Original Article

ENUCLEATION TRENDS AND RISK FACTORS OF RETINOBLASTOMA PATIENTS IN MALAYSIA

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ABSTRACT

A study was conducted to investigate the clinical presentation of retinoblastoma cases in Malaysia, with a focus on identifying risk factors associated with enucleation. We conducted a cross-sectional analysis of registry data from the National Retinoblastoma Registry spanning from 2004 to 2022. Results based on a cohort of 277 retinoblastoma patients, yield noteworthy insights. The median age at diagnosis was 16 months, with a predilection for unilateral presentation (65%) over bilateral (35%). Gender distribution exhibited no significant bias, with 55.6% males and 44.4% females. Ethnicity-wise, the Malay group demonstrated the highest incidence at 57.0%, followed by Chinese (19.1%) and Indian (7.2%) populations. Leukocoria emerged as the predominant initial symptom, manifesting in 65.4% of cases. Combining leukocoria and strabismus accounted for 12.3% of cases, while strabismus alone was observed in 4.5% of cases. Extraocular extensions, detected radiographically, were noted in 12% of patients, with optic pathway involvement being the most prevalent (3.5% unilaterally and 2.9% bilaterally). Risk factors for enucleation were also examined, revealing that unilateral cases carried a significantly higher enucleation risk (10.48 times) compared to bilateral cases. A family history of retinoblastoma was associated with a noteworthy 89% reduction in enucleation risk. Additionally, advanced International Intraocular Retinoblastoma Classification (IIRC) stages D and E correlated with an elevated likelihood of enucleation. In conclusion, our study underscores the importance of early detection, particularly in unilateral cases and advanced stages of retinoblastoma. These findings hold significant clinical relevance and can inform more informed clinical decision-making and patient counselling.

INTRODUCTION

Retinoblastoma, though rare, stands as the predominant primary intraocular malignancy in paediatric populations. Despite its rarity, global incidence approximates 1 in every 15,000 to 20,000 live births, translating to an estimated annual caseload of around 9,000 [1]. The key genetic event implicated in its pathogenesis pertains to the inactivation of the RB1 gene, located at the chromosomal locus 13q14, a known tumor suppressor gene. This inactivation typically transpires through mutation or deletion mechanisms affecting both alleles of this gene [2].

Globally, the predominant manifestation of retinoblastoma is leukocoria, accounting for approximately 60% of cases, according to recent research. Strabismus follows, presenting in about 10% of instances, with proptosis making up 7%, and a co-occurrence of leukocoria and strabismus in approximately 4% of pediatric cases [3]. 12% of patients exhibit symptoms indicative of advanced disease progression, such as proptosis, lid swelling, and ocular hyperemia. A comparative pattern of symptom presentation was observed in a study conducted by Shridevi et al., which investigated local retinoblastoma occurrences in Malaysia, identifying leukocoria as the leading presentation, followed by strabismus and proptosis [4]. Less frequent presentations in this study encompassed ocular erythema, preseptal cellulitis, epiphora, hyphema, secondary glaucoma, hemorrhagic ocular discharge, with one case noted incidentally post-cataract surgery.

The diagnosis of retinoblastoma principally relies on clinical observation during examination under anesthesia, supplemented by radiological tools including B-scan ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) scans. Due to the potential risk of seeding, biopsy for histopathological diagnosis is typically avoided. CT scans, which were initially the diagnostic standard, particularly for evaluating leukocoria, had a sensitivity rate of 81-96% for

identifying calcification [5]. However, the utility of CT scans is limited by the child's radiation exposure and its comparative inferiority to MRI in detecting optic nerve invasion. Current evidence indicates the superior sensitivity of MRI in assessing retinoblastoma, especially in detecting optic nerve infiltration, extraocular extension, and intracranial spread [5].

The classification model for retinoblastoma has undergone substantial evolution. The first proposed system, the Reese-Elsworth classification, was based on the probability of preserving the eye following external beam radiotherapy (EBRT) [6]. However, with the advent of intravenous chemotherapy in the 1990s, the Intraocular Retinoblastoma Classification (IIRC) was introduced, centered around the risk of treatment failure, enucleation, or EBRT [7]. This classification, while useful, was limited in its singular assessment of ocular loss risk, without reflecting the holistic risk to the child from retinoblastoma. Consequently, a modified classification, the Intraocular Classification of Retinoblastoma (ICRB), was developed, emphasizing the prediction of outcomes following intraocular chemotherapy [8]. Another widely utilized classification system is the American Joint Committee on Cancer (AJCC) classification, which employs TNM staging with a focus on primary site involvement [9].

