JAMA Oncology | Original Investigation

Global Retinoblastoma Presentation and Analysis by National Income Level

Global Retinoblastoma Study Group

IMPORTANCE Early diagnosis of retinoblastoma, the most common intraocular cancer, can save both a child's life and vision. However, anecdotal evidence suggests that many children across the world are diagnosed late. To our knowledge, the clinical presentation of retinoblastoma has never been assessed on a global scale.

OBJECTIVES To report the retinoblastoma stage at diagnosis in patients across the world during a single year, to investigate associations between clinical variables and national income level, and to investigate risk factors for advanced disease at diagnosis.

DESIGN, SETTING, AND PARTICIPANTS A total of 278 retinoblastoma treatment centers were recruited from June 2017 through December 2018 to participate in a cross-sectional analysis of treatment-naive patients with retinoblastoma who were diagnosed in 2017.

MAIN OUTCOMES AND MEASURES Age at presentation, proportion of familial history of retinoblastoma, and tumor stage and metastasis.

RESULTS The cohort included 4351 new patients from 153 countries; the median age at diagnosis was 30.5 (interquartile range, 18.3-45.9) months, and 1976 patients (45.4%) were female. Most patients (n = 3685 [84.7%]) were from low- and middle-income countries (LMICs). Globally, the most common indication for referral was leukocoria (n = 2638 [62.8%]), followed by strabismus (n = 429 [10.2%]) and proptosis (n = 309 [7.4%]). Patients from high-income countries (HICs) were diagnosed at a median age of 14.1 months, with 656 of 666 (98.5%) patients having intraocular retinoblastoma and 2 (0.3%) having metastasis. Patients from low-income countries were diagnosed at a median age of 30.5 months, with 256 of 521 (49.1%) having extraocular retinoblastoma and 94 of 498 (18.9%) having metastasis. Lower national income level was associated with older presentation age, higher proportion of locally advanced disease and distant metastasis, and smaller proportion of familial history of retinoblastoma. Advanced disease at diagnosis was more common in LMICs even after adjusting for age (odds ratio for low-income countries vs upper-middle–income countries and HICs, 17.92 [95% CI, 12.94-24.80], and for lower-middle–income countries vs upper-middle–income countries and HICs, 5.74 [95% CI, 4.30-7.68]).

CONCLUSIONS AND RELEVANCE This study is estimated to have included more than half of all new retinoblastoma cases worldwide in 2017. Children from LMICs, where the main global retinoblastoma burden lies, presented at an older age with more advanced disease and demonstrated a smaller proportion of familial history of retinoblastoma, likely because many do not reach a childbearing age. Given that retinoblastoma is curable, these data are concerning and mandate intervention at national and international levels. Further studies are needed to investigate factors, other than age at presentation, that may be associated with advanced disease in LMICs.

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Supplemental content

Group Information: The members of the Global Retinoblastoma Study Group appear at the end of this article.

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Retinoblastoma, the most common eye cancer of childhood, is fatal if left untreated. Prognosis of patients with retinoblastoma in high-income countries (HICs) has improved over the past 50 years, now reaching a near 100% disease-free survival rate.[1-3] This is attributed to several factors, including (1) creation of specialized referral centers, (2) decoding of the genetic basis of the disease, (3) formation of screening programs, and (4) the introduction of chemotherapy.[4] In HICs, retinoblastoma is a curable disease, and attention has now shifted to eye salvage[5,6] and improvement of quality of life.[7] In low- and middle-income countries (LMICs), where more than 80% of global retinoblastoma cases arise, the prognosis is poor, and it is assumed that this is because of delayed diagnosis and treatment.[8-10] Publications from LMICs are scarce, and many countries do not report their retinoblastoma data.[11] The stage of retinoblastoma at the time of diagnosis in low-income, middle-income, and high-income countries has not been surveyed globally. This information is important for policy and health care planning at national and international levels.

The objectives of this study are to (1) report the stage at diagnosis in a large global sample of patients with retinoblastoma, (2) examine associations between clinical variables at presentation and national-income level, and (3) investigate risk factors for advanced disease at diagnosis.

Key Points

Question Is the income level of a country of residence associated with the clinical stage of presentation of patients with retinoblastoma?

