

Factors associated with mortality among retinoblastoma patients in Malaysia: A retrospective cohort study

Zulkifli Nor-Aizura, MSc^{1,2}, Nadiah Wan-Arfah, PhD³, Nyi Nyi Naing, MMedStats¹, Syaratul Emma Hashim, MMed¹, Ismail Shatriah, MMed^{4,5}, Ahmad Sukari Ain-Nasyrah, MMed⁵, Norhafizah Hamzah, MS Ophthal⁶, Jamalia Rahmat, MS Ophthal⁷, Mohamad Aziz Salowi, MS Ophthal⁸

¹Faculty of Medicine, Universiti Sultan Zainal Abidin, Kuala Terengganu, Terengganu, Malaysia, ²Clinical Research Centre (CRC), Hospital Raja Permaisuri Bainun, Ipoh, Ministry of Health, Malaysia, ³Faculty of Health Sciences, Universiti Sultan Zainal Abidin, Kuala Nerus, Terengganu, Malaysia, ⁴Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, ⁵Hospital Pakar Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, ⁶Department of Paediatric Ophthalmology, Hospital Tunku Azizah, Kuala Lumpur, Malaysia, ⁷Department of Ophthalmology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia, ⁸Department of Ophthalmology, Hospital Selayang, Selangor, Malaysia

ABSTRACT

Introduction: Retinoblastoma is the most common primary intraocular cancer worldwide. Research into factors associated with mortality in retinoblastoma from the Southeast Asian region is currently limited. The present study aims to identify the associated factors that predict mortality among retinoblastoma patients in Malaysia.

Materials and Methods: A retrospective cohort study was conducted on retinoblastoma patients diagnosed between January 2004 and April 2023 at hospitals with paediatric ophthalmology services in Malaysia. Data were collected from the Retinoblastoma Registry of the National Eye Database and patients' medical records. The adjusted hazard ratio (AHR) was used in the multivariable Cox regression model to identify the factors associated with mortality among retinoblastoma patients.

Results: A total of 402 retinoblastoma patients were included in the study. Of these, 22 (5.5%) patients died, while 353 (87.8%) were alive and under follow-up at the end of the study, and 27 (6.7%) were lost to follow-up. The univariable Cox regression model identified laterality, lag time, and recurrence as the associated factors. The multivariable Cox regression model confirmed that bilateral (AHR: 3.64; 95% CI: 1.46, 9.02; $p=0.004$) and longer lag time (AHR: 4.03; 95% CI: 1.57, 10.35; $p=0.004$) were independent predictors of mortality.

Conclusion: This study found that bilateral and longer lag time were independent prognostic factors associated with higher mortality among retinoblastoma patients in Malaysia. These results highlight the utmost importance of early diagnosis and access to appropriate treatment to improve survival outcomes for retinoblastoma patients.

KEYWORDS:

Retinoblastoma, factors associated, mortality, Cox model, Malaysia

INTRODUCTION

Retinoblastoma is a tumour that develops in the retina and is the most common intraocular malignancy in children, contributing significantly to mortality worldwide. This type of cancer accounts for around 3% of all childhood cancers and usually affects children under the age of five when diagnosed.¹ The incidence rate of retinoblastoma is approximately 1 case per 15,000 to 20,000 live births, resulting in around 9000 new cases annually.² Early detection and treatment are essential for retinoblastoma to prevent severe consequences such as blindness, loss of the affected eye, or even death.³ Prompt treatment is essential for improving the overall prognosis of patients diagnosed with retinoblastoma.⁴

Previous studies have examined the prognostic factors associated with mortality across various regions. In high-income countries, factors such as age at diagnosis, gender, laterality of the disease, disease extension, and treatment abandonment were identified.⁵⁻⁸ Meanwhile, studies from middle-income countries highlighted the presenting signs, laterality of the disease, and disease extension as predictors of mortality.^{3,9-11} On the other hand, a study in low-income countries found that disease extension and acceptance of chemotherapy were significant predictors of mortality.¹²

Retinoblastoma poses a significant burden in paediatric patients in low- and middle-income countries, leading to a less favorable prognosis and increased chances of mortality.¹³ In Malaysia, delays in diagnosis and refusal of treatment can lead to lower survival rates.¹⁴ Given these disparities, a region-specific understanding of retinoblastoma prognosis is essential for optimizing patient management and improving survival outcomes. To the best of our knowledge, there is limited research investigating the factors associated with retinoblastoma mortality in Southeast Asian countries. Although a study in Malaysia has examined prognostic factors in patients with unilateral retinoblastoma, the combination evaluation of prognostic factors in both unilateral and bilateral cases remains underexplored.¹⁵ Thus, this study aimed to identify key prognostic factors that predict

This article was accepted: 28 April 2025

Corresponding Author: Nadiah Wan-Arfah

Email: wanwaj@unisza.edu.my

mortality in both unilateral and bilateral retinoblastoma patients in Malaysia.