The primary objectives of retinoblastoma treatment encompass achieving oncological remission, conserving the globe and vision where possible, and ultimately mitigating the risk of systemic metastasis or life-threatening outcomes for the patient [10]. The therapeutic approach to retinoblastoma has markedly evolved, transitioning from the historical norm of enucleation to efforts to salvage the affected globe. There are many treatment modalities currently utilised, each presenting its unique set of indications, benefits, and drawbacks. Mendoza et al. (2016) have systematically listed these options in their publication [11]. Broadly, these interventions can be divided into non-surgical and surgical categories. The non-surgical options can be further stratified into focal therapy, chemotherapy, and external beam radiotherapy. Focal therapy, confined to the globe, includes adjunctive treatments such as thermotherapy, photocoagulation, cryotherapy, and plaque brachytherapy. Chemotherapy, on the other hand, can be administered through various routes including intravenous, intra-arterial, intravitreal, and periocular methods.

Intravenous chemotherapy involves a 2, 3, or 4 drug regimen delivered through an intravenous catheter on a monthly basis for 6–9 consecutive months. In general, intravenous chemotherapy is used for patients with the following: germline mutation retinoblastoma, bilateral retinoblastoma, familial retinoblastoma, age of 4 months or younger, suspicious evidence of early optic nerve or choroidal invasion [12]. Intraarterial chemotherapy, first introduced by Akihiro Kaneko in 1990, is indicated for non-germline mutation retinoblastoma, unilateral retinoblastoma, age greater than 4 months, recurrent retinoblastoma following previous intravenous chemotherapy or plaque radiotherapy, recurrent subretinal seeds involving two or more quadrants, and recurrent vitreous seeds [12, 13]. Periocular chemotherapy, primarily indicated for bilateral advanced groups D or E, is utilized when a higher local dose of chemotherapy is desired or for recurrent localized tumors [12]. Intravitreal chemotherapy is typically employed for vitreous seeds nonresponsive to standard therapy, or vitreous seeds recurring after previous treatments [12].

Enucleation, a surgical intervention primarily reserved for advanced-stage disease, continues to be the gold standard in avoiding life-threatening complications associated with retinoblastoma. The procedure entails meticulous removal of the entire globe and a significant portion of the optic nerve, while minimizing globe trauma and reducing the risk of tumor dissemination into the orbit [14].

Extensive investigations have been conducted into the histopathological risk factors and metastatic risks associated with retinoblastoma. However, the literature presently lacks studies pertaining specifically to the risk factors related to enucleation in retinoblastoma patients. The primary objective of our study is to discern the risk factors associated with enucleation, with a focus on demographic, clinical, and radiological features of patients presenting in Malaysia. Additionally, we aim to offer updated demographic and clinical statistics of retinoblastoma patients diagnosed within tertiary care centers in Malaysia. Our aspiration is that the insights gleaned from this investigation will equip ophthalmologists with the ability to estimate the probability of enucleation in retinoblastoma patients before the initial examination under anesthesia. We envision that these findings will enable more precise and targeted counselling strategies for parents, thereby facilitating the complex decision-making process concerning the potential enucleation of their child's eye.

MATERIAL AND METHOD

This is a cross-sectional study with a retrospective review of registry data from the National Retinoblastoma Registry of Malaysia which is part of the Malaysian National Eye Database (NED) from January 2004 to December 2022. Approval was obtained from the Ethics Committee of the National Medical Research Registry (NMRR). This study was performed according to the Declaration of Helsinki and ICH guidelines for good clinical practice.