Findings In this cross-sectional analysis that included 4351 patients with newly diagnosed retinoblastoma, approximately half of all new retinoblastoma cases worldwide in 2017, 49.1% of patients from low-income countries had extraocular tumor at time of diagnosis compared with 1.5% of patients from high-income countries.

Meaning The clinical stage of presentation of retinoblastoma, which has a major influence on survival, significantly differs among patients from low-income and high-income countries, which may warrant intervention on national and international levels.

Methods

This study originated from a consortium of retinoblastoma treatment centers in 8 countries on 3 continents.[12] From June 2017 through December 2018, all known retinoblastoma treatment centers across the world were contacted by means of personal communications, presentations at scientific conferences, and linking to professional societies in the fields of ophthalmology and oncology to form a global network. All centers involved in the diagnosis and treatment of patients with retinoblastoma, at least by means of enucleation, were eligible to participate.

Study Design

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[13] It was a 1-year cross-sectional analysis that included all treatment-naive patients with retinoblastoma who presented to participating centers from January 1, 2017, to December 31, 2017, and who were treated or offered treatment for retinoblastoma. A predesigned form was used for data collection (eTable 1 in the Supplement). The data collected included country of residence, sex, first ocular symptom as noted by parents, age at first indication of symptom, age and ocular indication at presentation to the retinoblastoma treatment center, laterality, familial history of retinoblastoma, staging according to the *American Joint Committee on Cancer Staging Manual, Eighth Edition*[14] and the International Retinoblastoma Staging System,[15] and primary treatment. Data on country of residence, sex, and laterality were minimum criteria for patient enrollment. The staging classifications were simplified to include only the major subcategories (eTable 2 in the Supplement). For the primary tumor site (cT), the eye with the more advanced disease was used for analysis. Completed forms were electronically uploaded onto a secure server, after which a data quality assurance process was performed (eMethods in the Supplement).

The study was approved by the institutional review board at the London School of Hygiene & Tropical Medicine, which granted a waiver of patient informed consent. Participating centers applied for and received ethics clearance in their countries according to local institutional guidelines.

Statistical Analysis

All analyses were performed using R software, version 3.5.2 (R Foundation for Statistical Computing), and IBM SPSS Statistics, version 25.0 (IBM Corp). The crude birth rate, country population size, and country classification by national income level were obtained from the 2017 World Population Prospects.[16] The predicted number of new patients with retinoblastoma per country was calculated as follows: [country population × crude birth rate/1000/17 000], and predicted number per national income level was the sum result of all countries at the same level.

Unless otherwise indicated, summary statistics are presented as median and interquartile range (25%-75%). The *t* test was used to compare means of normally distributed continuous variables, Fisher exact and Pearson χ^2 tests were used to compare categorical variables, Spearman rank correlation test was used for nonnormal continuous and ordinal variables, and the Cochran-Armitage test[17,18] was used to test for trend in the proportions of patients with a given parameter across the income levels. Binomial logistic regression was used to model the effect of income level (upper-middle–income level and high-income level combined), presentation age (grouped by tertiles), familial retinoblastoma history, sex, and bilaterality, on the likelihood of children having advanced disease (cT4) at presentation. An α level of .05 and 2-tailed *P* values were used to determine statistical significance.

Results

The study sample included 4351 treatment-naive patients with retinoblastoma residing in 153 countries (**Figure**). The data

analyzed by national income level are shown in **Table 1**. Country-level and continent-level data are shown at http://globalretinoblastoma.org (password: Ret2017).

Geographic and Socioeconomic Characteristics

More than half (2276 [52.3%]) of the patients were from Asia, 1024 (23.5%) were from Africa, 522 (12.0%) were from Europe, 512 (11.8%) were from the Americas, and 17 (0.4%) were from Oceania. Of all patients, 533 (12.3%) came from low-income countries (LICs), 1940 (44.6%) from lower-middle, 1212 (27.9%) from upper-middle, and 666 (15.3%) from HICs.