MATERIALS AND METHODS

Study design and setting

A retrospective cohort study involved a record review of retinoblastoma patients diagnosed in hospitals with paediatric ophthalmology services in Malaysia between January 2004 and April 2023. These include Hospital Kuala Lumpur, Hospital Tunku Azizah in Kuala Lumpur, Hospital Wanita dan Kanak-Kanak Sabah, Hospital Queen Elizabeth in Sabah, Hospital Umum Kuching in Sarawak, Hospital Sultanah Nur Zahirah in Terengganu, and Hospital Pakar Universiti Sains Malaysia in Kelantan.

Inclusion and exclusion criteria

All patients with retinoblastoma were clinically diagnosed using indirect ophthalmoscopy, and those with tumour extension were further evaluated by imaging through computed tomography scan (CT scan) or magnetic resonance imaging (MRI). In some cases, the diagnosis was confirmed through histopathological examination. The study included patients who were clinically diagnosed with retinoblastoma. Those diagnosed with retinoblastoma who had an indefinite date of diagnosis or indefinite date of last clinical visit were excluded from the analysis.

Sample size and sampling method

A post-hoc sample size calculation for survival analysis was performed using Power and Sample Size Software to evaluate whether the study had sufficient power to detect the effect of disease extension between extraocular and intraocular retinoblastoma on mortality.¹⁶ The analysis was based on the prognostic factor of disease extension observed in the current study. Using the final sample size of 402 retinoblastoma patients and a median survival time of 12 months, the power to detect a hazard ratio comparing extraocular to intraocular disease of 8.43 was recalculated. A two-tailed significance level of 0.05 was applied. The ratio of intraocular to extraocular retinoblastoma patients, 1.41, was incorporated based on the study findings. The accrual period was 232 months, with an additional 12 months of follow-up. The post-hoc analysis yielded an observed power of 0.98, indicating that the study had sufficient statistical power to detect the effect between extraocular and intraocular disease and mortality in retinoblastoma patients. These findings suggest that the study was well-powered to support its conclusions regarding the prognostic impact of disease extension. Given the rarity of retinoblastoma and the limited number of available cases for study, probability sampling methods were not feasible to implement in order to maximize statistical power.

Data collection

This study obtained relevant data from the Retinoblastoma Registry of the National Eye Database (NED) and patients' medical records using a standardized data collection tool. The data collected encompassed patients' demographic characteristics, clinical features, treatments received, and outcomes. For cases of bilateral retinoblastoma, the analysis

included only the eye with the more advanced disease, as determined by the clinical staging criteria of the International Retinoblastoma Staging System (IRSS). These stages denote orbital extension or metastatic spread, indicating more severe disease progression. Additionally, the date of the last clinical visit and any missing information were retrieved from the patients' medical records.

Statistical analysis

This study conducted data analyses using the STATA/SE software version 15. The association between two categorical variables was compared using either the Pearson Chi-square test or Fisher's exact test. Survival analyses were based on time-to-event data, with survival time measured from the date of retinoblastoma diagnosis until the date of death or the last clinical visit date. Censored observations referred to patients who were alive at the end of the study period or were lost to follow-up. The event was defined as a patient who died from retinoblastoma. A preliminary analysis using the simple Cox regression model was conducted to identify potential prognostic factors with a p-value less than 0.25. Subsequently, an advanced multivariable Cox regression model was conducted to identify the independent prognostic factors associated with mortality among retinoblastoma patients. This analysis was guided by the principles of parsimony, biological plausibility, and statistical significance. The full stepwise selection method was employed for variable selection to ensure that the final model includes only the most significant predictors, and all possible multicollinearity and interaction effects were thoroughly examined.