All patients who were diagnosed and treated for retinoblastoma, whose data was entered into the retinoblastoma registry between the years 2004 to 2022 were recruited into the study. The subjects were eligible provided that: 1) They had a confirmed diagnosis of retinoblastoma clinically or by histopathological examination, 2) They had complete data entered into the registry pertaining to the scope of this study. No sampling was performed in this study due to the unknown size of the registry

between the years 2004 to 2022. However, based on a retrospective descriptive study by Shridevi et al (2018) in the Asian Pacific Journal of Cancer Prevention between the years 2004-2012, a sample size estimation was made using formulae for estimating a proportion without finite population correction. A minimum of 373 eyes are acquired to estimate a proportion of 58.6% enucleation based on the study with a 95% confidence interval and a margin of error of 5%.Sample size estimation was performed using Sample Size Calculator for Estimations, version 1.0.03 (2008).

Data was obtained from the vendor of the National Eye Database after approval by the person in charge of the National Eye Database and the National Retinoblastoma registry. The data that was collected included: age, gender, ethnicity, state of residence, presence of family history of retinoblastoma, symptoms of presentation, confirmation of diagnosis, laterality of disease, computed tomography (CT) findings if available, magnetic resonance imaging (MRI) findings if available and staging of the disease at time of diagnosis based on the International Intraocular Retinoblastoma Classification (IIRC). Out of a total of 384 patients entered into the registry for the duration of the study, only 277 patients met the inclusion criteria which accounted for a total of 374 eyes evaluated.

A descriptive analysis of all the demographic and outcome variables was performed. The results of the continuous variables were described with median and interquartile range and results of categorical variables were described with frequency and percentage. Chi Square test and Fisher Exact test were used to determine the association between categorical variables. Univariable and multivariable binomial logistic regression is carried out on the outcome variable to determine factors predisposing to the outcome. All statistical analysis was performed using Statistical Package for Social Science (SPSS) Ver 23.0 and *p -values of less than 0.05 were considered to be significant.*

RESULTS

In our analysis of 277 patients, Table 1 presents detailed information regarding the demographic characteristics of retinoblastoma patients in

Table 1: Demographic Characteristics of Retinoblastoma Patients in Malaysia.

Demographic Profile							
	Unilateral RE, n(%)	Unilateral LE, n(%)	p value[1]	Total Unilateral Cases, n(%)	Total Bilateral Cases, n(%)	p value[2]	Total (n, %)
Age of presentation [IQR: Total cases(6-33), Unilateral cases(6-33), Bilateral cases(6-36)]							
<1	11 (4.0)	12 (4.3)	0.735[3]	23 (8.3)	43 (15.5)	<0.001[3]	66 (23.8)
1- <2	17 (6.1)	26 (9.4)		43 (15.5)	28 (10.1)		71 (25.)
2- <3	27 (9.8)	21 (7.6)		48 (17.3)	18 (6.5)		66 (23.8)
3- <4	17 (6.1)	19 (6.9)		36 (13.0)	5 (1.8)		41 (14.8)
4- <5	5 (1.8)	7 (2.5)		12 (4.3)	1 (0.4)		13 (4.7)
5 and above	9 (3.3)	9 (3.3)		18 (6.5)	2 (0.7)		20 (7.2)
Gender							
Male	42 (15.2)	56 (20.2)	0.148[3]	98 (35.4)	56 (20.2)	0.614[3]	154 (55.6)
Female	44 (15.9)	38 (13.7)		82 (29.6)	41 (14.8)		123 (44.4)
Ethnicity							
Malay	45 (16.3)	59 (21.3)	0.313[3]	104 (37.6)	54 (19.5)	0.249[3]	158 (57.0)
Chinese	17 (6.1)	12 (4.3)		29 (10.5)	24 (8.7)		53 (19.1)
Indian	5 (1.8)	8 (2.9)		13 (4.7)	7 (2.5)		20 (7.2)
Others	19 (6.9)	15 (5.4)		34 (12.3)	12 (4.3)		46 (16.6)
Family History							
Positive	2 (0.7)	1 (0.4)	0.607[4]	3(1.1)	6 (2.2)	0.070[3]	9 (3.3)
Negative	84 (30.3)	93 (33.6)		177(63.9)	91 (32.9)		268 (96.8)

[1] *p value to determine significant association between variables and laterality in unilateral cases.*
[2] *p value to determine significant association between variables and laterality overall*
[3] *Chi square test*
[4] *Fisher exact test*

Malaysia. Our data demonstrated that more than 2/3rds of the total retinoblastoma cases in Malaysia were under the age of 3 years old. The age of presentation that exhibited the greatest number of bilateral cases was among children aged less than 1 year, accounting for 43 patients or 15.5% of the total sample size. Unilateral retinoblastoma was more prevalent in the age group 1- <2 years. An inverse relationship between age of onset and retinoblastoma incidence was observed across all categories. The median age of presentation was determined to be 16 months [IQR 6-33] overall and specifically 16 months [IQR 6-33] for unilateral cases and 15 months [IQR 6-36] for bilateral cases. With regards to gender, male patients accounted for a slightly larger proportion of retinoblastoma cases with 154 cases (55.6%) versus 123 female cases (44.4%).

