 patients (194/885; 21.9%) were treated at INEN and 15 patients (15/250; 6%) were treated at RH ($P = 0.001$). The baseline characteristics of the study population are shown in Table 1. The median duration of follow-up was 31 months.

Bivariate logistic regression analysis showed a significantly higher risk of abandonment for children living outside of Lima, the capital of Peru (Coast, odds ratio [OR] 2.03; Andean, OR 2.92; forest, OR 3.25; $P < 0.001$), those with prolonged travel time to a tertiary care center (>5 hr; OR 2.75, $P = 0.002$), those living in a rural setting (OR 3.44;

$P < 0.001$), and those whose parent(s) lacked formal employment (OR 4.39; $P = 0.001$). According to the specific cancer diagnosis, children diagnosed with retinoblastoma were at higher risk of abandonment (OR 1.79; $P = 0.020$) compared to those diagnosed with all other solid tumors. Age or gender was not significantly associated with a higher risk of abandonment in the bivariate analysis. In the multivariate logistic regression analysis, rural origin (OR 2.02, $P = 0.001$) and lack of formal parental employment (OR 2.88, $P = 0.001$) were independently predictive of abandonment (Table 2).

Forgone curative treatment was found in 77/1135 patients (6.8% of total patients); according to the type of cancer, it was more prevalent in children who had diagnoses of brain tumors (36.4%), lymphoma (13%), and bone/soft tissue sarcoma (11.7%), compared to those with retinoblastoma (3.9%).

Clinical follow-up data were available for 861/1135 (75.9%) patients. Regarding follow-up of the total studied cohort, 362 (31%) children were NED, 58 (5.1%) were AWD, 441 (38.8%) were DOD/DOC, and 274 (24.1%) were LFU (Table 3). Living patients had a median follow-up time of 42 months (range 23–69 months).

4 | DISCUSSION

In Peru, the prevalence of treatment abandonment is 18.4%, which is higher than the rates reported from other upper-middle income countries.[8,10,24] Worldwide, the reported abandonment rates in pediatric cancer seem to be highly variable.[25] According to a previous meta-analysis of abandonment in pediatric leukemia, a range of 0–74% has been described in LMIC,[7,26] whereas abandonment remains a rare phenomenon in HIC.[27,28] Our study shows results comparable to Central American countries where mainly multidisciplinary efforts and institutional support for decreasing abandonment have improved initially high rates.[14,29,30] Additionally, a global survey conducted by Friedrich et al.[26] that was geared toward childhood cancer professionals regarding treatment abandonment received responses from 101 countries, including HIC and LMIC. In that study, Peru had an estimated rate of abandonment of 6–15%, which was higher than those of other Latin American counterparts, such as Argentina, Chile, and Brazil, and similar to what was calculated for Mexico, Colombia, and Venezuela.[26] This is the first actual report on abandonment in pediatric cancer in Peru, showing higher rates than previously expected and higher rates compared to other upper-middle income countries.

Most reports about cancer treatment outcomes in LMIC lack abandonment data, although formal recommendations recognize that it is important to analyze abandonment in two ways[2,31,32]: as an event (relapse or death) and as censored, considering that upper and lower limits will reflect the true event-free survival estimate. Adequate treatment abandonment reporting would assist in designing strategies that decrease abandonment and improve treatment outcomes.[9] One factor that could limit the adequate quantification and reporting of abandonment is the lack of cancer registries.[33,34]

Important contributors to abandonment in pediatric cancer include social, demographic, economic, psychological, religious, and clinical

TABLE 2 Univariate and multivariate logistic regression of predicting factors of abandonment in children diagnosed with lymphoma and solid tumors in Peru (2012–2014)

Variable	Bivariate analysis			Multivariate analysis		
	OR	CI 95%	P	OR	CI 95%	P
Age (years)						
0–5	0.80	0.56–1.14	0.21			
5–9	0.96	0.64–1.42	0.84			
10–14	1	Reference				
Gender						
Male	1	Reference				
Female	0.92	0.68–1.25	0.63			
Type of cancer						
Lymphoma	1	Reference		1	Reference	
Brain tumor	0.62	0.36–1.07	0.09	0.69	0.39–1.22	0.21
Bone/soft tissue sarcoma	1.44	0.90–2.30	0.12	1.47	0.89–2.40	0.12
Retinoblastoma	1.79	1.09–2.94	0.02	1.51	0.90–2.55	0.11
Others	0.61	0.38–0.99	0.05	0.62	0.37–1.02	0.06
Type of household						
Urban	1	Reference		1	Reference	
Rural	3.44	2.46–4.81	<0.001	2.02	1.34–3.03	0.001
Place of residence						
Lima/Callao	1	Reference		1	Reference	
Coast	2.03	1.32–3.13	0.001	1.02	0.74–1.42	0.87
Andean	2.91	1.98–4.26	<0.001	1.18	0.85–1.72	0.71
Forest	3.25	1.95–5.42	<0.001	2.16	0.92–2.57	0.58
Time to travel to hospital (hr)						
Less than 2	1	Reference		1	Reference	
2–5	2.45	1.66–3.62	<0.001	1.03	0.46–2.28	0.07
More than 5	2.75	1.89–4.00	<0.001	1.04	0.42–2.31	0.06
Type of parental employment						
Informal	4.39	2.54–7.59	<0.001	2.88	1.60–5.21	<0.001
Formal	1	Reference		1	Reference	

CI, confidence interval; OR, odds ratio

TABLE 3 Abandonment rate and outcome status according to type of cancer in children with solid tumors in Peru (2012–2014)

