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GLOBAL ONCOLOGY: RESEARCH ARTICLE

Socioeconomic status and retinoblastoma survival: Experience of a tertiary cancer center in Brazil

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Abstract

Background: Little is known about socioeconomic status (SES) and its effects in childhood cancer survival. This study aims to discuss the association between SES and survival of patients with retinoblastoma (RB) from a tertiary treatment center.

Procedure: A retrospective cohort study was conducted, including all patients with RB referred to the Brazilian National Institute of Cancer in Rio de Janeiro (January 2000-December 2016).

Results: Data from 160 patients were analyzed with mean age at diagnosis of 22.85 months (SD ± 14.29). Eighty-three patients (51.9%) had an interval to diagnosis equal to or longer than six months, and 13 children (8.1%) abandoned treatment. Five-year overall survival rate for all patients was 78.8% (95% CI, 72.4%-85.9%). In a multivariate model, patients whose fathers had more than nine years of study had a lower death risk. Patients from families having more than one child under five years had a 213% higher risk of death compared with those living with no other small child. Treatment abandonment also had a profound effect on death risk.

Conclusion: Childhood cancer is notably important considering the potential years of life lost. RB has even more important elements, as the possibility of vision loss in cases with delayed diagnosis. Family characteristics seem to be highly related to RB survival, especially in low- and middle-income countries, where inequalities are still a public health issue. Strategies to improve survival should focus not only on large-scale settings such as improving national healthcare systems but also on more personalized actions that might help to mitigate disparities.

KEYWORDS
childhood cancer, paternal education, retinoblastoma, socioeconomic status, survival analyses, treatment abandonment

1 | INTRODUCTION

Social disparities in cancer outcomes have been well appraised in adult cancers.[1–3] In contrast, little is known about socioeconomic status (SES) and its effects in childhood cancer survival, and therefore, there is a growing necessity to understand factors influencing outcomes other than those related to treatment or tumor biology.[4]

Abbreviations: CI, confidence interval; CNS, central nervous system; HDI, human development index; HIC, high-income countries; HR, hazard ratio; IIRC, international intraocular retinoblastoma classification; INCA, Brazilian National Institute of Cancer; IRSS, international retinoblastoma staging system; LIC, low-income country; LMIC, low- and middle-income countries; RB, retinoblastoma; SES, socioeconomic status

One of the most important prognostic factors for a child with cancer is place of birth. This has been extensively proven in macroscopic settings studies comparing outcomes between countries with different levels of development.[5,6] Low SES seems to impact childhood cancer outcomes uniformly in low- and middle-income countries (LMIC) and more variably in high-income countries (HIC).[7] Some studies have shown an association between SES and inferior outcomes in pediatric cancer[4] but the mechanisms of connection are multifaceted, interrelated, and generally discussed only in theoretical terms with scarce empiric sources.[8] Beyond that, the impact of diverse aspects of SES differs between settings and cancer types.[7,8] For instance, a strong association between SES and acute lymphoblastic leukemia survival is explained by disparities in treatment adherence.[9]

Retinoblastoma (RB) is the most common intraocular malignancy of childhood, with survival rates approaching 100% in series from HIC.[10] In LMIC, RB is still life-threatening, with survival rates as low as 50%, triggered by poor socioeconomic conditions[8] and late diagnoses.[11–14] RB may present a unique setting to assess SES disparities for nonhematological solid tumors. Several socioeconomic factors and others related to health education can contribute to RB late diagnosis, including illiteracy, poverty, lack of trained health professionals, unawareness about early signs, precarious health care structure, lack of access to the health system, and vulnerability.[11,15,16] So, RB may present a unique setting to assess SES disparities for nonhematological solid tumors.

At the Brazilian National Institute of Cancer (INCA), located in Rio de Janeiro, Brazil, all patients receive complete treatment free of cost. We hypothesize, however, that despite all efforts, there are disparities in survival. The present study aims to discuss the association between SES and survival of patients with RB from a tertiary treatment center in Brazil.