The distribution of retinoblastoma across different ethnicities revealed that the Malay ethnic group had the highest incidence totalling 158 cases (57.0%). The Chinese ethnic group reported 53 cases (19.1%) while the Indian ethnic group had 20 cases (7.2%) overall. Other ethnicities reported a total of 46 cases (16.6%). In terms of family history, a positive history of retinoblastoma was reported in 3 unilateral cases (1.1%) and 6 cases (2.17%) of bilateral disease, totalling 9 cases (3.25%). The majority of patients (96.8%), however, did not have a familial history of the disease.

Statistical analyses utilizing the Chi-Square Test and Fisher Exact Test demonstrated an absence of statistically significant correlations between the prevalence of retinoblastoma in either the right or left eye among patients with unilateral presentations while accounting for variables including age, gender, ethnicity, and familial predisposition to the disease. However, a marked statistical significance was observed in comparing unilateral and bilateral instances with respect to age ($P<0.001$). Notably, our data showed that unilateral cases were more likely to present at an older age group compared to bilateral cases which had a tendency to present earlier comparatively.

Table 2 shows the distribution of presenting symptoms in our patients. Among the cases, leukocoria alone is the most common symptom, accounting for 65.4% of the total. Leukocoria, combined with strabismus, follows at 12.3%. Strabismus without leukocoria is observed in 4.3% of patients. Notably, advanced presentations, including redness, proptosis, vision loss, hyphema, lid swelling, cellulitis, and secondary glaucoma, collectively account for 16.2% of cases. Other symptoms, such as tearing, nystagmus, screening for RB, and incidental findings, are less frequent, each representing less than 1% of the total cases. Cornea opacity and eye discharge are the least reported symptoms, each at 0.4%. 2 cases (0.7%) from our dataset had retinoblastoma diagnosed after presenting with cataracts which had undergone cataract removal surgery.

Based on the examination of 374 eyes from a total of 277 retinoblastoma patients using imaging techniques namely computed tomography (CT) and magnetic resonance imaging (MRI) to detect extraocular extensions, 12% (45 eyes) showed evidence of extraocular extensions (Table 3). MRI scans (18.3%, 23 eyes) were found to be more sensitive than CT scans (9.2%, 27 eyes) in detecting these extensions. The Optic Pathway exhibits the highest prevalence of extraocular extension, with 13 cases (3.5%) in the unilateral and 11 cases (2.9%) in the bilateral group. The Orbit/Adnexa and Intracranial regions have lower frequencies, while cases involving multiple regions are less common.

The distribution of International Intraocular Retinoblastoma Classification (IIRC) staging was

Table 2: Distribution of Initial Presenting Symptoms in Retinoblastoma Patients in Malaysia.

Presenting Symptom	Unilateral, n(%)	Bilateral, n(%)	Total, n(%)
Leukocoria only	116 (41.9)	65 (23.5)	181 (65.4)
Leukocoria & Strabismus	25 (9.0)	9 (3.2)	34 (12.3)
Strabismus only	7 (2.5)	5 (1.8)	12 (4.3)
Proptosis	10 (3.6)	1 (0.4)	11 (4.0)
Redness	7 (2.5)	4 (1.4)	11 (4.0)
Poor vision/Loss of vision	5 (1.8)	1 (0.4)	6 (2.2)
Hyphaema	4 (1.4)	0 (0.0)	4 (1.4)
Lid swelling	2 (0.7)	1 (0.4)	3 (1.1)
Tearing	1 (0.4)	1 (0.4)	2 (0.7)
Secondary glaucoma	0 (0.0)	2 (0.7)	2 (0.7)
Cellulitis	0 (0.0)	2 (0.7)	2 (0.7)
Nystagmus	0 (0.0)	2 (0.7)	2 (0.7)
Screening for RB	0 (0.0)	2 (0.7)	2 (0.7)
Incidental finding post cataract surgery	2 (0.7)	0 (0.0)	2 (0.7)
Incidental finding (unspecified)	0 (0.0)	1 (0.4)	1 (0.4)
Eye discharge	1 (0.4)	0 (0.0)	1 (0.4)
Cornea Opacity	0 (0.0)	1 (0.4)	1 (0.4)

