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Original Article

Clinical characteristics, management, and survival of retinoblastoma patients: a five-year study at an Indonesian tertiary eye hospital

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Abstract

Background Studies on the clinical characteristics of retinoblastoma in Indonesia have been limited, even though retinoblastoma is the most common pediatric ocular malignancy worldwide and the second-most common pediatric malignancy in Indonesia. The estimated patient survival rate in lower-middle-income countries is 77%, and survival is highly dependent on early diagnosis and therapy.

Objective To identify the clinical characteristics of retinoblastoma in patients at the Cicendo National Eye Hospital, as an Indonesian tertiary eye hospital.

Methods This retrospective, observational study included pediatric patients ≤18 years of age diagnosed with retinoblastoma at the Cicendo National Eye Hospital, Bandung, West Java, between January 2018 and December 2022. We collected patients' medical record data on age, gender, laterality, chief complaints, stage of disease, grouping, histopathologic features, therapy, and survival.

Results Of 247 retinoblastoma patients (328 eyes) enrolled, 53.85% presented at 1-2 years of age and 50.61% were males. Patients mostly presented with unilateral (67.21%) retinoblastoma, leukocoria (51.82%) as the chief complaint, and classified as International Retinoblastoma Staging System (IRSS) stage III (33.20%). Tumors were mostly intraocular (58.84%), particularly group E (39.02%). Most tumors showed undifferentiated (45.43%) and high-risk features (54.27%). Most eyes were treated with combination therapy (74.09%), particularly local and systemic therapy (59.45%). Survival was noted at 18.62% of patients, but 62.75% of patients were lost to follow-up.

Conclusion Most patients present with advanced retinoblastoma. Most histopathological results show undifferentiated and high-risk features of the tumor. Delays in diagnosis and therapy may occur due to a lack of awareness and knowledge regarding clinical manifestations of retinoblastoma, which leads to worse prognosis.

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Keywords: *retinoblastoma; pediatric; clinical characteristics; management; survival*

Retinoblastoma is a rare pediatric cancer, yet it is the most common pediatric ocular malignancy worldwide and the second most common pediatric malignancy in Indonesia after leukemia.[1,2] Patients may present with manifestations of leukocoria, strabismus, decreased vision, red eye, phthisis bulbi, and/or proptosis.[3] Management of retinoblastoma is conducted based on the grouping and staging classification of the tumor.[4] Histopathological examination is also conducted to determine the administration of adjuvant chemotherapy after enucleation.[5] Prognosis is highly dependent on early diagnosis and therapy, which is influenced by awareness and knowledge of the community and healthcare workers regarding the clinical manifestations of retinoblastoma.[6] As a lower-middle-income country, the estimated survival of retinoblastoma patients in Indonesia is 77%.[6,7]

Previous studies regarding the characteristics of retinoblastoma in Indonesia were mainly focused on patients younger than 5 years and often did not review the staging of tumors. Histopathological features commonly studied were the high-risk features or only relating to the invasion of the optic nerve.

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Cicendo National Eye Hospital, Bandung, West Java, is a national eye center in Indonesia that treats many ocular cases. However, the most recent study regarding retinoblastoma patients at Cicendo National Eye Hospital was conducted in 2017. Hence, we aimed to identify the clinical characteristics, management, and survival of retinoblastoma patients at the Cicendo National Eye Hospital, in Indonesia.

Methods

This retrospective, observational, and cross-sectional study included pediatric patients aged <18 years diagnosed with retinoblastoma at the Cicendo National Eye Hospital, Bandung, West Java, who visited from January 2018 to December 2022. The total sampling method was selected to collect medical records of patients with the *International Classification of Diseases* (ICD)-10 code C69.2. The exclusion criteria were inaccessible or incomplete medical records due to a lack of chief complaint, grouping, and staging.

The variables reviewed in this study, included age, gender, laterality, chief complaint, staging, grouping, histopathological features, treatment, and survival rate. The age of patients was determined from the date of birth until diagnosis and was categorized according to the age classification by the *World Health Organization* (WHO) and the *Centers for Disease Control and Prevention* (CDC).[8,9] The laterality was determined from the location of the tumor, and was categorized as unilateral or bilateral. The chief complaint was defined as the clinical manifestations that urged patients to seek hospital examinations.