2 | METHODS

A retrospective cohort study was conducted, including all patients with RB referred to INCA in Rio de Janeiro between January 2000 and December 2016. INCA is a tertiary center for adult and pediatric patients, where integrated actions for cancer control and prevention are developed and implemented as an auxiliary branch of the Brazilian Ministry of Health.[17] Patients who had first treatment elsewhere were excluded as these would not give a true reflection of time to diagnosis, management and outcome. Trilateral retinoblastoma patients were also excluded as they have dismal survival in general.

Medical charts for all eligible patients were reviewed. A form was built to guide data extraction, which was performed by one of the authors (MC). Socioeconomic and household data were extracted from a standard form completed by social work staff at the beginning of treatment.

Age at diagnosis (months) was split into three categories: < 12, 12-23 and > 24. Race/color was grouped as White, Brown, or Black. As the Brazilian population is extremely heterogeneous, the term Color is capitalized to call attention to its special meaning in the census classification context, denoting the equivalent of the "race" term and based on self-identification.[17]

City of residence (at the time of RB diagnosis) was grouped as Rio de Janeiro City and metropolitan area, other cities of Rio de Janeiro state, and other Brazilian states. Household income was converted into minimum wages and grouped into four categories, using Brazilian currency REAIS (R$). Maternal and paternal education were categorized into two levels: < 9 or ≥ 9 years of study. Time to diagnosis (months) was defined as the interval from the perception of first signs and symptoms to date of diagnosis. Distance between household and treatment center in km, number of inhabitants per household, number of inhabitants under five years of age/household, and time to diagnosis interval were further divided into two categories based on median values. An absence of 30 days during treatment or treatment refusal was considered as treatment abandonment.[18] Patients who lost follow-up after completing treatment were not included in this category. Overall survival was calculated as time in years from date of diagnosis to death or last contact. Last date of follow-up was October 30, 2017. Patients who survived were censored at last healthcare visit recorded on medical charts.

The study received approval from Ethics Committee at INCA, under CAAE number: 55429116.7.0000.5274. Individual informed consent was waived because of study design (registry based).

2.1 | Statistical analyses

Descriptive statistics are presented to characterize the cohort. Survival was analyzed using the Kaplan-Meier method, and differences in curves were evaluated by the log-rank test. Hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) were estimated using Cox proportional hazard models, and Schoenfeld residuals test confirmed the proportional hazard assumption.

We have included in the multivariate model all variables with $P < 0.25$, using a hierarchical approach to build the final model. All analyses were performed using Stata 15.1.

3 | RESULTS

Out of the 190 patients enrolled as RB during the study period, 30 were excluded from analysis (24 patients had their first treatment elsewhere and six had trilateral RB). Four of six trilateral cases died from RB. Among patients who had their first treatment elsewhere, two died and two had missing information about death.

The final sample included 160 patients with RB, with a mean age at diagnosis of 22.85 months (SD ± 14.29); the sex ratio at registration was 1.16 (M/F).

One-hundred forty-seven (91%) patients were from families living with less than three times the minimum wage. Most mothers had more than nine years of education (57.5%), whereas 65 fathers (40.6%) had the same educational level. Only 24 patients (15%) had private health insurance. Most children and families had access to potable

TABLE 1 Number and percentage of patients with retinoblastoma according to demographic, socioeconomic, and disease-related variables