Table 3: Incidence of Extraocular Extensions in Retinoblastoma Patients in Malaysia based on Imaging Findings.

Extraocular Extension	Unilateral , n(%)	Bilateral , n(%)
Optic Pathway	13 (3.5)	11 (2.9)
Orbit/Adnexa	5 (1.3)	1 (0.3)
Intracranial	0 (0.0)	0 (0.0)
Optic Pathway and Orbit/Adnexa	4 (1.1)	2 (0.5)
Optic Pathway and Intracranial	1 (0.3)	0 (0.0)
Orbit/Adnexa and Intracranial	1 (0.3)	1 (0.3)
Optic Pathway, Orbit Adnexa and Intracranial	4 (1.1)	0 (0.0)

Footnote: Imaging that were performed for the patients were either a CT scan or MRI scan or Both. In cases where both imaging modalities were utilized the results of the MRI scan was taken due to its superiority in detecting extraocular extension.

Table 4: Distribution of International Intraocular Retinoblastoma Classification (IIRC) Staging in Malaysian Retinoblastoma Patients.

IIRC Stage	Unilateral, n (%)	Bilateral Right Eye, n (%)	Bilateral Left Eye, n(%)	Total, n(%)
Group A	0 (0.00)	13 (3.5)	11 (2.9)	24 (6.4)
Group B	1 (0.3)	14 (3.7)	13 (3.5)	28 (7.5)
Group C	8 (2.1)	10 (2.7)	7 (1.9)	25 (6.7)
Group D	28 (7.5)	23 (6.2)	16 (4.3)	67 (17.9)
Group E	143 (38.2)	37 (9.9)	50 (13.4)	230 (61.5)

analyzed, as presented in Table 4. The findings revealed varying proportions across the different IIRC stages. Among the different stages, Group E is the most prevalent, accounting for 38.2% of unilateral cases and 23.3% of bilateral cases, contributing to an overall representation of 61.5% of the total cases. Group D also holds significance, representing 7.5% of unilateral cases, and 10.5% of bilateral left eye cases, summing up to 17.9% of the total cases.

An extensive analysis was conducted to investigate the potential associations between various variables and the risk of enucleation among our patients by evaluating a total of 374 eyes. Single and multiple logistic regression analysis (Table 5) were performed, focusing on factors such as age, gender, ethnicity, laterality of disease, presence of family history, IIRC staging, and the presence of extraocular extension on imaging. We determined that the rate of enucleation from our dataset based on the number of eyes treated was 68.4%.

The single logistic regression revealed that age exhibits a noteworthy pattern, with increasing odds ratios for enucleation in relation to age groups, ranging from 2.18 to 5.99 for ages 1-2 years through ≥ 5 years. Notably, unilateral cases show significantly higher odds of enucleation compared to bilateral cases, with an odds ratio of 15.16. A positive family history of retinoblastoma significantly reduces the odds of enucleation (odds ratio: 0.15). IIRC Staging Group E and the presence of extraocular extension on imaging both have substantial odds ratios for enucleation, at 147.13 and 4.19, respectively. Other factors like gender, ethnicity, and IIRC Group B exhibit less impactful associations.

The multivariable logistic regression analysis revealed that three variables, namely laterality, family history, and IIRC Group, were found to be statistically significant in the main effect model. Adjusting for other confounders, patients with unilateral eye involvement had odds of enucleation that were 10.48 times higher than patients with bilateral eye involvement. Patients with a family history had odds of enucleation that were 90% lower compared to patients without a family history. Furthermore, patients in IIRC group D had odds of enucleation that were 5.11 times higher, while patients in group E had odds of 69.99, both compared to patients in group A. No interactions or multicollinearity were observed among the variables. The classification table yielded an accuracy of 90.6%. Furthermore, the Hosmer and Lemeshow test demonstrated no significant deviation from the expected values, with a p-value of 0.716 (>0.05). The Nagelkerke R2 value for the logistic regression was 0.707, indicating a substantial explanatory power.

