Risk Factors Associated with Abandonment of Care in Retinoblastoma: Analysis of 692 Patients from 10 Countries

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Financial Disclosures: All authors have no financial disclosures or conflicts of interest.

Word Count: 1,795

SYNOPSIS

Based on multinational data, risk factors for the high rates of care abandonment in retinoblastoma include country of residence, advanced disease, and female sex.

ABSTRACT

Background: Rates of care abandonment for Retinoblastoma (RB) demonstrate significant geographic variation; however other variables that place a patient at risk of abandoning care remain unclear. This study aims to identify risk factors for care abandonment across a multinational set of patients.

Methods: A prospective, observational study of 692 patients from 11 RB centers in 10 countries was conducted from January 1, 2019 to December 31, 2019. Multivariate logistical regression was used to identify risk factors associated with higher rates of care abandonment.

Results: Logistic regression showed a higher risk of abandoning care based on country (high risk countries include Bangladesh OR=18.1, Pakistan OR=45.5, Peru OR=9.23, $p<0.001$), female sex (OR=2.39, $p=0.013$), and advanced clinical stage (OR=4.22, $p<0.001$). Enucleation as primary treatment was not associated with a higher risk of care abandonment (OR=0.59, $p=0.206$).

Conclusion: Country, advanced disease, and female sex were all associated with higher rates of abandonment. In this analysis, enucleation as the primary was not associated with abandonment. Further research investigating cultural barriers can enable the building of targeted retention strategies unique to each country.

KEY MESSAGES

What is already known on this topic

- Care abandonment for retinoblastoma varies geographically and there have been several single-centered studies that have explored contributory variables in rates of care abandonment; however they remain discrete data points.

What this study adds

- This study is the first and largest multi-centered, multi-national cohort that has addressed risk factors for care abandonment in retinoblastoma.
- The data suggest that country of residence, advanced disease stage, and female sex are significant factors in care abandonment for retinoblastoma.

How this study might affect research, practice or policy

- Retinoblastoma centers and ophthalmologists should be aware that these factors may lead to subsequent care abandonment within their centers and increase effort and vigilance in the care continuum of patients who fit these characteristics.

INTRODUCTION

Retinoblastoma (RB), the most common primary intraocular malignancy affecting infants and children, represents about 4% of pediatric malignancies.[1,2] Worldwide, the incidence of RB has been estimated to be between 1:14,000-18,000 live births (~8,000 children globally each year) with mortality >3,000 children annually.[2,3] Rates of mortality are disproportionately higher in low- and middle-income countries (LMICs, mortality: 40-70%) compared to high-income countries (HICs, mortality: 3-5%).[3,4] The prognosis of RB has improved in HICs (>95% of disease-free survival rates) due to factors like increased specialization centers, improved screening and awareness, and availability of new treatment regimens.[5-7] The prognosis in LMICs remains guarded due to delay in diagnosis and treatment or abandonment of care attributed to various factors like socioeconomic status (SES) and healthcare access.[4,8,9]

Of the pediatric cancers occurring worldwide, it is estimated that only 20-30% are diagnosed and treated, with most of these being treated in HICs (>80%).[10-13] Rates of care abandonment in pediatric cancer are highest in LMICs, ranging up to 60% in some studies.[14,15] Abandonment of pediatric cancer care in LMICs is correlated with country income level, parental educational status, travel times, prognosis of the disease, and care affordability and accessibility.[14,16-21] In RB specifically, the data on abandonment are varied with single-center reports showing a range in care abandonment: 38% (35/91) in Tanzania, 22-35% in Central America, and 50% in India.[22-25] Studies from India have investigated risk factors for abandonment and have shown that abandonment is increased in rural children, financial concerns, unwillingness to enucleate, female sex, bilateral disease, and difficulty in attending outpatient appointments.[20,26,27] The prevalence and risk factors associated with abandonment of care in RB have not been studied in a multinational cohort. The purpose of this study is to investigate abandonment of care in RB across multiple countries, continents, and health care systems in order to identify factors associated with care abandonment.

MATERIALS AND METHODS

Details for the methodology for collection of data in this prospective observational study have been described in detail in Kaliki, et al.[28] Briefly, clinical and demographic information was gathered prospectively for all patients with newly diagnosed RB who presented to 11 international centers within 10 countries (Bangladesh, China, Ethiopia, France, India, Pakistan, Peru, Russia, UK, USA) during the calendar year 2019. Centers were selected from all continents and income ranges and they represent centers where prospective data could be collected over one year. The study was approved by all participating centers' respective Institutional Review Board and ethics committees. The study adhered to the tenets of the Declaration of Helsinki.