Variables	*n* (%)
Sex	
Male	86 (53.8)
Female	74 (46.2)
Age at diagnosis (months)	
<12	43 (26.9)
12-23	46 (28.8)
≥24	71 (44.4)
Race	
White	93 (58.2)
Black	15 (9.4)
Brown	49 (30.6)
Asian	1 (0.6)
Unknown	2 (1.2)
City of origin	
Rio de Janeiro metropolitanarea	116 (72.5)
Otherscities of Rio de Janeiro state	35 (21.9)
Other states of Brazil	9 (5.6)
Distance from tertiary center (km)	
≤ 39.3	81 (50.6)
> 39.3	79 (49.4)
Family monthly income (minimum wages)	
< 1	17 (10.6)
1-1.50	60 (37.5)
1.51-3.0	41 (25.7)
> 3.0	29 (18.1)
Unknown	13 (8.1)
Maternal education (years of study)	
≤9	32(20.0)
> 9	92 (57.5)
Unknown	36 (22.5)
Paternal education (years of study)	
≤9	44 (27.5)
> 9	65 (40.6)
Unknown	51 (31.9)
Private health insurance	
No	128 (80.0)
Yes	24 (15.0)
Unknown	8 (5.0)
Time to diagnosis(months)	
< 6	77 (48.1)
≥ 6	83 (51.9)
No. of inhabitants per household	
< 4	40 (25.0)
≥ 4	114 (71.3)
Unknown	6 (3.7)
Number of children under five/household	
1	99 (61.9)
> 1	55 (34.4)
Unknown	6 (3.7)
Safe drinking water available at home	
No	28 (17.5)
Yes	118 (73.8)
Unknown	24 (8.7)
Sewage availability	
No	22 (13.8)
Yes	124 (77.5)
Unknown	14 (8.7)
Electricity availability	
No	11 (6.9)
Yes	132 (82.5)
Unknown	17 (10.6)
Disease extension	
Intraocular	127 (79.4)
Extraocular	33 (20.6)
Disease laterality	
Unilateral	104 (65.0)
Bilateral	56 (35.0)
Treatment abandonment	
No	147 (91.9)
Yes	13 (8.1)

water (73.8%), treated sewage (77.5%), and electricity (82.5%). Household crowding (families with four or more members) was frequent (71.3%). Most patients had unilateral disease (65.0%) and intraocular retinoblastoma (79.4%). Eighty-three patients (51.9%) had an interval to diagnosis equal to or longer than six months, and 13 children (8.1%) abandoned treatment (Table 1). Eight patients declared upfront to have other cases of RB in their family. In genetic analysis achieved in 139 patients, 14 cases were familiar RB.

Out of the 104 unilateral cases, 61 (58.7%) had enucleation at diagnosis, and 39 (37.5%) had intravenous chemotherapy as first treatment. Among 56 patients with bilateral disease, 44 (78.6%) had intravenous chemotherapy as initial treatment, and only six (10.7%) had one eye enucleated at diagnosis. Six patients refused enucleation.

Five-year overall survival (5y-OS) rate for all patients was 78.8% (95% CI, 72.4%-85.9%). No significant differences in 5-y OS were observed according to sex ($P = 0.336$), race ($P = 0.678$), city of residence ($P = 0.787$), distance from tertiary center ($P = 0.719$), private health insurance ($P = 0.119$), number of habitants/household

($P = 0.189$), electricity at household ($P = 0.396$), or laterality ($P = 0.209$) (Table 2). Younger children (< 12 months, 5-y OS = 91.0% and 12-23 months, 5-y OS = 87.7%) presented higher survival rates compared with older children >24 months, 5-y OS = 67.6%) ($P < 0.001$). There was a significant gradient in 5-y OS, from lowest (56.0%) to highest family income (95.6%) ($P = 0.004$). Children with parents with better school attainment also presented better survival ($P < 0.001$ for both maternal and paternal education). Longer time to diagnosis was associated with lower survival rates (< 6 months = 87.7% and ≥ 6 months = 71.5%, $P = 0.017$), as well as safe drinking water availability at home (no, 5-y OS = 63.1%; yes, 5-y OS = 82.1%, $P = 0.007$). Children with extraocular disease (45.0%) presented lower survival rates compared with those with intraocular RB (88.8%) ($P < 0.001$), and treatment abandonment also harmed survival (Table 2).