The multiple logistic regression analysis revealed that three variables, namely laterality, family

Table 5: Single and Multiple logistic regression analysis evaluating demographic, clinical and radiographic risk factors for enucleation

		Crude Odds Ratio	**95% CI**		**P value**	**Adjust-ed Odds Ratio**	**95% CI**		**P value**
			Upper Limit	Lower Limit			Upper Limit	Lower Limit	
Age	< than 1	Ref	-	-		Ref	-	-	
	1 – 2 years	2.18	1.23	3.85	0.007	0.86	0.35	2.10	0.735
	2 – 3 years	2.51	1.36	4.62	0.003	0.98	0.34	2.84	0.971
	3 – 4 years	5.27	2.17	12.81	<0.001	1.21	0.27	5.49	0.808
	4 – 5 years	5.68	1.21	26.58	0.027	0.28	0.03	2.46	0.250
	5 years and above	5.99	1.68	21.44	0.006	0.68	0.08	5.61	0.721
Sex	Male	Ref	-	-		Ref	-	-	
	Female	1.21	0.78	1.89	0.402	1.19	0.57	2.50	0.642
Ethinicity	Malay	Ref	-	-		Ref	-	-	
	Chinese	0.84	0.49	1.46	0.544	1.33	0.52	3.37	0.551
	Indian	0.82	0.36	1.88	0.641	0.64	0.17	2.51	0.524
	Others	2.06	1.01	4.22	0.048	1.44	0.45	4.56	0.540
Laterality	Unilateral	15.16	8.06	28.49	<0.001	10.48	4.26	25.81	<0.001
	Bilateral	Ref	-	-		Ref	-	-	
Family Histo-ry	No	Ref	-	-		Ref	-	-	
	Yes	0.15	0.05	0.50	0.002	0.10	0.01	0.75	0.026
IIRC Group-ing	A	Ref	-	-		Ref	-	-	
	B	0.00	0.00	-	0.998	0.00	0.00	-	0.998
	C	0.28	0.48	15.79	0.257	1.05	0.15	7.36	0.964
	D	12.03	2.62	55.28	0.001	5.11	1.03	25.29	0.046
	E	147.13	31.73	682.22	<0.001	69.99	14.17	345.75	<0.001
EOE on Im-aging	No	Ref	-	-		Ref	-	-	
	Yes	4.19	1.61	10.90	0.003	1.11	0.26	4.82	0.892

history, and IIRC Group, were found to be statistically significant in the main effect model. Adjusting for other confounders, patients with unilateral eye involvement had odds of enucleation that were 10.48 times higher than patients with bilateral eye involvement. Patients with a family history had odds of enucleation that were 90% lower compared to patients without a family history. Furthermore, patients in IIRC group D had odds of enucleation that were 5.11 times higher, while patients in group E had odds of 69.99, both compared to patients in group A.

DISCUSSION

Our investigation demonstrated the median age of retinoblastoma presentation to be 16 months, with specific findings of 16 months for unilateral cases and 15 months for bilateral cases. This, however, contradicts an earlier Malaysian study by Subramaniam et al (2014), reporting a median presentation age of 22 months from 2004-2012 suggesting a possibility of improved detection rates and patient awareness in the country [4]. Asian research indicates a median presentation age of 29-34 months, with unilateral and bilateral cases at 34-36 months and 18-30 months respectively [15]. Global analyses on the other hand indicate a median age of 23.5 months, further specified as 14.1 months in high-income countries and 30.5 months in low-income countries [16]. Our findings align with these global trends, reflecting Malaysia's ongoing development towards a high-income nation. Malaysia's progress towards becoming a developed country has contributed to improvements in addressing the higher median age of retinoblastoma presentation. Efforts to overcome socioeconomic

challenges such as delayed diagnosis, limited healthcare access, lack of awareness about retinoblastoma, and inadequate infrastructure have been made. However, additional steps are needed to enhance screening programs, expand training for healthcare professionals, establish more specialized treatment centres, improve accessibility and financial support, address cultural factors, ensure proper counselling and support, and strengthen government and NGO involvement. By addressing these areas, Malaysia can further advance in the early detection and treatment of retinoblastoma, benefiting patients across the country.