Hazard function plot, log minus log plot, Schoenfeld partial residuals plot, scaled and non-scaled Schoenfeld, and C-statistics were performed to check the proportional hazards assumptions. Regression diagnostics were also conducted, using Cox-Snell residuals to evaluate model fitness, Martingale residuals to assess adequate functional form, and deviance residuals and influence analysis to determine the presence of outliers and its influence on the model fitness. The final best model was chosen based on the consideration of statistically significant and clinically important variables. Crude hazard ratios (CHR) and adjusted hazard ratios (AHR) were estimated with 95% confidence intervals (CI), Wald statistics, and corresponding p-values. The level of significance was set at 0.05 in a two-tailed test.

Ethical approval

The study was approved by the Medical Research Ethics Committee, Ministry of Health Malaysia (NMRR ID-22-00956-GJE (IIR)), UniSZA Human Research Ethics Committee (UniSZA/UHREC/2023/495(1)), and the USM Human Research Ethics Committee (USM/JEPeM/KK/24030236). Informed consent was not required as the secondary data were used in this study. However, permission to access patients' medical records was obtained from the participating hospitals. Confidential codes were used in the data collection sheet to represent each patient to protect their privacy and confidentiality.

Table I: Comparison of demographic and clinical characteristics of retinoblastoma patients (n = 402)

Characteristics	Total (%)	Died (%)	Alive (%)	p-value
Age at diagnosis				
Less than 12 months	96 (23.9)	3 (13.6)	93 (24.5)	0.641
12-23 months	111 (27.6)	8 (36.4)	103 (27.1)	
24-36 months	105 (26.1)	6 (27.3)	99 (26.0)	
More than 36 months	90 (22.4)	5 (22.7)	85 (22.4)	
Gender				
Female	174 (43.3)	10 (45.5)	164 (43.2)	0.833
Male	228 (56.7)	12 (54.5)	216 (56.8)	
Ethnicity				
Non-malay	147 (36.6)	9 (40.9)	138 (36.3)	0.664
Malay	255 (63.4)	13 (59.1)	242 (63.7)	
Family history				
No	387 (96.3)	21 (95.5)	366 (96.3)	0.577
Yes	15 (3.7)	1 (4.5)	14 (3.7)	
Leading sign				
Proptosis	20 (5.0)	3 (13.6)	17 (4.5)	0.101
Leukocoria	334 (83.1)	18 (81.8)	316 (83.2)	
Strabismus	48 (11.9)	1 (4.6)	47 (12.3)	
Laterality				
Bilateral	143 (35.6)	15 (68.2)	128 (33.7)	0.001
Unilateral	259 (64.4)	7 (31.8)	252 (66.3)	
Disease staging				
Stage A-E	345 (85.8)	0 (0.0)	345 (90.8)	0.001
Stage 0-II	30 (7.5)	1 (4.5)	29 (7.6)	
Stage III	8 (2.0)	2 (9.1)	6 (1.6)	
Stage IV	19 (4.7)	19 (86.4)	0 (0.0)	
Disease extension				
Intraocular	344 (85.6)	0 (0.0)	344 (90.5)	0.001
Extraocular	58 (14.4)	22 (100.0)	36 (9.5)	
Treatment received				
Radiotherapy	18 (2.4)	1 (2.3)	17 (2.3)	0.230
Focal therapy	136 (17.8)	4 (8.9)	132 (18.4)	
Chemotherapy	304 (39.8)	20 (90.9)	284 (39.6)	0.853
Enucleation	305 (40.0)	20 (44.4)	285 (39.7)	
Recurrence				
No	382 (95.0)	19 (86.4)	363 (95.5)	0.055
Yes	20 (5.0)	3 (13.6)	17 (4.5)	
Lag time				
Less than 6 months	285 (70.9)	7 (31.8)	278 (73.2)	0.001
More than 6 months	117 (29.1)	15 (68.2)	102 (26.8)	
Years of diagnosis				
2004-2008	84 (20.9)	4 (18.2)	80 (21.1)	0.766
2009-2013	90 (22.4)	6 (27.3)	84 (22.1)	
2014-2018	104 (25.9)	7 (31.8)	97 (25.5)	
2019-2023	124 (30.8)	5 (22.7)	119 (31.3)	