The staging classification used in this study was based on the *International Retinoblastoma Staging System* (IRSS), which classified patients as stage 0 (intraocular tumor), stage I (patient underwent enucleation with completed resection), stage II (patient underwent enucleation with microscopic tumor residue), stage III (regional tumor extension), or stage IV (metastasis).[10] The grouping classification was based on the *International Classification of Retinoblastoma* (ICRB) by Murphree. ICRB classified intraocular tumors as group A (small tumor with diameter <3 millimeters), group B (bigger tumor), group C (contiguous seeding), group D (diffuse seeding), or group E (extensive tumor).[5] Tumors in this study were classified after extensive examination and procedures needed for staging and grouping were conducted.

Histopathological characteristics may be observed in patients after the enucleation procedure to observe the differentiation of tumors and the presence of high-risk features.[11] Tumor differentiation in this study was classified per eye into differentiated (presence of Flexner-Wintersteiner rosettes), undifferentiated, and data not available.[12] High-risk features were determined from the invasion of tumor in the choroid (massive or more than 3 millimeters in diameter), post-laminar optic nerve, anterior chamber, iris, ciliary body, sclera, extrasclera, and/or combination of any thickness of choroid as well as any level of the optic nerve.[11] High-risk features in this study were classified per eye as present, absent, or data unavailable.

Treatment in this study was classified per eye as focal therapy, local therapy, systemic intravenous chemotherapy (IVC), combination therapy, or not receiving therapy. Focal therapy was specified as transpupillary thermotherapy (TTT) or cryotherapy. Local therapy was specified as enucleation or external beam radiotherapy (EBRT). Combination therapy was specified as local and systemic therapy, focal or systemic therapy, as well as focal, local, or systemic therapy.[5,13] Not receiving therapy in this study meant patients might have refused treatment procedures, received treatment procedures at another hospital, or were lost to follow-up. The survival of a patient was determined from the date of diagnosis until this study was conducted.[14] Survival was classified as alive, currently in observation, currently in therapy, dead, or lost to follow-up. Living patients were specified as alive at 1 year and 3 years. The observation category was defined as the living patient who had completed therapy, yet was still less than a year from the date of diagnosis. All the data were collected and analyzed using *Microsoft® Excel 2022* and subsequently presented in tables using values of frequency (n) and percentages (%).

Results

As shown in **Figure 1**, a total of 247 patients, specifically, 328 eyes, met the inclusion criteria. **Table 1**

shows that the most common subject age group was 1-2 years (133; 53.85%), followed by <1 year (54; 21.86%). There were 125 (50.61%) males and 122 (49.39%) females.

There were 166 (67.21%) patients with unilateral retinoblastoma and 81 (32.79%) bilateral patients. The most common chief complaint was leukocoria (128; 51.82%), followed by proptosis (48; 19.43%). The most common disease stage was in stage III (82; 33.20%), followed by stage I (74; 29.96%) (**Table 2**).

As shown in **Table 3**, there were 193 (58.84%) eyes with intraocular tumors and 135 (41.16%) eyes with extraocular tumors. The most common intraocular tumor grouping was group E (128 eyes; 39.02%). There were 149 (45.43%) eyes with undifferentiated tumors and 46 (14.02%) eyes with differentiated tumors. High-risk features were present in 178 (54.27%) eyes and absent in 32 (9.76%) eyes. Combination therapy was the most preferred therapy (243 eyes; 74.09%), especially local and systemic therapy (195 eyes; 59.45%).

Forty-six (18.62%) patients were confirmed alive and 22 (8.91%) patients were confirmed to have died by the time our study was conducted (**Table 4**). Thirty patients survived for a year and 16 patients survived for three years. However, 155 (62.75%) patients were lost to follow-up.

