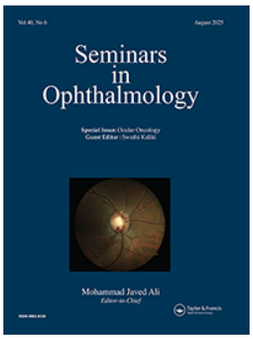

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Lag Time Between Onset of First Symptom and Treatment of Retinoblastoma: Outcomes at Three Years from Recruitment

Swathi Kaliki[a], Vijitha S Vempuluru[a], Akruti Desai[a], Xunda Ji[b], Yihua Zou[b], Riffat Rashid[c], Sadia Sultana[c], Sadik Taju Sherief[d], Nathalie Cassoux[e], Rosdali Y. Diaz Coronado[f], Juan Luis Garcia Leon[g], Arturo Manuel Zapata López[f], Vladimir G. Polyakov[h,i], Tatiana L. Ushakova[h,i], Andrey A. Yarovoy[j], Soma Rani Roy[k], Alia Ahmad[l], Lamis Al Harby[m], M. Ashwin Reddy[m,n], Mandeep S. Sagoo[m,n,o], Jesse L. Berry[p], Jonathan Kim[p], Ashley Polski[p], Nicholas J. Astbury[q], Covadonga Bascaran[q], Sharon Blum[r], Nir Gomel[r], Richard Bowman[q,s], Matthew J. Burton[o,q], Allen Foster[q], Andrew W. Stacey[t], David M. Steinberg[u], David Refaeli[u], Marcia Zondervan[q], and Ido Didi Fabian[q,r,v]

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ABSTRACT

Purpose: To evaluate the effect of lag time between diagnosis of retinoblastoma (RB) and treatment in patients from 10 countries.

Methods: Prospective study of 692 treatment-naïve RB patients from 10 countries followed up for 3 years from recruitment.

Results: The mean lag time from the onset of the first symptom to visit to the RB treatment center was 150 days. The mean follow-up duration was 26 months (median, 32 months; range, <1–51 months). A higher socioeconomic status of the country was associated with a lower risk of enucleation: Lower-middle-income countries vs. low-income countries (p<.001), Upper-middle-income vs. low-income countries (p = .009), and high-income countries vs. low-income countries (p = .014). A greater AJCC stage was associated with a greater risk of enucleation: T2 vs. T1 (p<.001) and T3 vs. T1 (p<.001). Increased lag time (p<.001) and AJCC T4 stage (T4 vs. T2; p<.001) were associated with increased risk of death. By Kaplan–Meier analysis, the cumulative incidence of enucleation at 3 months, 1 year, and 3 years was 49%, 55%, and 61%, respectively; and survival at 1, 2, and 3 years was 92%, 88%, and 87%, respectively. Three-year Kaplan–Meier survival estimates were 95% with a lag time of <3 months vs. 83% with a lag time of 3–12 months vs. 62% with a lag time of >12 months.

Conclusion: A lower socioeconomic status and greater AJCC stage were associated with an increased risk of enucleation. Increased lag time from the onset of the first symptom to visit the RB treatment center and AJCC T4 stage were associated with an increased risk of death from RB.

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Eye; global; lag time; retinoblastoma; tumor

INTRODUCTION

'Lag time', previously referred to as 'delay in diagnosis' or 'delay in treatment,' has been extensively studied in various cancers.[1] In retinoblastoma (RB), the most common pediatric eye cancer, it was shown that shorter lag time is associated with longer survival, similar to other pediatric malignancies such as soft tissue sarcoma and Wilms tumor.[2] Several studies have focussed on the lag time in RB (Supplemental Table 1), and various aspects pertaining to lag time have been looked into, including duration from the first symptom or sign to

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presentation to the first care provider; duration to establishment of the diagnosis of RB; and duration to initiation of treatment for RB.[3–24] Longer lag times in RB have been associated with bilaterality, advanced disease, extraocular tumors, need for enucleation, high-risk histopathological features post-enucleation, metastasis, and death.[5,7–9,14,19–21,23,24]

From a socio-demographic standpoint, longer lag times have been linked to parental lack of knowledge about the disease, older maternal age, fear of enucleation, financial constraints, and reduced access to RB treatment centers/travel.[8,9,23,24] Very few studies show a lack of relationship between lag time and age at presentation, ICRB group, and need for enucleation.[12,13,16] However, most of these inferences are drawn from single-center retrospective studies at different points in time, subject to heterogeneity in treatment protocols.[3–8,10–13,15,16,18–20,22,24]

With the emergence of the Global Retinoblastoma Study Group in 2017, several factors impacting the outcomes of children with RB have been looked into.[25–27] The lag time to RB treatment has been revisited on a global platform for 692 patients.[17] Our group has shown that the national income level significantly affected the lag time to RB treatment. After adjusting for the national income, an increased lag time was significantly associated with higher chances of American Joint Committee for Cancer (AJCC) T4 stage at presentation ($p < .001$), high-risk histopathological features ($p = .003$), metastasis at the time of presentation ($p < .001$) and death ($p < .001$) at the time of presentation.[17] We followed up with this cohort of patients to assess the outcomes over the subsequent 3 years and present our findings in this paper.