RESULTS

A total of 402 retinoblastoma patients were included in the final analysis. Of these, 353 (87.8%) were alive and under follow-up at the end of the study and 27 (6.7%) were lost to follow-up, while 22 (5.5%) patients died. Table I shows the comparison of demographic and clinical characteristics of retinoblastoma patients. Most of the patients (27.6%) were between 12-23 months old when diagnosed with retinoblastoma. Approximately 63.4% of patients were Malays, and 56.7% were males. Only one patient with family history died from retinoblastoma. The majority of patients with stage IV died from retinoblastoma (86.4%). The analysis showed statistically significant differences in disease staging ($p=0.001$), disease extension ($p=0.001$), laterality ($p=0.001$), lag time ($p=0.001$) between the two groups.

Table II displays the factors associated with mortality among retinoblastoma patients using the univariable Cox regression

model. The factors were considered important if the p -value < 0.250 . The results revealed that three predictors were deemed significant as prognostic factors. These include disease staging ($p<0.250$), laterality ($p=0.004$), lag time ($p=0.001$), and recurrence ($p=0.138$).

The proportional hazards assumptions were met. Table III exhibits the factors associated with mortality among retinoblastoma patients using the multivariable Cox regression model. The analysis identified two predictors as independent prognostic factors of mortality. These include laterality and lag time. Patients with bilateral cases had a significantly 3.64 times higher risk of dying than patients with unilateral cases (AHR: 3.64; 95% CI: 1.46, 9.02; $p=0.004$). Furthermore, patients who had lag time more than 6 months had a 4 times higher risk of dying than those who had lag time less than 6 months (AHR: 4.03; 95% CI: 1.57, 10.35; $p=0.004$).

Table II: Factors associated with mortality among retinoblastoma patients using the univariable Cox regression model (n = 402)

Characteristics	Regression coefficient (b)	Crude HR (95% CI)	Wald statistic	p-value
Age at diagnosis				
Less than 12 months	0.95	2.58 (0.68-9.74)	1.40	0.162
12-23 months	0.68	1.98 (0.50-7.92)	0.97	0.334
24-36 months	0.66	1.94 (0.46-8.14)	0.91	0.363
More than 36 months	0	1		
Gender				
Female	0.06	1.06 (0.46-2.45)	0.13	0.892
Male	0	1		
Ethnicity				
Non-malay	0	1		
Malay	-0.30	0.74 (0.32-1.73)	-0.69	0.488
Family history				
No	0	1		
Yes	0.26	1.30 (0.18-9.67)	0.26	0.797
Proptosis				
No	0	1		
Yes	0.70	2.02 (0.47-8.63)	0.95	0.344
Strabismus				
No	0	1		
Yes	-0.97	0.38 (0.05-2.83)	-0.94	0.345
Leukocoria				
No	0	1		
Yes	0.18	1.19 (0.35-4.03)	0.28	0.777
Laterality				
Unilateral	0	1		
Bilateral	1.32	3.76 (1.53-9.23)	2.89	0.004
Disease staging				
Stage 0-I	0	1		
Stage II	1.77	5.85 (0.65-52.35)	1.58	0.114
Stage III	2.02	20.51 (2.39-175.78)	2.76	0.016
Stage IV	3.76	38.22 (10.40-250.40)	3.47	0.0012
Recurrence				
No	0	1		
Yes	0.92	2.51 (0.74-8.51)	1.48	0.138
Lag time				
Less than 6 months	0	1		
More than 6 months	1.77	5.86 (2.39-14.38)	3.86	0.001
Years of diagnosis				
2004-2008	0	1		
2009-2013	0.26	1.30 (0.37-4.62)	0.41	0.682
2014-2018	0.39	1.48 (0.43-5.06)	0.62	0.535
2019-2023	0.58	1.78 (0.46-6.92)	0.84	0.402

CI: Confidence interval

Table III: Factors associated with mortality among retinoblastoma patients using the multivariable Cox regression model (n = 402)

Characteristics	Regression coefficient (b)	Crude HR (95% CI)	p-value	Regression coefficient (b)	Adjusted HR (95% CI)	p-value
Laterality						
Extension	1.32	3.76 (1.53-9.23)	0.004	1.27	3.64 (1.46-9.02)	0.004
Lag time	1.77	5.86 (2.39-14.38)	0.001	1.39	4.03 (1.57-10.35)	0.004

HR: Hazards ratio

CI: Confidence interval

Backward stepwise Cox proportional hazards regression model applied, multicollinearity and interaction term were unlikely, the preliminary final model was properly specified, hazard function plot, Nelson-Aalen cumulative hazard function, log-minus-log plot, partial residuals, scaled and non-scaled Schoenfeld residuals plot, and C-statistics were applied to check for model assumptions, regression diagnostics were conducted by Cox-snell residuals, Martingale residuals, Deviance residuals, and influence analysis, no influential outliers were detected in the model.