Completeness of Data

For 4116 (94.6%) of the study patients, data were reported on each study parameter, except for age at first ocular symptom of retinoblastoma (2175 [50.0%]; not included in the analysis). Analysis by national income level showed that reporting was nearly complete (≥98.5%) for patients from high-income and upper-middle–income countries, and more than 94.1% and 89.1% for patients from lower-middle–income countries and LICs, respectively.

Symptoms Leading to Referral

The most common first symptom of disease was leukocoria (n = 2638 [62.8%]), followed by strabismus (n = 429 [10.2%]), with a further 162 (3.9%) patients having a combination of leukocoria and strabismus (eTable 3 in the Supplement). Proptosis was reported in 309 (7.4%) patients. At least 1 symptom of advanced disease (ie, proptosis, swollen eyelids, red eye) was reported in 487 (11.7%) patients. A higher income level was associated with a lower proportion of patients with symptoms of advanced disease (z score = 10.9, dim = 4; $P < .001$; additional analysis is provided in eTable 4 in the Supplement).

Symptoms at Time of Diagnosis at Retinoblastoma Centers

Of all patients, 2998 (70.4%) presented with either leukocoria, strabismus, or a combination of these symptoms (eTable 3 in the Supplement). In LICs, combinations of proptosis, red eye, orbital cellulitis, and extraocular retinoblastoma (ie, advanced disease) were present in 248 (46.7%) patients. Analysis of patients who had only leukocoria and/or strabismus (ie, early disease) as the symptoms noticed by the parents, but who presented to retinoblastoma treatment centers with symptoms of advanced disease, showed a significantly larger proportion coming from LICs (z score = 18.4, dim = 4; $P < .001$; additional analysis is provided in eTable 4 in the Supplement).

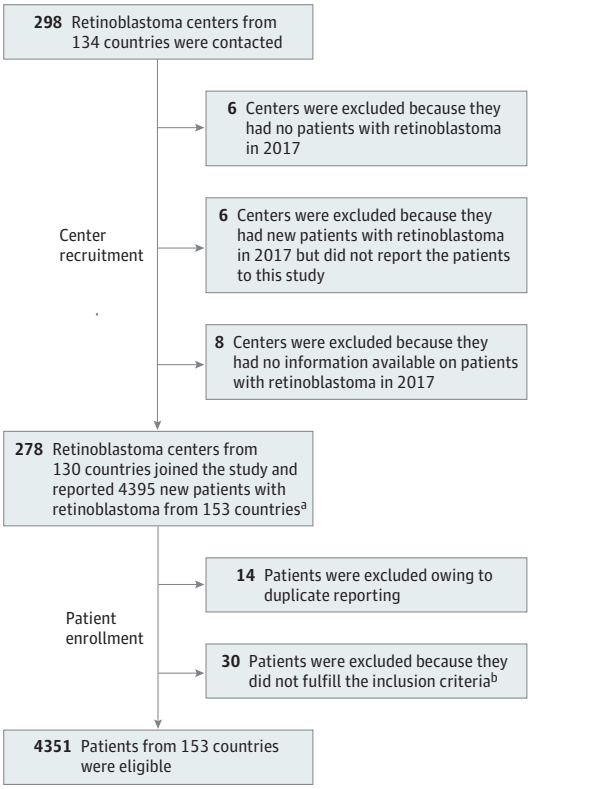
Age at Diagnosis

The overall median age at diagnosis was 23.5 months (interquartile range [IQR], 11.2-36.5 months; Table 1). The median age at diagnosis of patients from LICs was 30.5 months (IQR, 18.3-45.9 months) compared with 14.0 months (IQR, 6.2-26.6 months) for patients from HICs. There was a significant association between presentation age and national income level, with children in LMICs presenting at an older age (eTable 5 in the Supplement).

Tumor Staging

Globally, the most common cTNM stages were cT3 (n = 1933 of 4114 [47.0%]), N0 (n = 3303 of 4281 [77.2%]), and M0 (n = 3964 of 4275 [92.7%]) (Table 1). Extraocular retinoblastoma at time of diagnosis was reported in 926 of 4302 (21.5%) patients (256 [49.1%] in LICs vs 10 [1.5%] in HICs). Distant metastases were reported in 94 (18.9%), 157 (8.3%), 58 (4.8%), and 2 (0.3%) patients from low, lower-middle, upper-middle, and high income-level countries, respectively (z score = 11.9, dim = 4; $P < .001$). Higher economic grouping was associated with higher proportions of intraocular and earlier stage disease at diagnosis (Table 1).