METHODS

Treatment-naïve patients with RB who presented to 11 centers in 10 countries from January 1 to December 31, 2019, and followed up until May 30, 2023, were enrolled in a prospective multicenter cohort study.[17] Follow-up data on treatment details, enucleation, and death was obtained for all the 692 patients from the original cohort. The study adhered to the tenets of the Declaration of Helsinki and was approved by the London School of Hygiene & Tropical Medicine Institutional Review Board (Reference No. 15882). Informed consent was obtained from the parents/guardians of the children included in this study.

The statistical analysis was performed using R software.[28] Continuous variables were expressed as mean, median, and range, and categorical variables as proportions. Clustered Cox proportional hazard analysis was used to identify factors affecting the outcomes of enucleation (of the worse eye in bilateral cases) and death. To account for missing outcome data, the analyses used inverse probability weighting, assuming "missing at random".[29] Since lag time and distance to the RB treatment center were highly skewed, a square-root transformation was applied to reduce the skewness. For example, a lag time of 25 days was transformed to $\sqrt{25} = 5$, and a lag time of 100 days was transformed to $\sqrt{100} = 10$. The values 5 and 10 were the data points for the X-axis. The outcomes based on the socio-economic status and the 8th edition, AJCC T stage, were assessed using the Chi-square test. Kaplan Meier analysis was performed to study the risk of enucleation and death based on socioeconomic status (lower-income country (LIC), lower-middle-income country (LMIC), upper-middle-income country (UMIC), high-income-country (HIC)), AJCC T stage, and lag time. Lag time being a continuous variable, we divided it into three categories (<3 months, 3–12 months, or >12 months in order to arrive a possible cut-off for a red flag of lag time duration). For estimating the cumulative incidence of enucleation, the competing risk of death prior to enucleation was taken into consideration.

RESULTS

All the 692 patients enrolled in the previous study were included in the present analysis.[17] Demographics and clinical features at first presentation were described before by Kaliki et al.[17] Based on economic strata, 11% ($n = 74$) of the patients belonged to LIC, 43% ($n = 294$) to LMIC, 37% ($n = 254$) to UMIC, and 10% ($n = 70$) to HIC. The mean age at diagnosis was 24 months (median, 22 months; range 0–140 months), and the male-to-female ratio was 1.15. A majority ($n = 490$, 71%) had unilateral RB, and bilateral presentation (germline) was seen in 29% ($n = 202$). Among unilateral RB, germline RB was seen in 21% ($n = 103$), sporadic in 8% ($n = 39$), and 71% ($n = 348$) had no genetic testing.

The mean lag time from the onset of the first symptom to attendance at the RB treatment center was 150 days (median, 69 days; range < 1–1128 days). The parents/guardians had visited a mean of 2 (median, 1; range, <1–4) primary healthcare practitioners before being referred to the RB treatment center. The mean distance from home to the RB treatment center was 366 km (median, 195 km; range, <1–9757 km). The mean follow-up duration was 26 months (median, 32 months; range < 1–51 months).

A clustered Cox proportional hazard analysis of the factors affecting the outcomes is summarized in Table 1. Greater age at onset of the symptoms showed a significantly increased risk for enucleation (hazard ratio (HR), 1.005; 95% CI, 1.000–1.009; $p = .039$). Bilateral tumors were associated with lesser odds of enucleation (HR, 0.561; 95% CI, 0.3834–0.8205; $p = .003$). Compared to the reference category of LIC, the other categories of LMIC, UMIC, and HIC had lower odds of enucleation: HR, 0.533 (95% CI, 0.382–0.745; $p < .001$) vs. HR, 0.321 (95% CI, 0.136–0.758; $p = .009$) vs. HR, 0.486 (95% CI, 0.273–0.866; $p = .014$). Compared to the reference category of T1, the other categories of T2, and T3 stages had higher odds of enucleation: HR, 2.384 (95% CI, 1.739–3.268; $p < .001$) vs. 3.378 (95% CI, 1.996–5.719; $p < .001$). Comparison of T4 vs T1 did not reach statistical significance for enucleation, HR, 1.195 (95% CI, 0.495–2.888; $p = .692$). Overall, the highest percentage of enucleation was seen in the LIC (84%) and AJCC T3 (65%) cohorts. The square root of lag time was associated with an increased risk of death (HR, 1.056; 95% CI, 1.025–1.087; $p < .001$). Significant differences were noted between socioeconomic strata and AJCC T stages. T4 was associated with 12 times greater odds of death compared to T1, HR 11.935

Table 1. Clustered Cox proportional hazard analysis of the factors affecting the outcomes in 692 retinoblastoma patients from 10 countries.