DISCUSSION

This is the comprehensive study on determining the key associated factors that predict mortality among retinoblastoma patients in Malaysia. Retinoblastoma patients in high-income countries have experienced a remarkable improvement in prognosis over the past five decades, with survival rates now approaching 100%. These advancements are attributed to multiple factors, such as the establishment of specialized treatment institutions and the implementation of targeted screening initiatives.¹⁷ A global study by Tomar et al. found that retinoblastoma patients in upper-middle-income and lower-middle-income countries demonstrated a 10.3-fold and 9.3-fold greater risk of mortality respectively, compared to those from high-income countries.¹⁴ This study further reported that low-income countries were significantly associated with a higher risk of poor treatment outcomes for retinoblastoma patients.

In the current study, bilateral and longer lag time were found to have an impact on the mortality of retinoblastoma patients. Our findings indicated that patients with bilateral had an 3.64-fold higher risk of mortality from retinoblastoma compared to those with unilateral cases. Previous studies on regional disparities have consistently reported that laterality is associated with increased mortality for retinoblastoma patients globally.^{6,7} The AHR for mortality was found to be 3.78 in high-income countries,⁹ and 1.70 in middle-income country.¹⁰ Our findings are comparable to those seen in high-income countries. This occurs in patients who presented late and their prognosis are poor. This is likely due to a delayed presentation in seeking appropriate modern treatment, as some parents may opt for traditional treatment of care rather than pursuing the recommended medical interventions. Thus, patient education initiatives and financial support programs should be introduced to increase awareness and accessibility of retinoblastoma care. These strategies can help empower patients and their families, ensuring timely diagnosis and enabling access to critical treatment options, particularly for those from lower-income backgrounds.

Another important prognostic factor identified in this study was longer lag time. The risk effect of longer lag time with an AHR of 4 is noteworthy. A longer lag time between symptom onset and diagnosis was associated with mortality among patients with retinoblastoma. This delay likely reflects late recognition of symptoms, limited awareness, and challenges in accessing specialized care, leading to advanced disease at presentation. Similar findings have been reported in other developing countries, where prolonged lag time contributes to higher mortality. Notably, our study findings indicate that the tumour has remained intraocular suggesting that early treatment intervention was effective. The possible reasons for parents who had history of default treatment may be reluctance towards surgical interventions, preference for alternative traditional therapies, financial constraints, and concerns about the potential consequences of the treatment outcome.

In this series, the majority of retinoblastoma patients died at an advanced stage IV. The higher proportion of mortality observed in stage IV underscores the critical need for early detection and treatment to improve survival outcomes. A

recent study reported a higher frequency of patients diagnosed with the more advanced stage among the older age groups.²² In contrast, a study conducted by Zhang et al. in China showed that the advanced disease was found highly significant prognostic factor in the mortality of retinoblastoma patients ($p < 0.001$).¹⁰ This discrepancy could be attributed to the differences in healthcare access, and socioeconomic factors between the two countries.

In the present study, age at diagnosis was not identified as an independent prognostic factor for mortality. This contrasts with a study in the United States that found higher mortality risk among patients diagnosed between 1 to 9 years of age, compared to those below 1 year.⁸ This observation is further supported by Fernandes et al. who reported that retinoblastoma patients aged 1 to 3 years faced greater mortality risk than those younger than 1 year.²³ The differences observed between our study and others may be attributed to the relatively older age of diagnosis and the progression of the disease in the Malaysian population compared to high-income countries. This is attributed to the advancements in decoding the genetic basis of the retinoblastoma disease, which have enabled improved understanding and treatment approaches in high-income countries.¹⁴

The selection of appropriate treatment modalities for retinoblastoma is partially influenced by the tumour's laterality.^{24,25} A previous study conducted in China reported that patients with bilateral retinoblastoma exhibited a statistically significantly higher mortality risk compared to those with unilateral disease.¹¹ This finding was further supported by another study in the United States, which similarly indicated that bilateral cases were more likely to develop secondary tumours, leading to a higher risk of mortality.²³ This highlights that the majority of retinoblastoma patients in the current study setting had unilateral disease, which may have contributed to their relatively better prognosis compared to those with bilateral involvement.