Discussion

Most retinoblastoma patients in our study were diagnosed at 1-2 years of age at presentation (53.85%). Most patients in the United States are diagnosed before they even reach 1 year of age (42.7%).[15] While 90% of patients are usually diagnosed during the first five years of life, one of patients in our study was diagnosed with retinoblastoma at 10-year-old.[10] We also had four patients diagnosed at 6-year-old, two patients diagnosed at 7-year-old, one patient diagnosed at 8-year-old, and one patient diagnosed at 9-year-old. This age distribution illustrates that delays in diagnosing retinoblastoma are still common

Table 1. Subjects' demographics

Characteristics	(N=247)
Age, n (%)	
<1 year	54 (21.86)
1-2 years	133 (53.85)
3-5 years	51 (20.65)
6-11 years	9 (3.64)
12-14 years	0
15-18 years	0
Gender, n (%)	
Male	125 (50.61)
Female	122 (49.39)

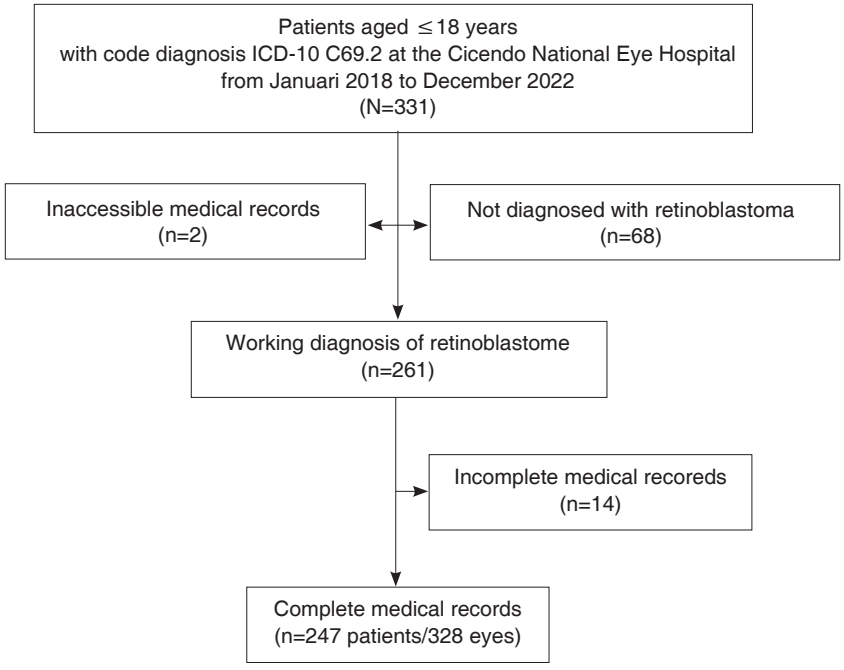

Figure 1. Flow diagram of this study

Table 2. Subjects' clinical characteristics

Characteristics	(N=247)
Laterality, n (%)	
Unilateral	166 (67.21)
Bilateral	81 (32.79)
Chief complaint, n (%)	
Leukocoria	128 (51.82)
Proptosis	48 (19.43)
Red eye	46 (18.62)
Decrease in vision	13 (5.26)
Strabismus	4 (1.62)
Phthisis bulbi	2 (0.81)
Other	6 (2.43)
Stage (IRSS), n (%)	
Stage 0	5 (2.02)
Stage I	74 (29.96)
Stage II	36 (14.57)
Stage III	82 (33.20)
Stage IV	50 (20.24)

IRSS=*International Retinoblastoma Staging System*

Table 3. Clinical characteristics of subjects' eyes

Characteristics	(N=328)
Group (ICRB), n(%)	
Intraocular	193 (58.84)
Group A	6 (1.83)
Group B	11 (3.35)
Group C	18 (5.49)
Group D	30 (9.15)
Group E	128 (39.02)
Extraocular	135 (41.16)
Histopathological features, n (%)	
Tumor differentiation	
Undifferentiated	149 (45.43)
Differentiated	46 (14.02)
Data unavailable	133 (40.55)
High-risk features	
Present	178 (54.27)
Absent	32 (9.76)
Data unavailable	118 (35.98)
Therapy, n(%)	
Focal therapy	1 (0.30)
TTT	1 (0.30)
Cryotherapy	0
Local therapy	18 (5.49)
Enucleation	18 (5.49)
EBRT	0
Systemic IVC	34 (10.37)
Combination therapy	243 (74.09)
Local and systemic therapy	195 (59.45)
Focal and systemic therapy	38 (11.59)
Focal, local, and systemic therapy	10 (3.05)
Did not receive therapy	32 (9.76)