	Enucleation		Death	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age (in months) at onset of 1st symptom	1.005 (1.000–1.009)	.039	1.004 (0.987–1.022)	.633
Female gender	0.931 (0.695–1.247)	.631	1.036 (0.736–1.459)	.838
Bilaterality	0.561 (0.383–0.821)	.003	1.445 (0.774–2.696)	.248
Heritable RB	1.071 (0.695–1.652)	.755	0.747 (0.437–1.278)	.288
No. of visits to primary healthcare practitioner	1.206 (0.911–1.595)	.191	1.173 (0.944–1.457)	.150
Square root of lag time	1.017 (0.993–1.043)	.166	1.056 (1.025–1.087)	<.001
Square root of distance	0.994 (0.974–1.015)	.571	0.960 (0.934–0.986)	.003
Socio-economic status				
LIC	Reference		Reference	Reference
LMIC	0.533 (0.382–0.745)	<.001	0.861 (0.481–1.542)	.615
UMIC	0.321 (0.136–0.758)	.009	0.823 (0.252–2.694)	.748
HIC	0.486 (0.273–0.866)	.014	*	*
AJCC stage				
T1	Reference		*	*
T2	2.384 (1.739–3.268)	<.001	Reference	Reference
T3	3.378 (1.996–5.719)	<.001	1.528 (0.530–4.402)	.432
T4	1.195 (0.495–2.888)	.692	11.935 (5.922–24.056)	<.001

LMIC: lower middle-income countries; UMIC: upper middle-income countries; HIC: high-income countries; *insufficient numbers for analysis; RB: retinoblastoma; AJCC=American Joint Committee for Cancer classification; significant values indicated in bold.

(95% CI, 5.922–24.056; $p < .001$). This trend was not seen with enucleation as the patients who died in T4 had succumbed to the disease before they could undergo secondary enucleation. Overall, the highest percentage of deaths was seen in LIC (29%) and T4 stages (53%) (Table 2).

By Kaplan–Meier analysis, the cumulative incidence of enucleation at 3 months, 1 year, and 3 years was 49%, 55%, and 61%, respectively; and survival at 1, 2, and 3 years was 92%, 88%, and 87%, respectively (Figure 1). For life salvage, the three-year Kaplan Meier survival estimates were compared between the socioeconomic strata, AJCC T stage, and lag time (Table 3, Figure 2). At 1, 2, and 3 years, cumulative survival was the highest in HIC (100%, 100%, 98%, respectively) and the lowest in LIC (80%, 68%, 64%, respectively). At 1, 2, and 3 years, AJCC T1 stage had the highest cumulative survival (100%, 96%, 96%, respectively), and T4 had the lowest (57%, 37%, 35%, respectively). Finally, at 1, 2, and 3 years, survival was the highest with a lag time under 3 months (99%, 96%, 95%, respectively) vs. 3 to 12 months (90%, 84%, 83%, respectively) vs. >12 months (69%, 62%, 62%, respectively).

Table 2. Outcomes based on economic status and AJCC T stage in 692 retinoblastoma patients from 10 countries.

	Enucleation, N (%)	p-value*	Death, N (%)	p-value*
Socio-economic status				
LIC	62 (83.8)	Reference	21 (28.4)	Reference
LMIC	183 (62.2)	<.001 (LMIC vs. LIC)	35 (11.9)	.615 (LMIC vs. LIC)
UMIC	109 (42.9)	.009 (UMIC vs. LIC)	15 (5.9)	.748(UMIC vs. LIC)
HIC	42 (60.0)	.014 (HIC vs. LIC)	1 (1.4)	(only 1 event)
AJCC T stage				
T1	9 (30.0)	Reference	1 (3.3)	(only 1 event)
T2	165 (53.7)	<.001 (T2 vs. T1)	13 (4.2)	Reference
T3	180 (65.0)	<.001 (T3 vs. T1)	17 (6.1)	.432 (T3 vs. T2)
T4	42 (53.8)	.692 (T4 vs. T1)	41 (52.6)	<.001 (T4 vs. T2)

*Chi-square test; LMIC: lower-middle-income countries; UMIC: upper middle-income countries HIC: high-income countries; AJCC: American Joint Committee for Cancer classification; T=primary tumor; significant values indicated in bold.

