



The risk factor of metastatic status of retinoblastoma patient in Yogyakarta Tertiary Hospital

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ABSTRACT

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The metastases of the tumor become a serious problem malignancy including retinoblastoma. This study aimed to observe the correlation between several risk factors with the metastatic status of retinoblastoma patients in Yogyakarta Tertiary Hospital. Records of patients with retinoblastoma treated between 2011 and 2017 were obtained for observational analytic study. The gender, laterality, age, Body Mass Index (BMI) classification, BMI for age, type of retinoblastoma, and metastatic status were analyzed. The association was statistically analyzed by the correlation ratio of Eta test. Thirty-seven cases of retinoblastoma were enrolled in this study, with mean age 29.44 (± 14.1) months; 14 females and 23 males. Ten patients (27.0%) have no metastases, while 27 patients (72.9%) exhibit metastases. The multivariate logistic regression analysis demonstrated that male gender (OR 8.3; 95% CI 1.07–64.5; $p = 0.04$) and age below 24 months (OR 17.6; 95% CI 1.26–248.31; $p = 0.03$) were a predictive of the metastatic status for retinoblastoma. On the other hand, the laterality, BMI classification, BMI for age, and types of retinoblastoma were not associated with the metastatic status of retinoblastoma. The gender and age were significantly associated with the metastatic status of retinoblastoma. Male patients and age below 24 months were more likely to have metastatic disease of retinoblastoma.

ABSTRAK

Metastasis tumor menjadi masalah serius termasuk retinoblastoma. Penelitian ini bertujuan untuk mengamati hubungan antara beberapa faktor risiko dengan status metastasis pasien retinoblastoma di Rumah Sakit Tersier Yogyakarta. Catatan pasien dengan retinoblastoma yang dirawat antara 2011 dan 2017 diperoleh untuk studi analitik observasional. Jenis kelamin, lateralitas, usia, klasifikasi Indeks Massa Tubuh (IMT), IMT untuk usia, jenis retinoblastoma, dan status metastasis dianalisis. Hubungan tersebut dianalisis secara statistik dengan rasio korelasi uji Eta. Tiga puluh tujuh kasus retinoblastoma terdaftar dalam penelitian ini, dengan usia rata-rata 29,44 ($\pm 14,1$) bulan; 14 wanita dan 23 pria. Sepuluh pasien (27,0%) tidak memiliki metastasis, sementara 27 pasien (72,9%) menunjukkan metastasis. Analisis regresi logistik multivariat menunjukkan bahwa jenis kelamin laki-laki (OR 8,3; 95% CI 1,07-64,5; $p = 0,04$) dan usia di bawah 24 bulan (OR 17,6; 95% CI 1,26-248,31; $p = 0,03$) merupakan prediksi metastasis status untuk retinoblastoma. Di sisi lain, lateralitas, klasifikasi BMI, BMI untuk usia, dan jenis retinoblastoma tidak terkait dengan status metastasis retinoblastoma. Jenis kelamin dan usia secara signifikan terkait dengan status metastasis retinoblastoma. Pasien pria dan usia di bawah 24 bulan lebih cenderung memiliki penyakit metastasis retinoblastoma.

Keywords:

retinoblastoma
sex
body mass index
familial
metastatic status

INTRODUCTION

Retinoblastoma is one of Mendelian disorders in ophthalmology that transmitted by autosomal dominant mode of inheritance.¹ Retinoblastoma has been reported in many studies as the most common primary intraocular cancer in children.²⁻⁴ Epidemiologic studies have shown that, retinoblastoma approximately affects 1 in 16.000 to 18.000 births. While the incidence of retinoblastoma has been reported around 7000 to 8000 new cases annually worldwide.⁵ Among Asia-Pacific countries, Indonesia was included as the country that account for 90% of retinoblastomas in the Asia-Pacific area.⁶ The 2013 data estimates that 43% (3452) of the global burden of retinoblastoma lives in Asia-Pacific region, and 8% (277) of those children were lived in Indonesia.⁷ Accurate diagnosis for retinoblastoma can be accomplished by a detailed history, physical and ocular examination, slit lamp examination, and indirect ophthalmoscopy.⁸ Recently, ultrasonography showed an excellent agreement compared with histopathological examination as a gold standard examination for retinoblastoma.⁹

A several previous studies have shown that there was no sex predisposition have been noted for retinoblastoma.¹⁰⁻¹² However, a male predominance has been reported by a number of studies in India.¹³⁻¹⁵ Metastatic status of malignancy increases the tumor burden and catabolism of endogenous substrate reserves becomes more profound. Thus, resulting in increasing weight loss and compromise of organ function which leading to malnutrition and cachexia on systemic level.^{16, 17} Malnutrition is an underrecognized potential complication of cancer in children and it has been associated with complications, reduced physical functioning and decreased survival on

cancer patients.^{18,19} Concordantly, several studies showed that body mass index (BMI) has been reported to plays an important role in metastatic malignancy, although the molecular mechanism was not fully elucidated.²⁰⁻²² One recent study has been postulated a theory, BMI may impacts cancer metastatic status with the mechanism that involve lipogenesis and lipid transport, enhanced vascularity, and decreased infiltration of macrophages.²³ The laterality was correlated with the type of retinoblastoma and the age of presentation. The unilateral cases predominantly found in previous studies and its reported to be presently late when compared to bilateral cases.^{7,13-15}

An understanding whether metastatic status of children with retinoblastoma and its correlation with several factors mentioned above, is a valuable part of managing retinoblastoma patients. The aim of current study was to evaluate a correlation between metastatic state and several risk factors in the retinoblastoma patients.