ICRB=*International Classification for Retinoblastoma;* TTT=transpupillary thermotherapy; EBRT=external beam radiotherapy; IVC=intravenous chemotherapy

Table 4. Survival of retinoblastoma patients

Survival parameter	(N=247)
Alive	46 (18.62)
1 year	30 (12.15)
3 years	16 (6.48)
Currently on observation	5 (2.02)
Currently on therapy	19 (7.69)
Died	22 (8.91)
Lost to follow up	155 (62.75)

in Indonesia. These delays may occur because of the lack of awareness or knowledge of parents or healthcare workers regarding clinical manifestations of retinoblastoma, which result in delays in seeking medical help or referral to a specialist.[6] The gender of retinoblastoma patients in our study was about the same (50.61% males and 49.39% females). Although no sex predilection in retinoblastoma was shown by a previous study, gender discrimination in access to health services in some Asian countries may contribute to a high male-to-female ratio.[16]

Unilateral tumors were noted in 67.21% of patients. Similarly, the *Global Retinoblastoma Study Group* showed that most countries reported that 69.2% of retinoblastoma cases were unilateral.[11,17] The most common chief complaints were leukocoria (51.82%), proptosis (19.43%) and red eye (18.62%). Only 1.62% of patients presented with strabismus as a chief complaint. A review reported leukocoria (61-83%) and proptosis (2.8-17%) as the most common presenting manifestations reported from studies in India.[7,18-20] Even though leukocoria is the most common manifestation reported, it is considered to be a late sign, because it is less visible at first.[21] A 9-year-old patient in our study reported phthisis bulbi at the first presentation, which indicated an advanced clinical manifestation of retinoblastoma.[2,3] The timing of these manifestations suggest that lack of awareness and knowledge regarding early clinical manifestations of retinoblastoma in middle-income countries may result in the late diagnosis of retinoblastoma.[6]

Extensive examinations to assess staging in retinoblastoma patients were conducted by orbital and regional lymph node examination, complete blood count, chest X-ray, abdominal ultrasonography, brain magnetic resonance imaging (MRI), lumbar puncture, bone marrow biopsy, and cerebrospinal fluid

cytology.[7,22] However, the bone marrow and lumbar puncture for staging examination started in 2019 after the only pediatric oncologist at Cicendo National Eye Hospital attained her academic subspecialty degree. Hence, patients admitted before 2019 were under a potential bias, since staging was established based on only the clinical or histopathology examination after the enucleation procedure. Therefore, the most common stage of disease in our study was stage III (33.20%), followed by stage I (29.96%). These results differed from the *Global Retinoblastoma Study Group* which reported stage I as the most common in low-income (33.8%) and lower-middle-income countries (43.0%). The study also reported stage 0 as the most common in upper-middle income (48.8%) and high-income countries (56.8%).[17]

The most common ICRB grouping in our study was intraocular (58.84%), mainly in group E (39.02%). Other studies from India and Taiwan also reported group E in 61.2% and 68.8% of eyes, respectively.[23,24] Group E eyes are mostly considered unsalvageable and associated with high-risk features.[4,25] However, a study in Turkey reported group B in 32.5% of eyes, group E in 27.6% of eyes, and group D in 25.6% of eyes.[26] Nevertheless, the grouping reported in this study may have had a potential bias for misclassification since the bone marrow and lumbar puncture exams were not performed in patients admitted before 2019.