Type of cancer	N	Abandonment rate, n (%)	Outcome status			
			NED, n (%)	AWD, n (%)	LFU, n (%)	DOD/DOC, n (%)
All diagnoses	1135	209 (18.4%)	362 (31%)	58 (5.1%)	274 (24.1%)	441 (38.8%)
Lymphoma	221	37 (16.7%)	42 (19.0%)	14 (6.3%)	43 (19.5%)	122 (55.2%)
Brain tumor	203	26 (12.8%)	48 (23.6%)	9 (4.4%)	64 (31.6%)	82 (40.4%)
Bone and soft tissue sarcoma	194	56 (28.9%)	83 (42.8%)	14 (7.2%)	31 (16.0%)	66 (34.0%)
Retinoblastoma	158	47 (29.7%)	54 (34.2%)	9 (5.7%)	37 (23.4%)	58 (36.7%)
Others	359	43 (11.9%)	135 (37.6%)	12 (3.3%)	99 (27.6%)	113 (31.5%)

factors.[2] In this study, age was not associated with the risk of treatment abandonment. Early age has been associated with higher rates of abandonment in some studies,[30,35,36] although there is not a complete understanding of the reason for this association. Gender and clinical stage were not associated with higher abandonment rates in our study, which is similar to the results in other studies.[30,37] In contrast, a report

by Li and Jin[8] found that Chinese females had a higher risk of refusal and abandonment, compared to males.

We found significant variation in abandonment rates between the two studied treatment centers. This may be explained by the difference in socio-economic conditions of the patients attending the two centers. Patients at INEN, where abandonment rates reached 21.9%,

mainly came from families with no formal employment and probably higher economic hardship, a well-documented factor associated with abandonment. At INEN, the lack of available beds is rather frequently cited, which could affect proper treatment administration despite the medicine being provided for free and could also affect the abandonment rate.

According to the type of malignancy, our study did not find a significant association between a higher risk of abandonment and the type of cancer after the multivariate analysis. Several pediatric leukemia studies have described highly variable treatment abandonment rates,[10,24,28] whereas studies on retinoblastoma[38,39] and sarcomas[40] report higher rates of abandonment when compared to other solid tumors.[13,25,41]

Socio-economic hardship is the main contributor to the abandonment of cancer treatment in LMIC[2,16,32,42] and includes financial and transportation difficulties, lack of medical insurance, loss of formal employment due to treatment, lack of coverage of essential drugs, and family disintegration.[2,37] We found that almost 20% of families came from rural settings, which may indicate that they were from households with insufficient income to cover their basic needs, according to the World Bank estimations. Although the social services provided in both centers include social workers who assess the situations of families, identify main problems, and provide counseling, the active follow-up of cases who abandon treatment remains low. Accurate data for families' economic statuses, education levels, and transportation hardships were not available, although these factors are clearly relevant.

Geographical factors such as the place of residency and the time needed to travel to a referral facility have been described by some studies as important factors for abandonment,[25,29,30,43] whereas other studies have found this factor to be inconsistent.[12] This study shows that children living in a rural setting had a significantly increased risk of treatment abandonment, as previously described by other authors.[36,37] Regarding the problem of distance and long-term stays or frequent travel, allocation of housing facilities near treating centers has been a successful strategy implemented in some countries.[14,24] In Peru, patients treated at both centers have free hostels near the treatment hospital where parents can stay while away from home; however, we have no data or measuring point to determine whether this housing resource helps to reduce abandonment. Unfortunately, the housing available is not always sufficient and the high demand by patients needing treatment affects the vacancies in these hostels, which causes financial problems for the families.

A special type of discontinuation of treatment that should be distinguished from treatment abandonment is having forgone curative treatment.[23] In our study, we documented these cases to be as high as 6.8%, revealing an important subset of patients who are not receiving curative-intent oncological treatment due to very advanced disease at onset or poor performance status. Other studies in LMIC have reported variable rates of children receiving palliative-only care, calling for an interdisciplinary approach for progressive, debilitating, or life-limiting illnesses such as cancer.[23,44] In Peru, advanced disease at diagnosis is found in as much as 37% of pediatric cancer cases.[5] Delayed diagnoses and aggressive biological behavior are possible explanations for this finding.[5,45–47]

The limitations of our study are inherent to its retrospective nature. First, the data from clinical records and local databases were missing for some variables. Second, leukemia patients were not included in the study because the oncologists from one center only treat children with solid tumors. These factors could affect generalization and comparison to other studies. The strengths of this study include the large number of patients studied in a relatively short study period, giving a general overview that might help inform the design of strategies for improving factors related to treatment abandonment in children with cancer. Currently, both institutions are in the process of implementing a hospital-based childhood cancer registry, and most of the findings described in this study could contribute to the identification of useful variables for data collection in future prospective research studies. Moreover, this study could serve as a baseline for the current status of childhood cancer abandonment prevalence in Peru.

The role of government and nonprofit institutions in establishing national programs, free care, financial support, and counseling to decrease abandonment is vital, and have led to striking reductions of treatment abandonment in Mexico,[10] Paraguay,[48] Brazil,[24] El Salvador,[11] and Guatemala.[14] In Peru, there is no established formal strategy, and the results from this study could help in the proposal and design of viable solutions that could reduce this high proportion of children who abandon treatment despite accessible and available free care.

5 | CONCLUSIONS

In Peru, this large study showed that the treatment abandonment prevalence in pediatric solid tumors is high and closely related to socio-economic factors, such as the rural origin of patients and the lack of formal parental employment, giving a baseline report that may help design potential strategies to address these specific factors.

Potential general interventions to lower abandonment rates include educational programs for parents of children with cancer, early psychological team intervention, and external financial support from the government and nonprofit organizations. However, a more complex analysis of abandonment is needed from national population-based prospective studies, where parental education levels, socio-economic factors of families, and the needs of patients from rural settings are explored.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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