In relation to the laterality of retinoblastoma, our study found that approximately two-thirds of patients exhibited unilateral retinoblastoma, and the remaining one-third displayed bilateral disease. The proportions were specifically 65.0% and 35.0% for unilateral and bilateral cases respectively, corroborating a large study by Zain et al over 41 years involving 1925 retinoblastoma cases [17]. This distribution was also mirrored in an Asian study by Sahu et al [18]. Our gender distribution findings suggest almost equal occurrence between males (55.6%) and females (44.4%), with a ratio of roughly 1.25:1. Fabian et al's large-scale study align with our results, suggesting no gender predilection in retinoblastoma across 4351 cases from 153 countries [19]. The distribution of retinoblastoma cases amongst the primary ethnic groups in Malaysia likely mirrors the nation's general population demographics, with Malays representing the majority of cases (57.0%), followed by the Chinese and Indian ethnic groups with 19.1% and 7.2% of cases respectively [20].

When examining the symptomatic presentation of retinoblastoma, our study found that leukocoria alone was the most prevalent initial symptom, reported in 65.4% of patients. This was followed by the dual occurrence of leukocoria and strabismus in 12.3% of cases, with strabismus presenting alone in 4.3% of patients. Symptoms characteristic of advanced stages of retinoblastoma, such as proptosis, secondary glaucoma, and cellulitis, were observed within a range of 0.4% to 4.0%, with proptosis being the next most common symptom after leukocoria and strabismus. These findings resonate with the global symptom presentation pattern for retinoblastoma as described by Prat et al [3].

Of note, we detected two cases (0.7%) where patients presented with a cataract. The tumor was only identified post-cataract surgery during fundus examination. Both patients were diagnosed with Group E unilateral retinoblastoma. This observation could be explained by the tumor's physical interaction with the natural crystalline lens or by the upregulation of the TGF-B growth factor by the tumor, leading to cataract development [21]. Considering that the standard use of ultrasound B-scan in the assessment of the posterior segment of patients with cataract that limit the view of the fundus, it is highly unlike that a sizeable mass would have been missed and it is possible that in these two isolated cases, the retinoblastoma may be of an infiltrative type which tends to grow horizontally along the retina instead of vertically and tumour cells inducing the cataractous changes seen [22].

Furthermore, our study documented only 2 cases (0.7%) of retinoblastoma which were picked up during screening. This could potentially be attributed to the absence of a comprehensive national screening program. Despite this, it is standard procedure in Malaysia to request other children in the family to undergo screening when a patient is diagnosed with retinoblastoma, especially when indications of a germline mutation are present.

The rate of enucleation in our study based on number of eyes treated was shown to be 68.4%. On performing a single logistic regression analysis, our results indicated that age, ethnicity, laterality, family history, IIRC grouping, and the presence of extraocular extensions on imaging were significant risk factors contributing to enucleation. However, multiple logistic regression analysis revealed only unilateral cases (OR: 10.48) and an advanced IIRC group (OR: 5.11 in group D and OR: 69.99 in group E) as significant predictors of enucleation. Surprisingly, the presence of a family history of retinoblastoma (OR: 0.10) seemed to inversely correlate with the likelihood of a patient undergoing enucleation.

The elevated risk of enucleation associated with unilateral cases could be due to a delayed diagnosis, as these cases might present fewer noticeable symptoms compared to bilateral cases. This could lead to larger tumor size and more advanced disease at the time of presentation, thereby limiting treatment options. A report by Rodriguez-Galindo et al (2007) states that enucleation alone, barring extraocular disease, is curative in 85-90% of children with unilateral retinoblastoma [23]. They suggest that enucleation is indicated for all Group E eyes and that laterality may strongly influence the decision to perform enucleation in Group D eyes. Similarly, Shields et al (2002) recommend considering enucleation in unilateral cases with Reese-Elsworth groups 4 and 5 [24]. Moreover, a study by Lu et al (2019) demonstrates that unilateral cases have a 3.9% chance of metastasis within a year of enucleation, yet this still results in a low rate of metastatic death in patients [25].