One of the key strengths of this study is the large sample size of retinoblastoma patients and the involvement of the majority of paediatric ophthalmology services across Malaysia. The researchers were able to analyze a sample of 402 retinoblastoma patients registered in hospitals with specialized paediatric ophthalmology departments throughout the country, which allows for a more robust and comprehensive statistical analysis. This broader representation of the retinoblastoma population in Malaysia enhances the generalizability and significance of the study findings.

The limitation of this retrospective study was the potential introduction of selection bias due to incomplete or missing information in the patient registry. The retrospective nature of the data collection process may have resulted in the unavailability of some relevant details, which could have influenced the analysis and interpretation of the findings. The observations that were excluded from the analysis may have had a worse prognosis, which could have resulted in an underestimation of potential confounding factors and

influenced the prediction of prognostic factors associated with mortality by the Cox regression model. These limitations should be taken into consideration when interpreting the findings of this study.

CONCLUSION

This large-scale study on retinoblastoma in Malaysia identified bilateral and longer lag time as independent prognostic factors associated with higher mortality. These findings underscore the importance of timely diagnosis and access to appropriate treatment for improving survival outcomes of retinoblastoma patients in Malaysia. Thus, this study's findings may contribute to the body of knowledge on survival outcomes and is of paramount importance as it lays the groundwork for future studies. Healthcare systems are encouraged to develop comprehensive nationwide or regional screening programs to detect retinoblastoma in its earliest stages, particularly among high-risk populations. Additionally, policymakers should prioritize increasing funding and resources for paediatric oncology services, ensuring all families, regardless of socioeconomic background, can access life-saving treatments and genetic counselling for children at risk of this disease.

FUNDING INFORMATION

This article received specific funding. All authors have declared that this article was supported by the Universiti Sultan Zainal Abidin (grant number: UniSZA/2022/DPU2.0/27).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

ACKNOWLEDGMENTS

The authors would like to thank the Director General of Ministry of Health Malaysia for granting permission to publish the findings from this study. The authors also acknowledge the support from the National Eye Database committee for providing access to the retinoblastoma registry. The authors would also like to express the utmost appreciation to the paediatric ophthalmologist and paediatric oncologist team for managing the patients, as well as staff of respective Department of Ophthalmology, respective hospitals, and Medical Records Unit for their cooperation with data compilation for this study. The study was supported by the internal grant of Universiti Sultan Zainal Abidin (grant number: UniSZA/2022/DPU2.0/27).