Figure. Cohort Recruitment Flowchart



[a] Patients from 23 countries with no retinoblastoma centers were treated outside of their country of residence.

[b] Inclusion criteria included reporting of country of residence, sex, and laterality. Patients for whom 1 or more of these parameters were not available were not included in the analytic sample.

Risk Factors for Advanced Disease at Time of Diagnosis

Sex ($\chi^2_1 = 1.016$; $P = .31$), bilaterality ($\chi^2_1 = 0.830$; $P = .36$) and familial history of retinoblastoma ($\chi^2_1 = 2.269$; $P = .13$) were found to be nonsignificant factors for the prediction of cT4 category (extraocular retinoblastoma) and hence were removed from the model. On logistic regression, low-income level and older presentation age were found to be independent and significant predictive factors for advanced disease (**Table 2**).

Familial History and Bilateral Retinoblastoma

Familial history of retinoblastoma was reported in 199 of 4215 (4.7%) patients (15 [3.1%], 75 [4.0%], 54 [4.5%], and 55 [8.4%] patients from low, lower-middle, upper-middle, and high

Table 1. Clinical Characteristics at Presentation of 4351 New Patients With Retinoblastoma Diagnosed in 2017

Parameter	National Income Level, No. (% within the national income level) [% within the evaluated parameter]				Total, No. (%)	Significance	*P* Value
	Low	Lower-Middle	Upper-Middle	High			
Age at diagnosis, median (IQR), mo							
Total sample	30.5 (18.3-45.9)	24.4 (12.2-37.3)	20.7 (10.1-33.8)	14.0 (6.2-26.6)	23.5 (11.2-36.5)	ρ: −0.22	<.001[a]
Unilateral	35.0 (22.2-48.0)	29.1 (18.1-42.9)	25.5 (12.9-37.6)	19.7 (9.0-32.4)	27.1 (15.0-41.0)		
Bilateral	22.9 (11.8-32.8)	14.4 (8.0-25.8)	11.4 (6.0-21.0)	8.1 (3.7-15.8)	12.3 (6.1-24.3)		
Reported cases, No. (%)	524/533 (98.3)	1909/1940 (98.4)	1192/1212 (98.3)	664/666 (99.7)	4289/4351 (98.6)		
Laterality at diagnosis[b]							
Unilateral	408 (76.5) [13.6]	1325 (68.3) [44.0]	847 (69.9) [28.1]	430 (64.6) [14.3]	3010/4351 (69.2)	NA	<.001[c]
Bilateral	125 (23.5) [9.3]	615 (31.7) [45.9]	365 (30.1) [27.2]	236 (35.4) [17.6]	1341/4351 (30.8)		
Familial history of retinoblastoma							
No	467 (96.9) [11.6]	1805 (96.0) [44.9]	1141 (95.5) [28.4]	603 (91.6) [15.0]	4016/4215 (95.3)	*z* score: −4.3, dim: 4	<.001[d]
Yes	15 (3.1) [7.5]	75 (4.0) [37.7]	54 (4.5) [27.1]	55 (8.4) [27.6]	199/4215 (4.7)		
Total, No. (%)	482/533 (90.4)	1880/1940 (96.9)	1195/1212 (98.6)	658/666 (98.8)	4215/4351 (96.9)		
Primary tumor							
cT1	5 (1.0) [1.8]	96 (5.1) [35.3]	67 (6.1) [24.6]	104 (15.9) [38.2]	272/4114 (6.7)	*z* score: 22.3, dim: 4	<.001[e]
cT2	62 (12.6) [4.9]	406 (21.7) [31.8]	482 (44.1) [37.8]	326 (49.7) [25.5]	1276/4114 (31.0)		