The most common therapy used in our study was the combination of local and systemic therapy (59.45%), primarily enucleation and IVC. Similarly, another study in Indonesia reported the combination of enucleation and chemotherapy in 75% of patients' therapy.[6] However, a study in Poland reported a combination of focal and systemic therapy in 76.76% of patients, as the most preferred therapy.[27] In addition a study reported a shifting of treatment preferences from EBRT to IVC, intraarterial chemotherapy, and intravitreal chemotherapy in Taiwan.[23] The shift occurred because of the risk of developing a secondary malignancy through radiation therapy, as well as the availability of more advanced treatment modalities. Also, patients who received intraarterial chemotherapy reported a better globe salvage rate than patients who did not receive it.[28]

Those are probably plausible explanations of the decline in the use of EBRT or enucleation in other countries. While low and middle-income countries are still concentrated on saving patients' lives in managing retinoblastoma, high-income countries have already focused on preserving organ and visual function.6 In our study, one patient was referred to receive intraarterial and intravitreal chemotherapy in Singapore, due to the unavailability of those treatment modalities at the Cicendo National Eye Hospital. This patient was still receiving TTT for the left eye by the time our study was conducted.

As many as 32 eyes (9.76%), or 21 subjects, did not receive any standard medical therapy for retinoblastoma at the Cicendo National Eye Hospital. Five patients initially agreed to follow the standard therapy. Nevertheless, one patient wanted to receive medical interventions back in their hometown, two patients already received their chemotherapy schedule but were later lost to follow-up, and two patients needed to postpone their surgical interventions due to health reasons but were later lost to follow-up. Furthermore, one patient refused treatment due to not having health insurance to cover the examination fees, and a patient refused treatment due to the long distance to the hospital and financial constraints. Moreover, four patients explicitly refused the treatment procedure and five patients were lost to follow-up after being informed of the treatment plan. Similarly, a previous study reported treatment refusal in 10 patients and treatment abandonment in 34 patients.[29] Many factors may affect the refusal of treatment, including lack of knowledge and awareness regarding retinoblastoma, poor access to health care, financial constraints, and aesthetic concerns regarding the outcome of surgery, as indicated by the treatment abandonment rate of 30-40% in low and middle-income countries, but only 1% in upper-middle-income countries.[6]

Cicendo National Eye Hospital regularly follows up families of retinoblastoma patients. However, most patients (62.75%) in our study could not be contacted by the hospital. Aside from that, there were 46 patients (18.62%) who completed therapy and survived for less than a year (2.02%), a year (12.15%), and three years (6.48%) after the diagnosis of retinoblastoma. Death was confirmed in 22 patients (8.91%) in this study. Due to the large number of lost follow-up patients, it is difficult to analyze the survival of retinoblastoma subjects. In contrast, a study on 61 retinoblastoma patients in Singapore, 57 patients were alive and 4

patients died by the last follow-up.[7] A previous study reported estimated survival of one year in 45% of patients, two years in 30% of patients, three years in 28% of patients, and more than three years in 25% of patients.[29]

In our study, of 328 eyes, 40.55% lacked data on tumor differentiation and 35.98% lacked data on high-risk features, as the data were unavailable from patient medical records. Since the anatomical pathology laboratory at the Cicendo National Eye Hospital was first established in March 2017, patients who underwent enucleation procedures before March 2017 did not receive histopathology examinations in our center. Hence, histopathological examination data were incomplete or inaccessible because they were conducted in other hospitals. Also, some eyes received adjuvant IVC before the enucleation procedure, which would potentially bias the high-risk features characteristics.

Patient visits before late 2020 at Cicendo National Eye Hospital were still recorded using paper-based medical records. Considering the limited research time, some paper-based medical records could not be accessed by the authors. Also, we focused on patients who visited the Cicendo National Eye Hospital from January 2018 to December 2022. Due to the small sample size of those not lost to follow up, it was difficult to analyze the standard five-year survival rate.

To summarize, patients observed in this study mostly presented with leukocoria at 1-2 years of age. There were a high number of group E intraocular and extraocular eye presentations, stage III patients, as well as those with undifferentiated and high-risk histopathological tumor features. Those were evidence of advanced disease, indicating that delays in diagnosing and treating retinoblastoma still occur in Indonesia. Most patients were treated with a combination of local and systemic therapy. Patient survival could not be concluded from this study due to the large number of lost to follow-up patients. The patients' demographic and clinical characteristics reported in this study may represent epidemiological data of retinoblastoma patients in Indonesia, since the Cicendo Eye Hospital is a national eye center that receives nationwide referrals for retinoblastoma cases.

Conflict of interest

None declared.

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