MATERIALS AND METHODS

Patients and data collection

This was analytical observational study with cross-sectional design that enrolled retinoblastoma patients treated at Dr. Sardjito General Hospital between 2011 until 2017. The inclusion criteria for the study subject including: no previous cancer diagnosis, body mass index was determined on first patient visit, metastatic status was determined on first month of patient visit. Cases were identified from the medical records and body weight, height, age, disease classification (international retinoblastoma staging system), metastatic status, stage of retinoblastoma, laterality, symptom at presentation, as well as metastatic status were obtained. All the patients already underwent a surgical removal of the tumor and diagnosed based on

pathological examination. We found 41 cases with retinoblastoma. Four cases (9.76%) were excluded from analysis because insufficient data to confirm metastatic status and to calculate body mass index at the point of first visit.

Statistical analysis

The pooled data were analyzed using SPSS 23 for Windows. Patients characteristics were presented as frequencies, mean \pm standard deviation (SD). Differences between metastatic and no metastatic group characteristics were analyzed using the Chi-square test. Univariate and multivariate logistic regression analyses were performed with metastatic status as a dependent variable to evaluate the association between related variables and its odds ratio.

RESULTS

The patient's characteristic was shown in TABLE 1. Thirty-seven cases of retinoblastoma were enrolled in this study, with mean age 29.44 ± 14.1 months and consist of 14 females and 23 males. The mean of BMI in this study was 16.02 ± 3.52 . We also found that the mean of gestational age at birth was 38.02 ± 1.89 . The main symptom at the presentation was leukocoria (94.6%), while proptosis, hyperemic conjunctiva and chemosis conjunctiva occurred in at least half of the subjects enrolled in this study. We also found that most of the tumor had invaded the sclera (70.3%). The invasion to the lymph node (10.8%) and optic nerve (48.6%) were also found in less

than half of the retinoblastoma patients (TABLE 1).

TABLE 1. Patients' characteristics.

Characteristic	Mean \pm SD
Age (months)	29.44 \pm 14.1
BMI	16.02 \pm 3.52
Gestational age (weeks)	38.02 \pm 1.89
Characteristic	Frequency (%)
Symptoms	
• Leukocoria	35 (94.6)
• Proptosis	22 (59.5)
• Hyperemic conjunctiva	21 (56.8)
• Chemosis conjunctiva	19 (51.4)
Invasion	
• Optic nerve	18 (48.6)
• Sclera	26 (70.3)
• Lymph nodes	4 (10.8)
Staging	
• II	10 (27.0)
• III	13 (35.1)
• IV	14 (37.8)

TABLE 2 has revealed the clinical characteristic of the patient in our study. Ten (27.1%) patients were found to have no metastases, while 27 (72.9%) patients exhibit metastases (TABLE 2). In general, the metastatic group showed similar parameter in terms of laterality, age group, BMI classification, BMI for age (WHO) and retinoblastoma type. In the other hand, male patients showed a tendency to had metastatic diseases. In the metastatic group the males have a proportion of 74.1%, while in non-metastatic group only 30%.

TABLE 2. Patients' clinical case mix characteristics

Characteristic	Total	Metastatic (%) n = 27	Non-metastatic (%) n=10	p	OR (95% CI)
Gender					
• Female	14	7 (25.9)	7 (70)	0.023	6.66 (1.34-33.1)
• Male	23	20 (74.1)	3 (30)		
Laterality					
• Unilateral	32	22 (81.5)	10 (100)	0.295	1.45* (1.15-1.84)
• Bilateral	5	5 (18.5)	0 (0)		
Age Group					
• Less than 24 months	16	9 (33.3)	7 (70)	0.067	4.66 (0.96-22.4)
• More than 24 months	21	18 (66.7)	3 (30)		
BMI Classification**					
• Underweight	31	23 (85.2)	8 (80)	0.653	0.69 (0.11-4.56)
• Normal - obese	6	4 (14.8)	2 (20)		
BMI for Age (WHO)					
• Severely wasted	3	2 (7.4)	1 (10)	0.445	
• Wasted	4	4 (14.8)	0 (0)		
• Normal	22	16 (59.3)	6 (60)		
• Overweight	5	3 (11.1)	2 (20)		
• Obese	3	2 (7.4)	1 (10)		
• Obese	3	2 (7.4)	1 (10)		
Retinoblastoma Type					
• Sporadic	26	18 (66.7)	8 (80)	0.688	2.0 (0.35-11.4)
• Familial	11	9 (33.3)	2 (20)		