The outcome of interest was abandonment of care. Centers were asked specifically if each child's care was abandoned. Detailed information about the reasons for abandonment or the type of abandonment was extracted from the questionnaire's free-text comments. Patient care was considered "abandoned" if the child was lost to follow-up and did not choose to obtain care from another known provider. Variables considered as potential risk factors for abandonment were included in a statistical model. These covariates included: age, country, laterality, vision at presentation, clinical tumors staging (AJCC 8th edition)[29], presence of lymph node disease, presence of metastases, distance to treatment center, sex, mother's age, birth order, lag time between symptoms and presentation, number of physicians seen prior to arriving at the treatment center, and enucleation as the primary treatment (labeled "Enucleation").

Statistical analysis

The statistical analysis was performed using R software and STATA v14.2 (StataCorp, College Station, TX, USA). A *p*-value of <0.05 was considered statistically significant. To examine the adjusted associations between the covariates of interest and care abandonment, we applied a multivariate logistic regression with care abandonment as the outcome and all covariates of interest as the independent variables except continent, country income, and vision at presentation. Continent and country income level are excluded as they do not very within country, and country is already included in the model. Vision at presentation was excluded due to missing vision data from over a third of the patients. The likelihood ratio test was used to assess the statistical significance of the group of regression coefficients for any nominal categorical variable with more than two levels, and the Wald test was used for all the other variables. For all the analyses outlined above, observations with missing values in any involved variable are excluded.

RESULTS

Data from 692 patients from 10 countries and 11 treatment centers were included in the analysis. **Table 1** shows demographic characteristics and features of these patients stratified by the 10 countries. Seventy-five patients abandoned care, 11% of this cohort. The distribution of each variable, stratified by abandonment, is reported in **Table 2**. Three countries reported care abandonment over 10%: Pakistan, Bangladesh, and Peru. Four countries reported no care abandonment: Russia, the UK, France, and the US.

Table 1. Distributed Demographics and Features of 692 Patients by Country.

		Number of Patients	Mean Age at Presentation (Months)	Sex M:F	Care Abandoned	AJCC 8th Edition Tumor Staging (worse eye)			
						T1	T2	T3	T4
Total		692	24	369:323	75 (11%)				
Country	Bangladesh	136 (20%)	20	71:65	42 (31%)	4	21	100	11

China	166 (24%)	22	82:84	5 (3%)	6	90	60	10
Ethiopia	74 (11%)	31	41:33	5 (7%)	5	25	24	20
France	49 (7%)	23	27:22	0 (0%)	6	24	18	0
India	128 (18%)	27	68:59	5 (4%)	5	58	49	16
Pakistan	30 (4%)	26	15:15	10 (33%)	0	16	8	6
Peru	46 (7%)	25	29:17	8 (17%)	1	32	7	5
Russia	42 (6%)	21	24:18	0 (0%)	1	22	9	10
UK	14 (2%)	18	9:5	0 (0%)	1	11	2	0
USA	7 (1%)	12	3:4	0 (0%)	1	6	0	0

Table 2. The Distribution of Each Covariate Stratified by Care Abandonment.

		Care Not Abandoned (n = 617)	Care Abandoned (n = 75)	Overall (n = 692)
Mean Age at Presentation (months)		24 (19)	24 (17)	24 (29)
Country	Bangladesh	94 (69%)	42 (31%)	136 (20%)
	China	161 (97%)	5 (3%)	166 (24%)
	Ethiopia	69 (93%)	5 (7%)	74 (11%)
	France	49 (100%)	0 (0%)	49 (7%)
	India	123 (96%)	5 (4%)	128 (18%)
	Pakistan	20 (67%)	10 (33%)	30 (4%)
	Peru	38 (83%)	8 (17%)	46 (7%)
	Russia	42 (100%)	0 (0%)	42 (6%)
	UK	14 (100%)	0 (0%)	14 (2%)
	USA	7 (100%)	0 (0%)	7 (1%)
Continent	Europe	105 (100%)	0 (0%)	105 (15%)
	Asia	398 (87%)	62 (13%)	460 (66%)
	Africa	69 (93%)	5 (7%)	74 (11%)
	Latin America	38 (83%)	8 (17%)	46 (7%)
	North America	7 (100%)	0 (0%)	7 (1%)
Country Income	Low	69 (93%)	5 (7%)	74 (11%)
	Low-middle	237 (81%)	57 (19%)	294 (42%)
	Upper-middle	241 (95%)	13 (5%)	254 (37%)
	High	70 (100%)	0 (0%)	70 (10%)
Distance to RB Center (miles)		387 (614)	192 (270)	366 (590)
Sex	Male	334 (91%)	35 (9%)	369 (53%)
	Female	282 (88%)	40 (12%)	322 (47%)
Mother Age at Birth (years)		27.7 (5.7)	25.9 (5.2)	27.5 (5.7)
Birth Order		2.0 (1.2)	2.0 (1.3)	2.0 (1.2)
Number of Physicians		1.4 (0.7)	1.6 (0.9)	1.4 (0.8)
Lag Time (days)		145 (193)	191 (222)	150 (197)
Laterality	Right	200 (92%)	18 (8%)	218 (32%)
	Left	232 (86%)	39 (14%)	271 (39%)
	Both	184 (91%)	18 (9%)	202 (29%)
Vision at Presentation (# eyes that can fix and follow)	Both	47 (98%)	1 (2%)	48 (11%)
	One	257 (83%)	53 (17%)	310 (74%)
	None	50 (82%)	11 (18%)	61 (15%)
AJCC 8th Edition Staging (worse eye)	T1	28 (100%)	0 (0%)	28 (4%)
	T2	295 (97%)	10 (3%)	305 (44%)
	T3	227 (82%)	50 (18%)	277 (40%)
	T4	64 (82%)	14 (18%)	78 (11%)