REFERENCES

- Barbosa AC, Magalhães-Barbosa MC, Moreira JP, Colombini GN, Prata-Barbosa A. Incidence of retinoblastoma in children and adolescents in Brazil: A population-based study. *Front Pediatr* 2022; 10: 1048792.
- Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. *Indian J Ophthalmol* 2020; 68: 2356.
- Yin F, Guo Z, Sun W, Hou C, Wang S, Ji F et al. Comparing overall survival between paediatric and adult retinoblastoma with the construction of nomogram for adult retinoblastoma: A SEER population-based analysis. *Asian J Surgery* 2024; 47(5): 2178-87.
- AlAli A, Kletke S, Gallie B, Lam WC. Retinoblastoma for paediatric ophthalmologists. *Asia Pac J Ophthalmol (Phila)* 2018; 7(3): 160-8.
- Berry JL, Pike S, Rajagopalan A, Reid MW, Fabian ID. Retinoblastoma outcomes in the Americas: A prospective analysis of 491 children with retinoblastoma from 23 American countries. *Am J Ophthalmol* 2023; 260: 91-101.
- Guo X, Wang L, Beeraka NM, Liu C, Zhao X, Zhou R et al. Incidence trends, clinicopathologic characteristics, and overall survival prediction in retinoblastoma children: SEER prognostic nomogram analysis. *Oncologist* 2023; 29: e275-e281.
- Hussain Z. Impact of laterality on cumulative survival in patients diagnosed with retinoblastoma: A retrospective cohort analysis of 1925 cases in the Surveillance, Epidemiology, and End Results (SEER) program. *Clin Ophthalmol* 2021; 15: 991-1001.
- Mattosinho C, Moura AT, Grigorovski N, Araújo LH, Ferman S, Ribeiro K. Socioeconomic status and retinoblastoma survival: Experience of a tertiary cancer center in Brazil. *Pediatr Blood Cancer* 2020; 68: 1-8.
- Zhang Y, Wang Y, Zhi T, Jin M, Huang D, Ma X. Clinical characteristics, treatment and prognosis of infants with retinoblastoma: A multicenter, 10-year retrospective analysis. *BMC Pediatr* 2023; 23: 229.
- Luo Y, Zhou C, He F, Fan J, Wen X, Ding Y et al. Contemporary update of retinoblastoma in China: Three-decade changes in epidemiology, clinical features, treatments, and outcomes. *Am J Ophthalmol* 2021; 236: 193-203.
- Chen P, Kao L, Chao A, Wu W, Sun M, Su W et al. Retinoblastoma in Taiwan: Survival and clinical characteristics. *Japanese J Ophthalmol* 2021; 65: 546-53.
- Lukamba RM, Budiongo AN, Monga BB, Yao A, Bey P, Chenge GB et al. Treatment adherence in retinoblastoma: A retrospective cohort study in Ivory Coast and the Democratic Republic of Congo. *Cancer Reports* 2023; 7: e1949.
- Tomar AS, Finger PT, Gallie B, Kivela TT, Mallipatna A, Zhang C et al. Global retinoblastoma treatment outcomes. Association with national income level. *Ophthalmology* 2021; 128: 740-53.
- Jamalia R, Sunder R, Alagaratnam J, Goh PP. Retinoblastoma registry report-Hospital Kuala Lumpur Experience. *Med J Malaysia* 2010; 65: 128-30.
- Ain-Nasyrah AS, Rahmat J, Ghani SA, Shatriah I. The survival outcomes of unilateral retinoblastoma in Malaysia. *Med J Malaysia* 2025; 80(2): 113-17.
- Dupont WD, Plummer WD. Power and sample size calculations: A review and computer program. *Controlled Clin Trials* 1990; 11: 116-128.
- 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: e1128-40.
- Billbeisi T, Almasry R, Obeidat M, Mohammad M, Jaradat I, Halalsheh H, et al. Causes of death and survival analysis for patients with retinoblastoma in Jordan. *Front Med* 2023; 10: 1244308.
- Pant G, Verma N, Kumar A, Pooniya V, Gupta SK. Outcome of extraocular retinoblastoma in a resource limited center from low middle income country. *Pediatr Hematol Oncol* 2018; 34: 419-24.
- Chawla B, Hasan F, Azad R, Seth R, Upadhyay AD, Pathy S et al. Clinical presentation and survival of retinoblastoma in Indian children. *Br J Ophthalmol* 2016; 100: 172-8.
- Huang D, Zhang Y, Zhang W, Wang Y, Zhang P, Hong L et al. Study on clinical therapeutic effect including symptoms, eye preservation rate, and follow-up of 684 children with retinoblastoma. *Eur J Ophthalmol* 2013; 23(4): 532-8.

22. Bas Z, Dalvin LA, Tadepalli S, Rao R, Shah A, Leahey AM et al. Outcomes of intravenous chemotherapy (chemoreduction) for retinoblastoma based on patient age in 964 eyes of 554 patients. *Asia Pac J Ophthalmol (Phila)* 2021; 10(4): 373-80.
23. Fernandes AG, Pollock BD, Rabito FA. Retinoblastoma in the United States: A 40-year incidence and survival analysis. *J Pediatr Ophthalmol Strabismus* 2018; 55: 182-8.
24. Shields CL, Fulco EM, Arias JD, Alarcon C, Pellegrini M, Rishi P et al. Retinoblastoma frontiers with intravenous, intra-arterial, periocular, and intravitreal chemotherapy. *Eye* 2013; 27: 253-264.
25. Gregersen PA, Olsen MH, Urbak SF, Funding M, Dalton SO, Overgaard J et al. Incidence and mortality of second primary cancers in Danish patients with retinoblastoma, 1943-2013. *JAMA Netw Open* 2020; 3(10): e2022126.