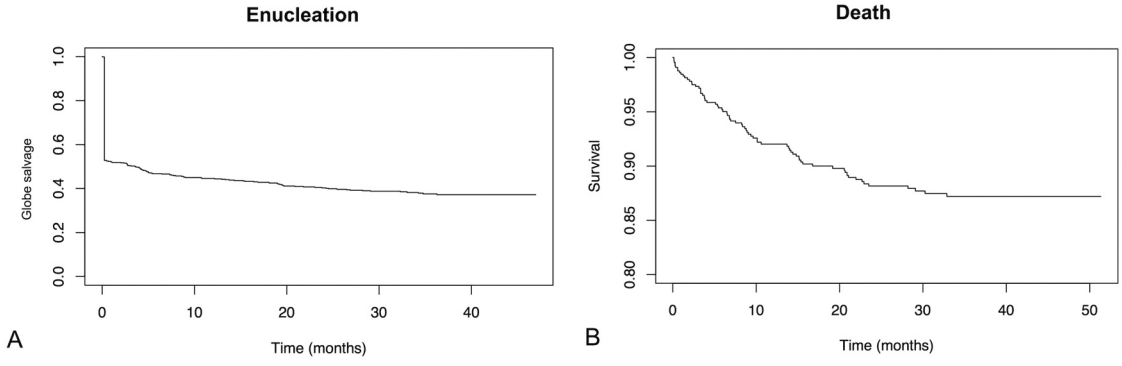

Figure 1. Kaplan Meier curves for globe salvage and death in 692 patients of retinoblastoma.

Table 3. Kaplan Meier survival analysis in 692 retinoblastoma patients from 10 countries based on socioeconomic status, AJCC T stage, and lag time.

Follow-up	Cumulative incidence (95% confidence intervals)			
Socioeconomic status	LIC	LMIC	UMIC	HIC
1 year	0.806 (0.716 to 0.907)	0.891 (0.852 to 0.932)	0.960 (0.935 to 0.986)	1.000 (1.000 to 1)
2 years	0.678 (0.569 to 0.807)	0.848 (0.801 to 0.897)	0.936 (0.903 to 0.969)	1.000 (1.000 to 1)
3 years	0.644 (0.527 to 0.788)	0.840 (0.791 to 0.891)	0.931 (0.898 to 0.966)	0.984 (0.953 to 1)
AJCC T stage	T1	T2	T3	T4
1 year	1.000 (1.000 to 1)	0.974 (0.956 to 0.993)	0.949 (0.921 to 0.977)	0.574 (0.467 to 0.706)
2 years	0.963 (0.895 to 1)	0.956 (0.931 to 0.982)	0.929 (0.896 to 0.963)	0.372 (0.267 to 0.518)
3 years	0.963 (0.895 to 1)	0.946 (0.917 to 0.975)	0.922 (0.887 to 0.959)	0.352 (0.248 to 0.499)
Lag time	<3 months	3 to 12 months		>12 months
1 year	0.985 (0.972 to 0.998)	0.899 (0.855 to 0.944)		0.687 (0.587 to 0.803)
2 years	0.961 (0.939 to 0.983)	0.841 (0.786 to 0.900)		0.623 (0.519 to 0.749)
3 years	0.949 (0.924 to 0.975)	0.832 (0.775 to 0.893)		0.623 (0.519 to 0.749)

LIC: low-income countries; LMIC: lower-middle-income countries; UMIC: upper middle-income countries; HIC: high-income countries; AJCC = American Joint Committee for Cancer classification; T = Primary tumor.