In the final multivariate model, patients whose fathers had more than nine years of study had a lower risk of death compared with those with lower educational level (HR: 0.11; 95% CI, 0.03-0.38). Patients from families having more than one child under five years at home had a 213% higher risk of death compared with patients living in families with no other small child (HR: 3.13; 95% CI, 1.51-6.51). Treatment abandonment also had a profound effect on death risk (HR: 7.00; 95% CI, 3.17-15.49). As compared with intraocular disease at diagnosis, patients with metastatic or extraocular stage had also a significant increase in death risk (HR: 9.40; 95% CI, 4.52-19.58) (Table 3).

4 | DISCUSSION

Brazilian citizens have full access to a universal and free healthcare system, warranted by the Constitution since 1988.[19] Thus, in theory, every child in our cohort would have similar access to treatment. However, survival was far from equal, and SES characteristics, such as paternal education and number of children under five years of age living in household, affected retinoblastoma survival, independently from stage at diagnosis, and treatment abandonment.

The association between parental education and pediatric cancer survival has been previously established.[20,21] Our study indicates that higher parental education (above nine years of study) was directly associated with higher survival for both paternal and maternal education on univariate analysis. However, in the final model, only paternal education remained as an independent predictor, showing that children with RB born from highly educated fathers had an 89% reduction in risk of death compared with those children with less-educated fathers. Mothers' perceptions of leukocoria are often dismissed by health professionals,[13] and we speculate that more educated fathers are also more prepared to notice first signs or respond adequately to mothers' complaints and seek medical help sooner. Beyond that, paternal education is strongly associated with family income; thus, more educated fathers have better income, expediting not only the prediagnosis period but also treatment adherence.

Registry-based studies have shown that pediatric cancer survival depends on family resources.[16] The number of children living in a household may influence childhood cancer survival overall[21,22] and also for specific malignancies such as CNS tumors.[23] The risk of death was 3.1 times higher for children living in households with more than a child under five. In households with many small children, parents' attention to each child individually might plausibly be reduced, causing a late perception of first symptoms, delay in seeking medical attention, and poor adherence to treatment. Having a high number of siblings has effects before and after cancer diagnosis.[24]

Treatment abandonment is a significant cause of therapeutic failure, affecting up to 50%-60% of cases in LMIC.[25,26] Abandonment is related to SES, parents' education, travel time to hospital, and affordable and locally available treatment.[25] RB outcome is extremely time-related, and late diagnosis is a recognized cause of poorer prognosis.[11,12,27,28] Consequently, delay to start or proceed with treatment causes similar adverse effects on outcomes. It has been demonstrated that RB, as well as CNS tumors, has a high treatment abandonment rate,[29] possibly because it frequently involves a mutilating procedure such as enucleation in order to achieve cure. Treatment refusal is also a frequent problem in RB, described in up to 50% of publications from less developed countries.[30,31] Children with bilateral disease are often submitted to multiple procedures, with enucleation of the worse eye and preserving therapies applied to the remaining eye.[10,32] In another study, RB had more abandonment than other solid tumors despite prevention strategies implemented since 2012 that led to a general low abandonment rate to all patients.[31]

Racial and ethnic disparities mark pediatric cancer survival. Whites have a significant survival advantage over Blacks and Hispanics for several childhood cancers, but the mechanisms behind these disparities are not yet fully understood.[33–35] Higher percentages of advanced disease are found among nonwhite and Hispanic children with RB.[36] Also, these two groups were more likely to receive enucleation, independent of stage of diagnosis, implying a more substantial inequality in care.[37] The Brazilian population is extremely heterogeneous, a consequence of centuries of admixture among Amerindians, Europeans, and sub-Saharan Africans.[17] Therefore, it is challenging to establish patient ethnicity, and no differences in survival were observed between whites and nonwhites in our cohort.