Lymph Node Disease	Not Examined	277 (96%)	12 (4%)	289 (44%)
	No	289 (83%)	58 (17%)	347 (53%)
	Yes	16 (80%)	4 (20%)	20 (3%)
Metastasis	No	581 (90%)	61 (10%)	642 (94%)
	Yes	29 (76%)	9 (24%)	38 (6%)
Enucleation	No	328 (91%)	31 (7%)	359 (55%)
	Yes	285 (90%)	31 (10%)	316 (45%)

The results of the multivariate logistic regression of complete cases are presented in **Table 3**. The multivariate analysis identified four covariates that are independently associated with care abandonment: country (p-value <0.001), advanced clinical staging (OR 4.22, 95% CI, 1.99-9.60, *p*-value <0.001), no metastases at presentation (OR 0.17, 95% CI, 0.03-0.89, *p*-value = 0.047; patients with metastasis were less likely to have care abandoned), and female sex (OR 2.39, 95% CI, 1.21-4.84, *p*-value = 0.013). On average, increasing clinical stage was associated with increasing odds of care abandonment (OR 4.22, 95% CI, 1.99-9.60, *p*-values = <0.001) in the group with higher clinical stage. When comparing a group of female patients to another group of male patients who are otherwise the same, the odds of care abandonment also increased (OR 2.39, 95% CI, 1.21-4.84, *p*-value = 0.013) higher in female patients. Notably, enucleation as the primary treatment (OR 0.59, 95% CI, 0.26-1.33, *p*-value = 0.206) is not statistically significant in its association with care abandonment.

Table 3. Multivariate Logistic Regression of Associations Between Care Abandonment and All Covariates Except Continent, Country Income and Vision at Presentation for Complete Cases.

Variable		Odds Ratio (95% CI)	*p*-value
Age at Presentation (Months)		1.00 (0.99, 1.00)	0.331
Country*			**< 0.001**
	Bangladesh	18.1 (0.69, 238)	
	China†	0.00 (-)	
	Ethiopia†	0.00 (-)	
	France†	0.00 (-)	
	Pakistan	45.5 (1.45, 828)	
	Peru	9.23 (0.28, 157)	
	Russia†	0.00 (-)	
	UK†	0.00 (-)	
Distance (Log Transformed)		0.94 (0.69, 1.27)	0.666
Sex	Female	2.39 (1.21, 4.84)	**0.013**
Mother Age at Birth (Years)		0.99 (0.91, 1.07)	0.755
Birth Order		1.23 (0.83, 1.87)	0.309
Number of Physicians		0.91 (0.58, 1.40)	0.666
Lag Time (Log Transformed)		0.87 (0.65, 1.16)	0.344
Laterality			0.089
	Left Eye	2.28 (1.01, 5.35)	
	Both Eyes	1.09 (0.41, 2.92)	
Clinical Staging		4.22 (1.99, 9.60)	**< 0.001**
Lymph Node Disease			0.823
	No	0.50 (0.05, 11.2)	
	Yes	0.36 (0.02, 13.1)	
Metastasis	Yes	0.17 (0.03, 0.89)	**0.047**
Enucleation	Yes	0.59 (0.26, 1.33)	0.206

*: India is chosen as the reference, as the rate of care abandonment ranks in the middle; no result for the US as all patients have missing age, hence excluded from the multivariate regression.

†: All patients have retained their care in this country. Point estimate of the odds ratio is 0. Wald-type confidence intervals have length infinity and are not meaningful.