*Relative Risk

**BMI Classification = Underweight (<18.5), Normal – Obese (18.5 – 22.9, and >22.9)

Our study showed that the subject's gender significantly correlated with the metastatic status of retinoblastoma (OR 6.7; 95% CI 1.34–33.1; p = 0.023). The multivariate analysis (TABLE 3) also showed that gender significantly associated with the metastatic status of retinoblastoma (OR 8.3; 95% CI 1.07–64.5; p = 0.04). While the univariate analysis of age group showed a slight significant association with metastatic status (OR 4.7; 95% CI 0.96–22.4; p = 0.067), the multivariate analysis (TABLE 3) revealed significant association between age group with the metastatic status (OR 17.6; 95% CI 1.26-248.31; p = 0.03). We also analyzed the laterality, BMI classification, BMI for age (WHO) and type

of retinoblastoma with the metastatic status of retinoblastoma. However, none of these factors were significantly associated with the metastatic status of retinoblastoma, both in univariate as well as multivariate analysis.

TABLE 3. Associations of gender and age group with retinoblastoma metastasis.

Characteristic	Multivariate	
	OR (95% CI)	p
Gender	8.3 (1.07-64.5)	0.04
Age group	17.6 (1.26-248.31)	0.03
BMI for age (WHO)	0.7 (0.34-1.52)	0.39

DISCUSSION

To the best of our knowledge, the present study is first study reported the correlation of several factors that related to the metastatic status of retinoblastoma in Indonesia. Our findings showed that metastatic status has significant correlation with gender, in which male patients associated with higher risk of metastatic disease in retinoblastoma. We found no studies available at the moment that provides direct comparisons with our findings. Other previous studies conducted in India revealed that there was male preponderance in retinoblastoma case.¹³⁻¹⁵ In the other hand, multiple studies suggest that there is no race or sex-based predisposition to the development of retinoblastoma.²⁴ Although, a study of epidemiological and genetic analyses on sporadic and familial retinoblastoma indicate that an X-chromosome-linked gene is involved in the genesis of a significant fraction of new bilateral cases of the disease. The activity of this gene results in sex-ratio distortion in favor of males among patients with bilateral sporadic disease.²⁵ In agreement with these studies, thus, our findings suggest that there is an increased risk of metastasis in male patients.

The laterality and the type of retinoblastoma also shown no correlation with the metastatic status of retinoblastoma. However, in the current study, the age group shows a significant association with the metastatic disease of retinoblastoma. Previous studies have shown that extraocular retinoblastoma cases were reported with the mean age of patients at presentation was 33 and 38 months.^{26, 27} Indeed, other studies also mentioned that the risk of metastatic disease was higher in patients with delayed diagnosis of retinoblastoma.^{28,29} While the mean age that presented in current study was 29 months, our result showed that a patient with

the age below 24 months was at the greater risk for developing metastatic disease. In agreement with our study, a previous study have shown that there are differences in metastasis occurrence according to the age group in the Ewing sarcoma.³⁰ A study in a zebrafish model showed that retinoblastoma cells invaded adjacent tissues and spreading hematogenously at the early stage of tumor.³¹ This might explain that retinoblastoma cells could develop into metastatic disease even at the early stage of the tumor.

Both BMI classification and BMI adjusted for age have no correlation with the metastatic status of retinoblastoma. These findings were similar to a study in 121 children with retinoblastoma from Brazil. They found that there was no correlation between BMI and metastatic status in retinoblastoma patients.²² Although, their results at point of diagnosis showed that 2.2% was underweight, 73.3% had normal BMI and 24.4% was overweight. In the current study, 31 (83.7%) of the patients fall into underweight category. Given that poor nutritional status in several part of Indonesia, the baseline BMI of the patients might attributable to the lower BMI of retinoblastoma patients in current study. The location of the tumor indeed shows a big impact in the nutritional status. A previous study reported that severe malnutrition was more prevalent in cancer of the upper gastrointestinal tract (28.3%), while lung (10.1%) and breast (5.1%) cancer only showed small number of malnutrition status.³² Therefore, retinoblastoma metastatic status may not affect the nutritional status of the patient because retinoblastoma primarily found on eye and frequent site of metastases were bone, lymph node, lung and central nervous system which seldom affects gastrointestinal organs directly. Thus, metastatic status of retinoblastoma might be independently associated with

the BMI of the patients.

Our findings emphasize that there is significant correlation between metastatic status and the gender and age in retinoblastoma patients, in which male patients and the younger age patients are at a greater risk to develop metastasis disease. To further rule out the gender preference and invasiveness of tumor that might attributable in retinoblastoma pathogenesis, a genetic abnormalities examination is necessary. The limitation of this study is its cross-sectional design, which did not allow the assessment of the impact of the systematic and sequential nutritional intervention. Further research may be needed with bigger sample size in different center, because bigger sample size provides opportunities to determine the average values of data more accurately and avoid misleading statistics from testing a small number of possibly atypical samples.

CONCLUSION

The present study demonstrated that the gender and age were associated with of metastatic status in retinoblastoma patients. Male gender and patient younger than 24 months old are at the higher risk for developing metastatic disease of retinoblastoma.

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