cT3	209 (42.6) [10.8]	1013 (54.1) [52.4]	488 (44.6) [25.2]	223 (34.0) [11.5]	1933/4114 (47.0)		
cT4	215 (43.8) [34.0]	359 (19.2) [56.7]	56 (5.1) [8.8]	3 (0.4) [0.4]	633/4114 (15.4)		
Total, No. (%)	491/533 (92.1)	1874/1940 (96.6)	1093/1212 (90.2)	656/666 (98.5)	4114/4351 (94.6)		
Regional lymph node							
NX	105 (20.7) [12.6]	350 (18.4) [42.1]	267 (22.2) [32.1]	109 (16.4) [13.1]	831/4281 (19.4)	*z* score: 8.3, dim: 4	<.001[f]
N0	360 (71.0) [10.9]	1475 (77.3) [44.7]	912 (75.9) [27.6]	556 (83.6) [16.8]	3303/4281 (77.2)		
N1	42 (8.3) [28.6]	82 (4.3) [55.8]	23 (1.9) [15.6]	0	147/4281 (3.4)		
Total, No. (%)	507/533 (95.1)	1907/1940 (98.3)	1202/1212 (99.2)	665/666 (99.8)	4281/4352 (98.4)		
Distant metastasis							
M0	404 (81.1) [10.2]	1749 (91.8) [44.1]	1147 (95.2) [28.9]	664 (99.7) [16.8]	3964/4275 (92.7)	*z* score: 11.9, dim: 4	<.001[g]
cM1	65 (13.1) [30.4]	110 (5.8) [51.4]	39 (3.2) [18.2]	0	214/4275 (5.0)		
pM1	29 (5.8) [29.9]	47 (2.5) [48.5]	19 (1.6) [19.6]	2 (0.3) [2.1]	97/4275 (2.3)		
Total, No. (%)	498/533 (89.1)	1906/1940 (98.2)	1205/1212 (99.4)	666/666 (100)	4275/4351 (98.3)		
Hereditary trait							
HX	360 (72.7) [14.2]	1211 (63.8) [47.9]	736 (61.6) [29.1]	221 (33.4) [8.7]	2528/4250 (59.5)	NA	NA
H0	0	44 (2.3) [17.3]	59 (4.9) [23.2]	151 (22.8) [59.4]	254/4250 (6.0)		
H1	135 (27.3) [9.2]	643 (33.9) [43.8]	400 (33.5) [27.2]	290 (43.8) [19.8]	1468/4250 (34.5)		
Total, No. (%)	495/533 (92.9)	1898/1940 (97.8)	1195/1212 (98.6)	662/666 (99.4)	4250/4351 (97.7)		
Extraocular retinoblastoma							
No	265 (50.9) [7.8]	1393 (73.0) [41.3]	1062 (88.0) [31.5]	656 (98.5) [19.4]	3376/4302 (78.5)	*z* score: 21.8, dim: 4	<.001[h]
Yes	256 (49.1) [27.6]	515 (27.0) [55.6]	145 (12.0) [15.7]	10 (1.5) [1.1]	926/4302 (21.5)		
Total, No. (%)	521/533 (97.7)	1908/1940 (98.4)	1207/1212 (99.6)	666/666 (100)	4302/4351 (98.9)		
International Retinoblastoma Staging System							
Stage 0	44 (8.7) [3.0]	459 (24.2) [31.3]	585 (48.8) [39.9]	378 (56.8) [25.8]	1466/4264 (34.4)	NA	NA
Stage I	170 (33.8) [1.0]	816 (43.0) [47.9]	444 (37.0) [26.1]	272 (40.8) [16.0]	1702/4264 (39.9)		
Stage II	58 (11.5) [27.2]	111 (5.9) [52.1]	40 (3.3) [18.8]	4 (0.6) [1.9]	213/4264 (5.0)		
Stage III	101 (20.1) [26.1]	242 (12.8) [62.5]	41 (3.4) [10.6]	3 (0.5) [0.7]	387/4264 (9.1)		
Stage IV	94 (18.7) [29.9]	157 (8.3) [50.0]	60 (5.0) [19.1]	3 (0.5) [1.0]	314/4264 (7.4)		
NA	36 (7.2) [19.8]	111 (5.9) [61.0]	29 (2.4) [15.9]	6 (0.9) [3.3]	182/4264 (4.3)		
Total, No. (%)	503/533 (94.4)	1896/1940 (97.7)	1199/1212 (98.9)	666/666 (100)	4264/4351 (98.0)		

Abbreviations: IQR, interquartile range; NA, not applicable.