DISCUSSON

Studies from various countries have identified different factors to be statistically significant in effecting RB care abandonment, including distance, socioeconomic status, patient sex, parental educational status, and apprehension of enucleation.[10,14,21,24,27,30] Multivariate modeling of our data identified that country, female sex, and advanced clinical stage were positively associated with abandonment, whereas metastasis was negatively associated with abandonment.

It is widely reported in oncology literature that country is significantly associated with higher abandonment rates, which is supported by our composite international data. Abandonment of care or treatment refusal is often not analyzed in high-income country (HIC) data because it is primarily seen in low- and middle-income countries (LMICs), usually attributed to resource constraints. Similarly, our study shows abandonment of care in every LMIC in the study, while none of the HICs show abandonment. Similarly, Kaliki, et al. found country income level significantly impacts lag time for diagnosis of RB in this data set.[28] Financial barriers have long remained astute in their role in impacting health outcomes. Nuances of these results should be further explored, particularly in relation to family income, costs of treatments, and subsidies provided by the government or private entities for care provision and treatment. This information was not readily available to analyze in our dataset but may be a potential confounder in our results. These data cannot discern a difference in abandonment of care based on overall cost of treatment, though this would be an important question in the future.

Advanced clinical stage at the time of presentation is associated with higher rates of abandonment. Of the patients who died during this study's short follow-up period, nearly 50% of them had abandoned care, indicating increased mortality in this subsection. Assuming an equal risk between each stage, the odds ratio from each successive clinical stage was 4.22. Conversely, presence of metastasis at diagnosis was found to be a protective factor for care abandonment. The variables of clinical tumor stage and metastasis are correlated, but the data suggest they are unique. The reason for this finding is unknown and more investigation is required.

Female sex is associated with higher rates of care noncompliance. Previous studies have come to various conclusions regarding sex and care abandonment. They range from finding child cancer care abandonment to be higher in LMICs, overall, with no sex bias[31] to finding female sex plays a minor role in childhood cancer treatment abandonment, but more so in LMIC than HIC[32]. Similarly, previous studies on RB have shown variable results in the significance of association between compliance and female sex.[20,27,33]

Enucleation was not related to abandonment. It has long been known that apprehension for enucleation is a risk factor for abandonment in many countries. Many centers have altered their treatment philosophy to address this issue. A large referral center in Uganda recently reported that its program of recommending up-front chemotherapy, even when a globe is not salvageable, was found to reduce the rate of care abandonment and increase the likelihood that after a few initial cycles of chemotherapy, families would be more willing to accept enucleation.[34] This program also included other features like minimal hospital stay, provision of transportation and food costs, and benefits of peer support that may also be compounding factors that affect decisions for care retention.[34] Likely, centers enrolled in our study have adapted their treatment philosophies in similar ways, which introduces a statistical bias when analyzing patients in whom enucleation was primary treatment.

Limitations of this study include a limited sample size. While this is the largest multinational cohort that has addressed risk factors for care abandonment in RB, the sample size in some countries is relatively small with an unequal distribution of patients among the countries. Each RB was chosen based on its ability to provide one year of detailed prospective data and opted into the study, introducing another level of bias in our results, especially with regard to ensuring appropriate comparisons by income brackets. Nevertheless, this is the most extensive study to date with all income levels and most continents with statistically significant results that make it more widely applicable than other single-centered results. These issues are important to consider in future studies. Our multivariate analysis excluded vision at presentation because over 40% (263) of the data was missing. While it is possible that vision may be an additional predictor of care abandonment, studies have shown that vision is highly correlated with disease stage[35], and this study has robust data on patient disease stage.

CONCLUSION

Findings of the present study show that risk factors for the abandonment of care in RB include the patient's country of residence, advanced disease stage, and female sex. The data suggest that international differences are more compelling and involved in RB abandonment than other factors. Importantly, enucleation as the primary treatment was not categorically associated with higher rates of abandonment in this study, but this may be due to current practice patterns. RB centers should be aware that advanced disease, female sex, and lack of metastasis in children with advanced RB might be factors leading to subsequent care abandonment within their centers.

Contributorship Statement

Conception and design of study: AWS. Data acquisition: XJ, YZ, SS, RR, STS, NC, JLGL, RYDC, AMZ, TLU, VGP, SRR, AA, MAR, MSS, LAH, JWK, JLB, AP, NJA, CB, SB, RB, MJB, AF, NG, NK, SM, MZ, SK, IDF, and AWS. Statistical analysis: XL and MG. Data interpretation: TN, AWS, and XL. Initial drafting of the manuscript: TN, AWS, and AC. Critical revisions of article and important intellectual content: All authors. Final approval of manuscript: TN and AWS. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: TN and AWS.

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