Lag time, high-risk histopathological features, metastasis, and survival interrelation in retinoblastoma: a perspective from lower-middle income country

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Abstract

- **AIM:** To investigate the impact of lag time to metastasis and survival rates among patients with retinoblastoma.
- **METHODS:** This retrospective study was conducted with 52 patients from the Department of Ophthalmology and the Department of Pediatrics of Dr. Sardjito General Hospital, between 1st January 2014 and 31st December 2020. Lag time was defined as the time delay between the first sign of retinoblastoma to the diagnosis of retinoblastoma. The subjects with lag time > one year were included in the case group, while the subjects with lag time < one year were included in the control group.
- **RESULTS:** The lag time was significantly correlated with American Joint Committee on Cancer and Intraocular Classification of Retinoblastoma staging of retinoblastoma ($P=0.005$ and $P=0.006$, respectively). The lag time was also significantly correlated with both metastasis event [odds ratio (OR): 5.06, 95%CI: 1.56-16.44, $P=0.006$] and mortality (OR: 4.54, 95%CI: 1.37-15.07, $P=0.011$). The follow-up was continued for 32 subjects for 3y after initial diagnoses. Survival analysis revealed a significant difference among these two groups ($P=0.021$). Furthermore, lag time was significantly correlated with survival of retinoblastoma ($r=-0.53$, $P=0.046$).

- **CONCLUSION:** The study highlights the importance of lag time between the onset of first symptoms and the time of retinoblastoma diagnosis which significantly contribute to metastasis and mortality of patients with retinoblastoma. Examinations for the early detection of retinoblastoma should be performed for individuals at-risk to minimize lag time and improve the outcomes.
- **KEYWORDS:** retinoblastoma; lag time; metastasis; survival; staging; laterality

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INTRODUCTION

Retinoblastoma is the most prevalent intraocular cancer in children. It is predicted every year that there are around 9000 new cases or roughly 1 in every 15 000 to 20 000 live births across the world were diagnosed with retinoblastoma⁵⁻³. The incidence rate of retinoblastoma may differ among countries in the world. In the most developed countries, retinoblastoma was reported as 4 cases per million population (pmp), whereas it is estimated to be 6–10 cases pmp in the developing countries⁴⁻⁶. The mortality rate varies dramatically throughout continents, with 70% in Africa, 40% in Asia, 5% in Europe, and 3% in Northern America⁷⁻⁸. The staging of retinoblastoma has been linked to socioeconomic factors⁹⁻¹¹. One study mentioned that access to health insurance was also associated with high-risk histopathologic characteristics of retinoblastoma¹². Another factor that might be attributable to the discrepancies of mortality rates globally is a delay in diagnosis or lag time. Several studies have described that a shorter lag time
was associated with an earlier stage of the illness upon presentation, which was also linked to lower mortality and blindness\textsuperscript{[13-14]}. Other studies have reported that a delayed diagnosis of retinoblastoma resulted in advanced disease upon presentation, with a higher likelihood of high-risk histological characteristics, a lower probability of globe salvage, and the requirement for adjuvant chemotherapy\textsuperscript{[12,15-17]}. In agreement with those previous studies, lag time was also shown to be significantly correlated with an increased mortality in retinoblastoma\textsuperscript{[18]}. Although there were many studies that have already focused on lag time in retinoblastoma, investigations about this important concern in lower-middle income countries, including Indonesia, are limited. This study aimed to assess the lag time and its relationship with metastasis and mortality in patients with retinoblastoma.

**SUBJECTS AND METHODS**

**Ethical Approval** The protocol of this study was reviewed and approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada and Dr. Sardjito General Hospital, Yogyakarta, Indonesia (No.KE/FK/0167/EC/2021).