Survival was significantly associated with family monthly income in univariate analysis. Previous studies have revealed that combined parental income was associated with pediatric cancer mortality.[4,7] Survival of children living in households with income exceeding three minimum wages was 95% compared with 56% for those living with less than one minimum wage. Low income may affect survival in many ways; economic restrictions limit parents from traveling to treatment center, resulting in late diagnosis. Access can be difficult even for short distances if the family has significant budget limitations. Low SES may also interfere with treatment adherence, producing a higher rate of treatment abandonment. Families with higher SES are generally more educated and consequently more capable of early identification of first signs and symptoms.

In most pediatric malignancies, disease extension at diagnosis is more related to tumor biology than late diagnosis.[38–40] However, in RB, a strong association exists between time to diagnosis and disease extension.[11–13,28,41] A classic study connecting time to diagnosis and

TABLE 2 Cumulative probabilities of five-year survival (95% CI) for children with retinoblastoma according to demographic, socioeconomic and clinical variables

Variables	Five-year OS (95% CI)	*P* value
Sex		
Male	75.8 (64.1-84.2)	0.336
Female	82.9 (71.8-89.9)	
Age at diagnosis (months)		
< 12	91.0 (74.6-97.0)	<0.001
12-24	87.7 (73.0-94.7)	
> 24	67.6 (54.9-77.4)	
Race		
White	81.3 (71.1-88.1)	0.678
Nonwhite	78.2 (65.3-86.8)	
Unknown	50.0 (0.6-91.0)	
City of residence		
Rio de Janeiro metropolitan rea	78.1 (68.7-85.0)	0.787
Other cities of Rio de Janeiro state	80.6 (61.7-90.8)	
Other states of Brazil	88.9 (43.3-98.4)	
Distance from tertiary center (km)		
> 39.3	78.1 (66.6-86.0)	0.719
≤ 39.3	80.4 (68.9-88.0)	
Family monthly income (amount of minimum wages)		
< 1	56.0 (29.0-76.2)	0.004
1-1.5	75.8 (61.7-85.2)	
1.6-3.0	82.1 (65.8-91.1)	
> 3.0	95.6 (72.9-99.4)	
Unknown	79.1 (36.7-94.7)	
Maternal education (years)		
< 9	53.4 (33.8-69.6)	<0.001
≥ 9	88.7 (79.2-94.0)	
Unknown	78.9 (60.6-89.4)	
Paternal education (years)		
< 9	61.8 (45.1-74.7)	<0.001
≥ 9	93.8 (81.7-98.0)	
Unknown	76.9 (61.9-86.6)	
Private health insurance		
No	76.0 (67.1-82.9)	0.119
Yes	95.6 (72.9-99.4)	
Unknown	80.0 (20.4-96.9)	
Time to diagnosis[a] (months)		
< 6	87.7 (76.7-93.7)	0.017
≥ 6	71.5 (59.9-80.3)	
Number of inhabitants per household		
< 4	87.4 (72.4-94.6)	0.189
≥ 4	76.7 (67.3-83.7)	
Number of children under five years of age/household		

(Continues)

TABLE 2 (Continued)

Variables	Five-year OS (95% CI)	*P* value
1	86.4 (77.1-92.1)	0.005
> 1	66.8 (51.9-77.9)	
Unknown	75.0 (12.8-96.0)	
Safe drinking water availability at home		
No	63.1 (42.1-78.2)	0.007
Yes	82.1 (73.1-88.3)	
Unknown	88.9 (43.3-98.4)	
Sewage availability		
No	58.4 (35.2-75.8)	0.002
Yes	82.0 (73.4-88.1)	
Unknown	88.9 (43.3-98.4)	
Electricity availability		
No	81.8 (44.7-95.1)	0.396
Yes	77.6 (68.9-84.2)	
Unknown	91.7 (53.9-98.8)	
Disease extension		
Intraocular	88.8 (81.0-93.5)	
Extraocular	45.0 (27.6-60.9)	<0.001
Disease laterality		
Unilateral	77.5 (67.7-84.6)	
Bilateral	82.7 (68.1-91.0)	0.209
Treatment abandonment		
No	83.9 (76.2-89.3)	
Yes	28.8 (7.8-54.5)	<0.001