In Malaysia, cultural stigma plays a significant role in various aspects of life, including the medical field, due to its multiracial nature and emphasis on traditions and religion. As a result, cases of retinoblastoma sometimes present late as parents initially opt for traditional treatments or are hesitant to consider enucleation or chemotherapy for their children, choosing instead traditional or alternative medicine. Such decisions lead to delays in effective management, potentially exacerbating the condition and having fatal consequences for the child. The Child Act 2001 (611) is in place to protect children in the country, requiring doctors to intervene and

provide care if a child needs treatment or if parents refuse necessary medical intervention [26]. However, enforcement of this act is hampered by cultural and religious considerations, leading to a lack of action. Strengthening the enforcement of existing laws and empowering healthcare providers to act decisively may help address this issue.

It's important to note that the rate of enucleation in advanced unilateral retinoblastoma has been decreasing, particularly with the introduction of systemic and targeted chemotherapy methods, such as intraarterial chemotherapy. However, this approach may not always achieve the desired outcome and enucleation still has its role in certain cases, especially in those with persistent vitreous seeding caused by poor vitreous penetration, an inactive state of tumor seeds within the avascular vitreous cavity, and resistance to chemotherapy drugs [27]. While pre-enucleation chemotherapy can be used to shrink the tumor, Zhao et al found no significant survival difference in children receiving 1-3 cycles, and a worsened survival rate in those receiving 4 or more cycles [28]. Furthermore, they observed a higher incidence of high-risk histopathology and decreased survival in children with Group E retinoblastoma who underwent pre-enucleation chemotherapy compared to those who underwent primary enucleation.

Similarly, patients with a negative family history could be diagnosed later than those with a positive family history, likely because they are more prone to sporadic mutations and tend to present with a more advanced tumor. Jagadeesan et al explain that sporadic retinoblastoma, which accounts for 65-75% of cases, typically results in late-onset, unilateral, and unifocal tumors [29]. Draper et al further elucidate that among children who possess a mutation but have no family history of the disease, 30% develop bilateral disease and 60% develop unilateral retinoblastoma [30]. These findings support that patients with a negative family history may be more likely to develop unilateral tumors, which can present later and at a more advanced stage compared to bilateral cases. Recognizing these key risk factors associated with increased enucleation risk could enable medical professionals to tailor approaches better. This knowledge can also assist in patient counselling, enabling parents to better understand potential findings and accept proposed treatment plans.

Our study has several strengths that underscore the value of its findings. The large sample size used in this research enhances the power and reliability of the results, allowing for a more accurate and detailed analysis of the retinoblastoma cases in Malaysia. The study's utilization of multiple logistic regression analysis offers a more controlled insight into potential confounding factors, therefore adding strength to the validity of the results. The study's continuous comparisons to previous research allow for a broader context and validation of the findings, increasing its value and implications for the field.

This study, while robust in its findings, does have certain limitations that must be acknowledged. There could be an inherent selection bias present as the data is taken from a specific geographical area. This could potentially limit the generalizability of the results to the wider global population. In addition, the retrospective nature of this study may have introduced inaccuracies related to historical data and potential missing information. For instance, a retrospective study may not have complete data for all variables of interest, such as socio-economic status, genetic factors or access to healthcare, which could act as confounding factors influencing the disease presentation and outcome. We should also acknowledge that human error may contribute to discrepancies in data during data entry which could ultimately affect the overall outcome of the study. It is important that future research considers these variables in the data collection and analysis to control these potential confounders.

CONCLUSION

This study provides valuable insights into retinoblastoma's epidemiology and clinical features, emphasizing enucleation risk factors. The study revealed a median presentation age of 16 months, mostly unilateral cases with no gender bias, and an ethnic distribution reflecting national demographics. Leukocoria was the common initial symptom, highlighting the need for early detection. Unilateral cases and advanced IIRC groups were linked to higher enucleation risk, while a family history of retinoblastoma appeared protective. The study recorded a 68.4% enucleation rate. These findings may help aid clinicians in early identification and treatment decisions, benefiting parent counselling. The results stress the importance of early detection, interventions, and improved strategies, particularly for unilateral cases and advanced IIRC groups.

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