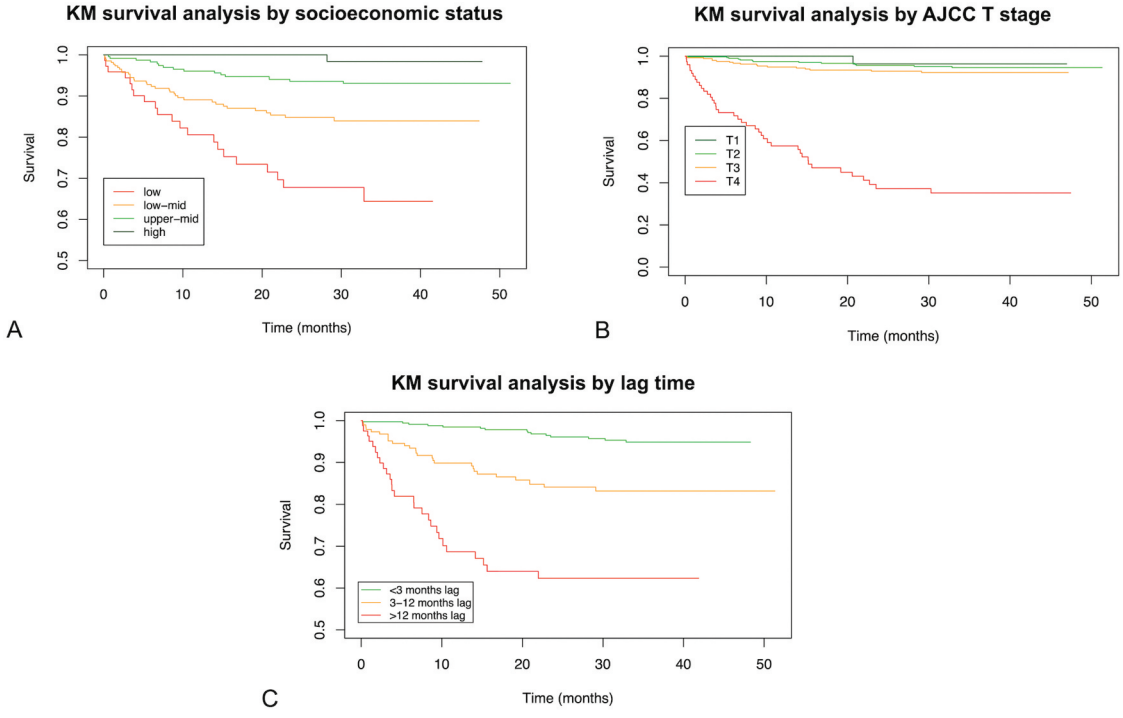

Figure 2. Kaplan Meier curves for survival in 692 patients of RB based on country's socio-economic status (A), AJCC T stage (B), and lag time (C).

DISCUSSION

The two primary treatment goals in RB are life salvage and globe salvage, with the former taking precedence over the latter. Treatment outcomes are affected by:

- Patient factors such as age at presentation, AJCC stage, and presence of high-risk histopathology features
- Care provider factors such as lag time to presentation and treatment, adherence/refusal to treatment
- Social factors such as income status of the country of origin, access to treatment facilities, and availability of resources.[25]

Our previous study showed that increased lag time significantly differed between countries. After adjusting for national income, an increased lag time was associated with higher chances of advanced presentation, high-risk histopathology features, metastasis, and death during the 1-year study period.[17] In this 3-year follow-up study, we add that the hazard for enucleation was higher for older age at presentation and AJCC T2 and T3 stage. The lag time or distance to RB treatment did not affect the odds of enucleation. Nearly 50% of the patients requiring enucleation underwent the procedure in the first 3 months from presentation. In a study on 30 Syrian refugees and 150 local citizens with RB in Jordan, Yousef et al. noted that the refugees had a longer lag time and nearly twice the enucleation rates compared to citizens with RB.[24] Outside of crises, the enucleation outcome does not appear to be influenced by the lag time itself, as seen in this study. However, one would expect greater chances of globe salvage with less lag time; hence, we discuss

the possible reasons for this here. A majority of patients in this cohort were unilateral (71%), belonged to the T2 stage (44%) and T3 stage (33%), and were from LMIC (57%), all of which favor the decision towards enucleation, and this explains the enucleation rates of 49% in the first 3 months. The availability of globe salvaging treatment modalities such as intravenous and intra-arterial chemotherapy is also significantly different between the LMIC and HICs; thus, the scope for globe salvage is greater in HICs.[27] Further, at the mean lag time of 5 months (150 days), most tumors (77%) were at AJCC stages 2 or 3 at presentation, implying the presence of tumor seeding or advanced intraocular tumor. Based on limited case reports, the tumor doubling time in RB reported in the literature is as low as 15 days in vivo and 3 days in vitro.[30,31] A growth of 1.3 times in basal dimensions over 15 days has been documented. In terms of tumor volume, 5 months allows the tumor 10 doubling time intervals, enough to fill the globe. However, this, in real-time, may be limited to various dynamics in the tumor microenvironment. Nevertheless, a lag time of 5 months theoretically does allow the tumor to reach a stage where the eye is not salvageable. A positive finding is that the cumulative incidence of enucleation over time did not increase significantly, i.e., 49% at 3 months and 61% at 3 years, emphasizing the effectiveness of therapeutic regimens in local tumor control available across the 10 participating countries.