[a] Spearman rank correlation.

[b] Inclusion criteria: 100% reporting.

[c] Fisher exact test for proportion of bilateral cases.

[d] Cochran-Armitage test for proportion of familial history of retinoblastoma.

[e] Cochran-Armitage test for proportion of cT3 or greater.

[f] Cochran-Armitage test for proportion of cases with lymph node involvement.

[g] Cochran-Armitage test for proportion of cases with distant metastasis.

[h] Cochran-Armitage test for proportion of cases with extraocular disease.

Table 2. Logistic Regression Analysis: Predictors of Advanced Disease at Presentation[a,b]

Variable	B (SE)	Corrected *P* Value	Odds Ratio (95% CI)
Income level			
Low vs (upper-middle + high)	2.886 (0.166)	<.001	17.92 (12.94-24.80)
Low-middle vs (upper-middle + high)	1.748 (0.148)	<.001	5.74 (4.30-7.68)
Age at diagnosis			
14.27-31.20 mo	1.343 (0.167)	<.001	3.83 (2.76-5.31)
>31.20 mo	2.026 (0.160)	<.001	7.58 (5.54-10.38)
Constant	−4.602 (0.190)	<.001	0.01

[a] The logistic regression model was statistically significant ($\chi^2_4 = 727.27$; $P < .001$). The model explained 28.5% (Nagelkerke R^2) of the variance and correctly classified 85.1% of cases. Area under the curve was 0.813.

[b] Advanced disease is defined as cT4.

income-level countries, respectively). Bilateral disease at time of diagnosis was seen in 1341 of 4351 (30.8%) patients (125 [23.5%], 615 [31.7%], 365 [30.1%], and 236 [35.4%] patients from low, lower-middle, upper-middle, and high income-level countries, respectively) (Table 1). Significantly more familial (z score = −4.3, dim = 4; $P < .001$) and, independently, more bilateral cases were seen in HICs compared with LICs.

Diagnostic Facilities and Treatment Modalities

The available diagnostic and treatment modalities are shown in eTable 6 in the Supplement. The majority of patients (4201 [96.6%]) were diagnosed in a center that contained resources for computed tomography and/or magnetic resonance imaging. A histopathology service was available for 4236 (97.4%) participants, and intravenous chemotherapy for 4263 (98.0%).

Global Magnitude of Retinoblastoma and Representativeness of the Study

Given that the mean age at the time of diagnosis was approximately 2 years old, the 2015 birth rate data were used for calculation of the number of new retinoblastoma cases.[16] According to these data, the predicted annual number of new retinoblastoma cases worldwide ranged from 7752 to 8914. Using an average incidence figure of 1 of 17 000 live births, capture rates were 88.2%, 56.5%, 48.7%, and 39.9% of expected cases from high, upper-middle, lower-middle, and low-income countries, respectively. No data were received from 65 countries and principalities, mainly with small populations; the estimated number of missing cases from these countries was 46.

Discussion

Findings of this study show a large disparity in the presentation patterns of retinoblastoma between HICs and LMICs. A total of 666 children were from HICs, 99% of whom had at the time of diagnosis a tumor confined to the eye and thus a favorable prognosis. In comparison, of the 3685 patients from LMICs, 25% were diagnosed with tumor spread beyond the globe, for which the prognosis is much worse.[19,20] It is likely that the real gap in the pattern of retinoblastoma presentation is even wider owing to unreported patients in LICs who never arrived at a retinoblastoma treatment center and for whom death from metastatic disease is inevitable.

Late cancer diagnosis, also in the pediatric population, is a major issue in LMICs.[21-25] This study confirms this finding for retinoblastoma, which, if detected early, can be cured. These findings are consistent with a recent study of global disease burden that found that cancer among 0- to 4-year-olds accounts for 37% of the global disease-adjusted life year; this proportional burden is greater in LMICs.[26]

The factors causing delay in retinoblastoma diagnosis and treatment in LMICs are beyond the scope of this study. However, the findings here suggest that late recognition of signs of retinoblastoma, as well as delay in reaching a dedicated retinoblastoma treatment center once ocular symptoms have been detected, likely play a role, and both factors are associated with national income level. These findings indicate clinically significant progression of signs between parental detection and presentation to a specialist center in LMICs. Earlier recognition of leukocoria or strabismus and urgent referral for diagnosis is very important if children are to receive treatment before extraocular spread occurs.