**Research Design and Subjects** This retrospective study was conducted at the Department of Ophthalmology and Department of Child Health of Dr. Sardjito General Hospital, Yogyakarta, Indonesia from January 1\textsuperscript{st}, 2014 to December 31\textsuperscript{st}, 2020. The data were collected from medical records and used to establish a database. Most of the patients (n=47) in this study underwent a systemic chemotherapy and followed by enucleation, while only 5 patients were subjected to primary enucleation. In this study, we use vincristine sulfate, etoposide phosphate, and carboplatin (VEC) for 5 cycles as chemotherapeutic regimen. The routes and dosage were mentioned in other study\textsuperscript{[19]}. The study sample was comprised of a total of 52 patients diagnosed with retinoblastoma by histopathological examination of an enucleated eye in the Department of Pathological Anatomy of Dr. Sardjito General Hospital. The neoadjuvant therapy was only performed in 12 patients with high-risk histopathological features. All the patients were admitted to either the Department of Ophthalmology or Department of Pediatrics of Dr. Sardjito General Hospital.

**Data Collection** The following data: sex, age at presentation, pattern of hereditary (sporadic or familial), and laterality (unilateral or bilateral) were included in the demographic variables collected from the medical records. Patients with incomplete medical records or could not be contacted by the end of December 2021 were excluded from this study. All eligible patients were classified according to the American Joint Committee on Cancer (AJCC) staging and Intraocular Classification of Retinoblastoma (ICRB) staging of retinoblastoma after histopathological examination of enucleated eye\textsuperscript{[20-21]}. The classification of high-risk histopathological features was mentioned in the other study\textsuperscript{[14]}. In brief, the presence of 1 or more of the following features was then categorized as high-risk retinoblastoma: anterior chamber or iris infiltration, ciliary body infiltration, choroidal invasion, optic nerve infiltration, or scleral infiltration. The presence or absence of these features on histopathology examination was recorded. The first sign of retinoblastoma in this study was defined as leukocoria, squint, and/or proptosis that was reported by parents. Lag time was defined as the time delay between the first sign of retinoblastoma to the diagnosis of retinoblastoma by an ophthalmologist at Dr. Sardjito General Hospital. The subjects with lag time > one year were included into the case group, while the subjects with lag time < a year were included into the control group.

**Statistical Analysis** All data were collected and managed using a Microsoft Excel spreadsheet. Then, the data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The mean of age and lag time between two groups were compared by independent t-tests. Categorical variables were presented as frequency and percentage, while associations between two parameters were analyzed using Chi-square tests. The correlations between AJCC staging/ICRB staging with lag time was performed using Spearman’s Rho. The Kaplan-Meier analysis was used to determine the distribution of survival times and log-rank tests were also used to compare results between groups. The $P<0.05$ was considered significant.

**RESULTS**

In this study, the patients were split into those with lag time less than a year and those with lag time more than a year (respectively, 5.10±3.47, 18.54±7.41mo, $P<0.001$). A significant difference was found in age (in month) from patients with lag time < one year and patients with lag time > one year (22.95±12.59, 33.02±16.34, $P=0.016$). Table 1 shows the comparison of the other demographic characteristics between the two groups. Figure 1 shows the distribution of admission between the two groups. The AJCC staging system revealed that most of patient lag time < one year fell into pT1, pT2, and pT3 category, while most of patient lag time > one year were in the pT4 category (Figure 2A). Similar finding also found in ICRB staging, wherein most of patient with lag time > one year were fall in the E group (Figure 2B). Increased lag time was found significantly correlated with higher AJCC staging (correlation coefficient: 0.387, $P=0.005$) and ICRB staging (correlation coefficient: 0.379, $P=0.006$). Almost all the cases in this study were unilateral, although some cases were bilateral. Further analysis showed that lag time was significantly correlated with the laterality of retinoblastoma cases (Table 2). Remarkably, results also indicated that lag
time was significantly correlated with both metastasis event and mortality (Table 2).