In contrast to enucleation, the hazard ratio for death was related to the lag time and advanced T4 stage. Further, with increasing lag time, the cumulative incidence of death increased over the 3-year follow-up period. The cumulative survival was highest for a lag time of <3 months (95%) and the least for a lag time of >12 months (62%). These findings are consistent with previous reports, although the cut-off values for comparison vary.[4–6,17,19,20] The finding of lag time affecting the survival and not enucleation can be explained as follows: First, a cohort of patients belonging to AJCC stage T4 succumbed to the disease even before they could undergo secondary enucleation. Second, a possibility of micro-metastasis may exist from the onset of the tumor to the initiation of treatment or even while undergoing globe-salvage treatment modalities such as IVC, IAC, focal treatment, or IViC, which were the primary treatment modalities in 43%, 14%, 15%, and 3%, respectively, in this cohort.[17] Also, it has been documented that delayed metastasis can result even months after ocular tumor control has been achieved, thus affecting survival.[32]

What do the findings from this study mean in clinical practice? A lag time of <3 months has a favorable prognosis, and patients with a lag time of >1 year must be managed aggressively and followed closely over the next 3 years. The type of systemic surveillance in such cases could be tailored based on the availability of resources, but a comprehensive systemic assessment by a pediatrician/medical oncologist is important. Regarding detecting micro-metastasis, various newer techniques, from imaging to artificial intelligence, are being explored,[33] of which estimation detection of cell-free DNA holds promise. Its use in RB, however, is likely to be limited by the availability, turnaround time, and cost, at least for the next few years. In real-time, what can readily be done is to target a reduction in the lag time through combined efforts of healthcare workers and policymakers by improving awareness about RB. This can be achieved through (i) improving awareness about retinoblastoma, especially in LICs and LMICs with a high population growth rate, accounting for most of the global disease burden. Awareness programs should target the general public, including parents, caregivers and teachers, primary care physicians, pediatricians, and healthcare/community workers who interact with parents and children (ii) strengthening referral systems to expedite access to RB treatment center once RB is suspected and (iii) overcoming social barriers such as refusal to seek healthcare by engaging volunteers from the community.

The strengths of this study lie in the large sample size, heterogeneity of centers covered, and the follow-up period. The aspects that were out of the scope of this study were reasons for increased lag time and the social factors involved. Another factor that could have influenced the outcomes of this study was the onset of the COVID-19 pandemic during the follow-up period. Although most RB centers did not halt services, travel restrictions impacted the continuity of care of children with RB.[34] Lastly, given the multicentric nature of the study, the differences in treatment protocols, and individual criteria for enucleation could certainly influence outcomes. However, an attempt was made to obtain the specific reasons for enucleation such as a massive primary tumor, tumor recurrence, or media opacity obscuring tumor visualization.

In summary, according to this multicenter study, lag time plays a critical role in the prognosis of RB. One of the challenges remains creating awareness amongst caregivers about the most common signs of RB and ensuring prompt referral to ophthalmologists or ocular oncologists within 3 months of the onset of symptoms. Aggressive management and thorough systemic surveillance are important in children with prolonged lag times to seek RB care. It is well known that the burden of disability-adjusted life years (DALY) from RB still remains concentrated in LICs and LMICs.[35] Although evidence specific to RB is scarce, it has been shown that the economic cost of DALYs in LICs and LMICs are much higher than their GDP fraction of healthcare expenses.[36,37] Thus, reducing the lag time can have profound implications for LMICs in reducing the morbidity of the disease.

ABBREVIATIONS

AJCC	American Joint Committee on Cancer
GDP	Gross Domestic Product
HIC	High Income Country
LIC	Low Income Country
LMIC	Lower Middle Income Country
PHP	Primary Healthcare Practitioner
RB	Retinoblastoma

UMIC Upper Middle Income Country

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the author(s).

PRÉCIS

In a study of 692 retinoblastoma (RB) patients from 10 countries followed up for 3 years, greater lag time was associated with increased risk of RB-related death (hazard ratio, 1.056; 95% CI, 1.025–1.087; $p < .001$).