A familial history of retinoblastoma followed the same pattern, with relatively fewer cases in lower-income countries. A possible explanation could be underreporting or inadequate medical record keeping in resource-limited settings. However, a more plausible explanation would be that children with familial history of disease are diagnosed and treated early in HICs so that they survive to childbearing age, whereas this may not be the case in LMICs.

Nearly all essential diagnostic and therapeutic modalities were available in most participating treatment centers. Enucleation surgery, which was available in all treatment centers, can save lives, and intravenous chemotherapy, which was available for 98.0% of the patients in this study, can save lives and also result in globe salvage if patients are diagnosed and treated in time.[27,28]

The results of this study point to an urgent need to improve retinoblastoma detection and access to treatment in LMICs. Several initiatives are addressing this challenge by implementing twinning programs that link centers from higher-resource and lower-resource countries.[12,29-32] However, there is a pressing need for coordinated action on a global level. In a rare yet curable cancer such as retinoblastoma, with approximately 8000 new patients annually worldwide, such an action is feasible to make retinoblastoma a zero-death cancer.[33] The World Health Organization Global Initiative for Childhood Cancer aims to raise survival for key childhood cancers, including retinoblastoma, to 60% by the year 2030 by helping health systems in LMICs integrate childhood cancer into their national strategies and improve their capacity to diagnose and deliver curative treatment.[34] In this context, accu-

rate retinoblastoma-specific data are essential. The results of this study serve as a report of the current retinoblastoma presentation status, against which future interventions can be measured, and demonstrate the need for a strong global partnership to improve outcomes for patients with retinoblastoma everywhere.

Results of the present study showed that older age at presentation and, independently, national income level were associated with advanced disease, which suggests that other factors besides age may be important in disease progression. It has been suggested that infection by the human papillomavirus, which is more prevalent in LMICs, is associated with the development of nonhereditary retinoblastoma, and it is possible that this could be associated with more aggressive disease behavior.[35] Another possible explanation relates to the genetic landscape of retinoblastoma and especially to cases with no *RB1* mutation but a high level of amplification of the oncogene *MYCN*.[36] These cases are unilateral, develop at an early age, and show aggressive features. They were found only in 1.4% of unilateral retinoblastoma cases, all from cohorts in HICs,[36] but have not been evaluated in patients from LICs. Notably, in the present study, there were substantially more unilateral cases in LICs as compared with other income levels, in keeping with the above-mentioned hypotheses. However, these speculations, warrant further studies.

Limitations

This study has several limitations. First, it included a convenience sample and therefore had an inherent potential bias. Nevertheless, to our knowledge, it is the largest and most geographically comprehensive study in the field of retinoblastoma, and we believe its findings can be generalized. Second, data collection was mostly retrospective, with the exception of treatment centers that were recruited early in 2017. However, the simplicity of the study design and quality assurance process enabled the collection of almost complete data, also from LMICs. Third, the socioeconomic status of individual families was not included as a variable, and the national income level was used as a surrogate, an approach that assumes that all families from the same country are of the same socioeconomic level.

Conclusions

The findings of this cross-sectional global analysis of retinoblastoma at the time of diagnosis revealed important differences in presentation among patients from different countries, depending on their national income level. Patients with retinoblastoma from HICs present with early disease and are, therefore, likely to survive. In contrast, patients from lower-income settings present with late disease, many with extraocular extension and some already with metastasis, and their prognosis is poorer. A familial history of retinoblastoma is relatively uncommon in lower-income countries, likely owing to death related to late-disease presentation before childbearing years. A surprise finding of this study is that more advanced disease at presentation in lower-income countries is not entirely explained by older age. Further research is warranted to investigate what factors other than age play a role in disease progression in low-income settings. Prompt action at national and international levels is warranted to improve health education about retinoblastoma, as well as access to early diagnosis and treatment in retinoblastoma treatment centers in LMICs.

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