Metastasis was found in both lag time groups. Expectedly, the metastasis was detected in 69% of patients with lag time > one year, while the metastasis was only observed in 31% of patients with lag time < one year were (Figure 3A). Both groups showed several metastasis locations such as brain, bone marrow, lymph nodes, and spinal cord (Figure 3). However, only those with lag time more than a year had multiple metastasis locations (Figure 3B). Since the stage at presentation, age at diagnosis, and lag time might be correlated with systemic metastasis, we then performed univariate and multivariate logistic regression analysis for these three factors. We found that stage at presentation, age at diagnosis, and lag time were significantly correlated with metastasis in univariate analysis. Meanwhile, only lag time was significantly correlated with metastasis in the multivariate analysis (Table 3).

Among total 52 subjects in this study, the follow-up was continued with 32 subjects for 3y after initial diagnosis of retinoblastoma. The other 20 patients who were diagnosed in 2019 and 2020 were not suitable for the three years survival analysis due to the insufficient time for follow up. Of the total 32 subjects, 15 subjects were grouped as lag time < one year and 17 subjects in the grouped as lag time > one year. We found that 10 subjects with lag time < one year and 3 subjects with lag time > one year had survived within 3y after diagnosis.
of retinoblastoma. Concordantly, we also found that 4 subjects with lag time < one year and 15 subjects with lag time > one year had died during the 3y follow-up. The overall survival analysis of these 32 subjects revealed a significant difference among the two groups \( (P = 0.021) \). Further analysis revealed that lag time was significantly correlated with overall survival of retinoblastoma \( (r = -0.53; P = 0.046) \). Figure 4A illustrates the Kaplan-Meier curves and Figure 4B illustrates the simple linear regression between lag time and overall survival.

**DISCUSSION**

This study aimed examine the question about delayed retinoblastoma diagnosis and its impact on several outcomes of the disease. This study’s results show there were significant correlations between lag time with laterality, metastasis, and mortality of patients with retinoblastoma. Conversely, previous studies mentioned that the delayed diagnosis occurrence was similar in both unilateral and bilateral cases of retinoblastoma\[^{22-23}\]. The inconsistency in the findings from our study compared to previous studies might be due to the difference in total unilateral cases \((n=41)\) and bilateral cases \((n=11)\). Remarkably, we found that the risk of metastasis was associated with lag time, but not the age at presentation nor stage at presentation. Concordantly, several studies mentioned that longer lag time has been correlated with retinoblastoma metastasis\[^{14,24-25}\]. Another study also mentioned that longer lag time was significantly correlated with higher risk of extracocular invasion\[^{24}\].

Additionally, the risk of mortality was also increased in the patients with lag time > one year. A similar result was observed in several studies, which mentioned that the diagnostic delay was significantly correlated with mortality in retinoblastoma\[^{25-27}\]. In contrast and comparison, another study mentioned similar some conflicting results that showed significant correlations of lag time with mortality in bilateral cases, but not for unilateral cases\[^{27}\]. Poorer countries were reported to have the highest rates of metastatic and mortality in retinoblastoma\[^{21,28}\]. In agreement with previous research, another study found that the lag times in poorer countries were significantly different from those in high-income countries\[^{29}\].

Several factors were postulated to be the related to the longer lag time which were correlated with increased of metastasis and mortality. These potential factors included a lower parental education, older parental (especially mother) age, the lack of disease awareness, and difficult access to health care\[^{24,30-32}\]. Application of retinoblastoma staging systems might help the ophthalmologist to predict the prognosis of the disease. Our results show that most of patients with lag time > one year were categorized as advanced stages. We also found that the AJCC and ICRB staging was significantly correlated with lag time. In contrast, a previous study found no significant correlation between lag time and staging of retinoblastoma\[^{13}\]. In our study, the median lag time was longer \((12\text{mo})\) when compared to previous studies which were 7 and 9mo\[^{33-34}\]. Longer lag time and advanced stage have also been mentioned as predictors for poor prognosis in retinoblastoma\[^{15-37}\]. Thus, the longer lag time might be attributable to the distinct result between this study and previous study. Furthermore, we found that stage at presentation, age at diagnosis, and lag time were significantly correlated with metastasis in the univariate analysis. Previously, the stage at presentation was reported to