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REFERENCES

1. Barr RD. "Delays" in diagnosis: a misleading concept, yet providing opportunities for advancing clinical care. *J Pediatr Hematol Oncol*. 2014;36(3):169–172. doi: 10.1097/MPH.0000000000000108.
2. Brasme J-F, Morfouace M, Grill J, et al. Delays in diagnosis of paediatric cancers: a systematic review and comparison with expert testimony in lawsuits. *Lancet Oncol*. 2012;13(10):e445–e459. doi: 10.1016/S1470-2045(12)70361-3.
3. Antoneli CB, Steinhorst F, de Cássia Braga Ribeiro K, et al. Extraocular retinoblastoma: a 13-year experience. *Cancer*. 2003;98(6):1292–1298. doi: 10.1002/cncr.11647.
4. Luo X, Ye H, Ding YG, Du Y, Yang H. Clinical characteristics and prognosis of patients with retinoblastoma: 8-year follow-up. *Turk J Med Sci*. 2015;45(6):1256–1262. doi: 10.3906/sag-1402-144.
5. Chang CY, Chiou TJ, Hwang B, Bai LY, Hsu WM, Hsieh YL. Retinoblastoma in Taiwan: survival rate and prognostic factors. *Jpn J Ophthalmol*. 2006;50(3):242–249. doi: 10.1007/s10384-005-0320-y.
6. Bowman RJ, Mafwiri M, Luthert P, Luande J, Wood M. Outcome of retinoblastoma in east Africa. *Pediatr Blood Cancer*. 2008;50(1):160–162. doi: 10.1002/pbc.21080.
7. Kashyap S, Meel R, Pushker N, et al. Clinical predictors of high risk histopathology in retinoblastoma. *Pediatr Blood Cancer*. 2012;58(3):356–361. doi: 10.1002/pbc.23239.
8. Nyamori JM, Kimani K, Njuguna MW, Dimaras H. Retinoblastoma referral pattern in Kenya. *Middle East Afr J Ophthalmol*. 2014;21(4):321–327. doi: 10.4103/0974-9233.142270.
9. Ramírez-Ortiz MA, Ponce-Castañeda MV, Cabrera-Muñoz ML, Medina-Sansón A, Liu X, Orjuela MA. Diagnostic delay and sociodemographic predictors of stage at diagnosis and mortality in unilateral and bilateral retinoblastoma. *Cancer Epidemiol Biomarkers Prev*. 2014;23(5):784–792. doi: 10.1158/1055-9965.EPI-13-1069.
10. Brown BJ, Adeleye AO, Ibeh JN. A prospective study on the causes of delayed diagnosis of childhood cancer in Ibadan, Nigeria. *Pediatr Hematol Oncol*. 2015;32(6):365–373. doi: 10.3109/08880018.2015.1040933.
11. Leila S, Ibtissam H, Hafsa E, Abdeljalil M. Extra-ocular retinoblastoma: about 12 cases followed at the mohamed VI university hospital of marrakech. *Pan Afr Med J*. 2016;25:131. doi: 10.11604/pamj.2016.25.131.8599.
12. Posner M, Jaulim A, Vasalaki M, Rantell K, Sagoo MS, Reddy MA. Lag time for retinoblastoma in the UK revisited: a retrospective analysis. *BMJ Open*. 2017;7(7):e015625. doi: 10.1136/bmjopen-2016-015625.
13. Jin L, Zhang W, Pan H, et al. Retrospective investigation of retinoblastoma in Chinese patients. *Oncotarget*. 2017;8(65):108492–108497. doi: 10.18632/oncotarget.18174.
14. Xiao W, Ye H, Zeng H, et al. Associations among socioeconomic factors, lag time, and high-risk histopathologic features in eyes primarily enucleated for retinoblastoma. *Curr Eye Res*. 2019;44(10):1144–1149. doi: 10.1080/02713683.2019.1623898.
15. Meel R, Kashyap S, Bakhshi S, Singh Bajaj M, Wadhwani M. Retinoblastoma in children older than 6 years of age. *Ocul Oncol Pathol*. 2020;6(6):395–404. doi: 10.1159/000509040.
16. Kim HA, Yoon YH, Kim JG, Lee JY. Clinical features and long-term prognosis of retinoblastoma according to age at diagnosis. *Korean J Ophthalmol*. 2020;34(3):242–250. doi: 10.3341/kjo.2019.0097.
17. Kaliki S, Ji X, Zou Y, et al. Lag time between onset of first symptom and treatment of retinoblastoma: an international collaborative study of 692 patients from 10 countries. *Cancers (Basel)*. April 19, 2021;13(8):1956. doi: 10.3390/cancers13081956.
18. Hordofa DF, Daba KT, Mengesha AA. Clinical presentation of retinoblastoma in Ethiopia: a case of jimma university medical center pediatric oncology unit, Southwest Ethiopia. *Ethiop J Health Sci*. 2021;31(5):963–968. doi: 10.4314/ejhs.v31i5.7.
19. Utomo PT, Respatika D, Ardianto B, et al. Lag time, high-risk histopathological features, metastasis, and survival interrelation in retinoblastoma: a perspective from lower-middle income country. *Int J Ophthalmol*. 2022;15(12):1994–2000. doi: 10.18240/ijo.2022.12.15.
20. Nindyastuti H, Rusmawatiningtyas D, Makrufardi F, Supriyadi E. Lag time to diagnosis as a predictor of mortality in children with extraocular retinoblastoma: experience from a developing country. *Asia Pac J Clin Oncol*. 2022;18(6):706–713. doi: 10.1111/ajco.13767.
21. Sherief ST, Mulatu DG, Wu F, O'Banion J, Dimaras H. Clinicopathological presentation of retinoblastoma in Ethiopia. *Ocul Oncol Pathol*. 2022;8(3):168–174. doi: 10.1159/000525113.
22. Yang L, Fang X, Jin M, Sandner D, et al. Analysis of cause-specific mortality in patients with retinoblastoma. *J Ophthalmol*. 2022;2022:1–7. doi: 10.1155/2022/2470890.
23. Sherief ST, Wu F, O'Banion J, Teshome T, Dimaras H. Referral patterns for retinoblastoma patients in Ethiopia. *BMC Health Serv Res*. 2023;23(1):172. doi: 10.1186/s12913-023-09137-9.
24. Yousef YA, Abu Salim QF, Mohammad M, et al. Presentation and management outcomes of retinoblastoma among Syrian refugees in Jordan. *Front Oncol*. 2023;12:156963. doi: 10.3389/fonc.2022.1056963.
25. Vempuluru VS, Maniar A, Kaliki S. Global retinoblastoma studies: a review. *Clin Exp Ophthalmol*. January 23, 2024;52(3):334–354. doi: 10.1111/ceo.14357. Epub ahead of print.
26. Retinoblastoma Study Group G, Fabian ID, Abdallah E, et al. Global retinoblastoma presentation and analysis by national