TABLE 3 Crude and adjusted hazard ratios for death among patients with retinoblastoma

Variables	Crude HR (95% CI)	Adjusted HR (95% CI)
Paternal education (years of study)		
<9	Ref.	Ref.
≥ 9	0.11 (0.03-0.38)	0.14 (0.04-0.52)
Unknown	0.58 (0.27-1.23)	0.43 (0.20-0.93)
Household number of children under five years of age		
1	Ref.	Ref.
>1	3.13 (1.51-6.51)	2.86 (1.35-6.07)
Unknown	1.64 (0.21-12.61)	7.01 (0.82-59.79)
Treatment abandonment		
No	Ref.	Ref.
Yes	7.00 (3.17-15.49)	1.94 (0.83-4.54)
Disease extension		
Intraocular	Ref.	Ref.
Extraocular	9.40 (4.52-19.58)	6.76 (3.03-15.08)

outcome in RB, conducted in Brazil, showed a median time to diagnosis of five months.[28] It is alarming that 30 years later, despite several campaigns to raise awareness, the median time to diagnosis remains around six months, with a significant association with poor survival. Worldwide, time to diagnosis ranges from 38 days in the United Kingdom,[42] to 60 in China,[43] whereas in São Paulo, Brazil, a study reported 5.8 months.[44] In HIC, a long time to diagnosis is frequently related to high-risk pathology, but not to survival because deaths are now infrequent.[42,45] Several campaigns to raise awareness of RB early diagnosis have been undertaken worldwide, with a particular case of success in Honduras, where an educational program was associated with vaccination campaigns.[46]

The use of medical records as our primary data source is one study limitation; throughout the span period, digital charts and social service forms were implemented gradually, and those changes could produce an information bias. Another major weakness is lack of a uniform classification and treatment protocol. RB treatment and classifications has evolved drastically in the last decades. External beam radiotherapy was used in the past as a tool for eye preservation, and was later replaced by intravenous chemotherapy and local therapies until a paradigm change with the adoption of intra-arterial chemotherapy.

There is no particular gold-standard indicator of SES, and its influence on survival in childhood cancer may be heterogeneous and cancer-specific.[33] Low SES affects health in many different ways: higher exposure to infectious diseases, poor nutritional status, and difficulties in access to healthcare. All those factors may also influence cancer outcomes, and it is challenging to assess the exact effect triggered by eachof them. The study of SES and its effects on cancer outcomes is a complex subject; methodologies are not uniform and generally do not use the same measures. It is common to assess SES using well-established scores such as the Human Development Index (HDI) and child health indicators.[30,47,48] HDI was associated with retinoblastoma survival in a systematic review of outcomes in LIC.[30]

Our study strengths reside on cohort size, uniform data collection, and the sets of SES variables. Social workers were responsible for filling the standard forms available in medical charts; their experience in obtaining and registering socioeconomic data may have been helpful in order to reduce bias and missing data.

The INCA is the main pediatric oncology center of Rio de Janeiro state receiving the majority of all solid pediatric cancer and particularly most patients with retinoblastoma as it is the only cancer center offering eye-preserving treatments as intrarterial and intravitreous chemotherapy. No private centers take care of RB patients in Rio de Janeiro. Therefore, the cohort probably represents the majority of RB cases in this region.

Family characteristics such as paternal education and number of children under five years of age along with treatment abandonment were all significantly related to retinoblastoma survival. Therefore, strategies to improve RB survival must focus not only on large-scale settings, such as improving national healthcare systems and poverty reduction, but also on more personalized actions that might help to mitigate disparities. Treatment abandonment prevention can be achieved by supervising missed appointments, and early interventions to provide resources to assist families during treatment.[31] Families with more than one child under five years of age and lower paternal education could be more closely supervised by social workers after diagnosis in order to help and monitor them through retinoblastoma treatment.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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