### Table 3 Univariate and multivariate logistic regression for predictors of metastasis in retinoblastoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>1.09</td>
<td>0.005</td>
</tr>
<tr>
<td>Stage at presentation</td>
<td>1.88</td>
<td>0.023</td>
</tr>
<tr>
<td>Lag time</td>
<td>1.14</td>
<td>0.004</td>
</tr>
</tbody>
</table>

OR: Odds ratio.
be important in predicting the metastasis as well as metastasis related mortality\[38\]. The clinical stage of AJCC (cT categories) was also reported as a helpful instrument to predict the high-risk histopathological features in retinoblastoma\[39\]. In addition, the age at diagnosis was also mentioned to be associated with worse prognosis in metastatic retinoblastoma\[38\]. Finally, the multivariate analysis found that only lag time was significantly correlated with the metastasis. Although the relationship between lag time and advanced stage of retinoblastoma is complicated and not linear, generally, it is seen that the reduction of the lag time will contribute to the better treatment options which affect the survival of patients with retinoblastoma.

In high income countries, the survival rate of retinoblastoma has improved dramatically over several decades, while in contrast, it still varies in poorer countries\[40\]. Europe and United States reported a 5-year survival rate of 95% and 87%, respectively\[41\]. Other studies also reported a 5-year survival rate as high as 66.6% in Uzbekistan, 82.2% in Turkey, 86% in China, and 89.1% in Taiwan, China, while Japan reported the 10-year survival rate as high as 98.5\%\[42-46\]. In contrast, the survival rate in lower middle-income countries was significantly lower when compared to developed countries. The 5-year survival rate was reported as 37% in Indonesia, 46% in Namibia, 48% in India, 55% (for unilateral cases) in Malaysia, and 55% in Thailand\[47-51\]. Although social economic factors play an important role in the retinoblastoma survival rate, other important factors might also affect it.

In this study, the survival rates in patients with shorter lag time were significantly higher when compared to patients with longer lag time. In addition, our results highlight a significant correlation between lag time and survival in retinoblastoma. However, these findings may not suggest a causative relationship since other confounding factors have not been ruled out in the analysis. Several factors might influence the longer lag time for the patients with retinoblastoma in Indonesia. The extensive belief in alternative medicines and extended delay until symptoms get worse were the most reported motives in delays for seeking medical treatment in Indonesia\[52-53\]. Moreover, a major treatment-related delay also occurred due to direct non-medical expenses such as transportation and accommodation for the patient’s caregivers\[54-56\]. Despite the development of cancer treatment modalities, these socioeconomic factors remain an immense challenge for cancer treatment in Indonesia, especially retinoblastoma. Interestingly, other study showed that the presentation of an advanced stage retinoblastoma has been decreased as a result of increased public and primary care provider awareness\[57\]. While preparing the more robust treatment for retinoblastoma (i.e., intraarterial chemotherapy or targeted therapy), the concept to raise retinoblastoma awareness among health care provider and parents is promising strategy to reduce the lag time of retinoblastoma presentation in lower-middle income country. Furthermore, the shorter lag time possibly promote a better overall survival for patient with retinoblastoma\[25\].

The present study’s limitations include the relatively small number of subjects followed by the uneven distribution of the subjects for survival analysis and an insufficient follow-up duration to draw precise conclusions on disease outcomes. It is conceivable that several outcomes such as metastases or mortality may have occurred after the study was completed. Furthermore, the subjects were divided into groups based on extended lag time, which might lead to differences in outcomes within each of the groups.

In conclusion, this study highlights the importance of lag time between the onset first symptoms and the time of retinoblastoma diagnosis which contribute an important role in metastasis and mortality of patients with retinoblastoma. There was a significantly large gap of lag time that led to worse survival rates for retinoblastoma patients with longer lag time. Longer lag time was also linked to advanced stages of the disease at presentation and significantly associated with worse prognosis. In order to minimize lag time, routine ophthalmology screening of individuals at-risk (i.e., any suspected infant and those with a positive family history) or those presenting with retinoblastoma symptoms is needed with adequate follow-up.

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