income level. *JAMA Oncol*. 2020;6(5):685–695. doi: 10.1001/jamaoncol.2019.6716.
27. Global Retinoblastoma Study Group. The global retinoblastoma outcome study: a prospective, cluster-based analysis of 4064 patients from 149 countries. *Lancet Glob Health*. 2022;10(8):e1128–e1140. doi: 10.1016/S2214-109X(22)00250-9.
28. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2023. https://www.R-project.org/.
29. Barlow WE, Ichikawa L, Rosner D, Izumi S. Analysis of case-cohort designs. *J Clin Epidemiol*. 1999;52(12):1165–1172. doi: 10.1016/S0895-4356(99)00102-X.
30. Abramson DH, Schefler AC, Beaverson KL, Rollins IS, Ruddat MS, Kelly CJ. Rapid growth of retinoblastoma in a premature twin. *Arch Ophthalmol*. 2002;120(9):1232–1233. doi: 10.1001/archopht.120.9.1232.
31. Shah PK, Narendran V, Kalpana N. In vivo growth of retinoblastoma in a newborn infant. *Indian J Ophthalmol*. 2010;58(5):421–423. doi: 10.4103/0301-4738.67066.
32. Vempuluru VS, Jakati S, Kaliki S. Delayed metastasis in patients with intraocular retinoblastoma: a review of three cases. *Eur J Ophthalmol*. 2021;31(4):2042–2047. doi: 10.1177/1120672120946285.
33. Mao X, Mei R, Yu S, et al. Emerging technologies for the detection of cancer micrometastasis. *Technol Cancer Res Treat*. 2022;21:15330338221100355. doi: 10.1177/15330338221100355.
34. Fabian ID, Stacey AW, Bowman R, et al. Retinoblastoma management during the COVID-19 pandemic: a report by the global retinoblastoma study group including 194 centers from 94 countries. *Pediatr Blood Cancer*. 2021;68(1):e28584. doi: 10.1002/pbc.28584.
35. Li X, Chang Y, Zhao X, et al. Global health inequities in retinoblastoma: a 1990–2021 analysis across socio-demographic index regions. *Front Public Health*. 2025;13:1513526. doi: 10.3389/fpubh.2025.1513526.
36. Dalal K, Svanström L. Economic burden of disability adjusted life years (DALYs) of injuries. *Health*. 2015;7(04):487–494. doi: 10.4236/health.2015.74058.
37. Oostvogels AJ, De Wit GA, Jahn B, et al. Use of DALYs in economic analyses on interventions for infectious diseases: a systematic review. *Epidemiol Infect*. 2015;143(9):1791–1802. doi: 10.1017/S0950268814001940.