RESEARCH ARTICLE

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Systemic Immune Inflammation Index as High-Risk Retinoblastoma Survival Predictor

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Abstract

Objective: To determine the ability of SII as a predictor of five-year survival in high-risk Rb. **Methods:** A retrospective cohort study, from August to September 2024 at Dr. Cipto Mangunkusumo Hospital. **Results:** We conducted the analysis on 157 high-risk Rb subjects between 2016 and 2024. The cut-off point based on the Receiver Operating Characteristic (ROC) curve, with the maximum Youden index value, was identified at an SII of 351.72. The five-year overall survival (OS) and event-free survival (EFS) were 35.9% (SE ± 4.8%) and 32.1% (SE ± 4.8%), respectively. The median OS and EFS were 17 months and 16 months, respectively. High baseline SII (≥351.72) was associated with five years median OS of 11 months (SE ± 9.38; 95% CI: 9.16–12.84), a survival rate of 14.5% (SE ± 4.7 High SII (SII ≥351.72). Both baseline and serial high SII were associated with poorer 60-month overall survival in high-risk retinoblastoma (aHR 1.94; 95% CI, 1.11–3.40; p=0.02 and aHR 3.59; 95% CI, 2.49–5.19; p<0.01, respectively). **Conclusion:** SII may predict survival in high-risk Rb.

Keywords: SII, high-risk Rb, survival

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Introduction

The systemic immune-inflammation index (SII) is an inflammation marker, an index calculated from platelets (P), neutrophils (N), and lymphocytes (L) using the formula SII = P × N/L [1]. A high SII may indicate poor overall survival of various types of solid tumors (e.g., osteosarcoma, medulloblastoma, neuroblastoma) [2-4].

Retinoblastoma (Rb) is children's most common intraocular malignancy, caused by mutations in the Rb gene (Rb1) located on chromosome 13q14.2. The incidence of Rb is about 1 in 17 000 live births, with approximately 8,000 new cases diagnosed each year worldwide. In the Department of Child Health at Dr. Cipto Mangunkusumo Hospital, Rb cases comprise 751 (24.6%) of the 3 067 solid tumor cases, or 11.9% of all malignancies in children (6 314) since 1995. Retinoblastoma is the most common solid tumor and the second most common malignancy in children after leukemia. The survival gap for Rb still exists. Survival rates can reach over 95-98% in high-income countries, but conversely, in low-income countries, e.g., in an African country, it is only around 30% [5]. Delayed diagnosis, socio-cultural practices, economic factors, and disparities in healthcare provision are some of the causes [6].

Research on SII as a predictor of solid tumor survival in children is still limited. Currently, there is no survival marker for Rb. The systemic immune-inflammation index has not yet been confirmed as a survival marker in Rb. This study aims to determine the ability of the SII as a survival predictor of high-risk Rb. The specific objectives of this study are to determine the survival of high-risk Rb at Dr. Cipto Mangunkusumo hospital and to assess the discriminative ability of SII in predicting five-year survival in high-risk Rb. Platelet, neutrophil, and lymphocyte levels as markers of inflammation have the potential to be simple survival predictors that can be useful in determining the progression of solid tumors, including Rb.

Materials and Methods

Study Design

This study uses a retrospective cohort design conducted on high-risk Rb patients at Cipto Mangunkusumo Hospital, August–September 2024. The target population is all high-risk Rb patients, while the accessible population includes all high-risk Rb patients with medical records. Inclusion criteria include age <18 years, a complete peripheral blood examination, and a leukocyte differential count at

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the time of diagnosis. Exclusion criteria include patients with comorbidities (aplastic anemia, myelodysplastic syndrome (MDS), immune thrombocytopenia (ITP)), patients undergoing long-term immunosuppressive therapy, patients who have received platelet and/or red blood cell transfusions within the past 14 days, and patients experiencing acute infections within the past 14 days. Based on the calculation of the survival sample size formula, a minimum sample size of 156 subjects was obtained [7-10].

Data Collection

The study sample was obtained using consecutive sampling from medical records of retinoblastoma (Rb) patients from 2016 to September 2024. Data included age, sex, nutritional status, diagnosis, hematological parameters for systemic immune-inflammation index (SII) (absolute neutrophil, platelet, and lymphocyte counts), treatment modalities, and 60-month survival outcomes. SII parameters were assessed at baseline (at diagnosis) and serially prior to subsequent treatment or event occurrence. Patients who do not return for follow-up were contacted via phone or text message to ascertain their current condition or time of death. Patients who cannot be contacted and/or for whom there were no clarity were considered lost to follow-up. Data was entered into the database and processed using SPSS. The determination of the SII cutoff point was obtained from the maximum value of the Youden index calculation (sensitivity + specificity – 1) from the ROC (Receiver Operating Characteristic) curve [11].

The independent variable in this study is the SII in high-risk Rb, the dependent variable is survival at 60 months, and the confounding variables include age, gender, retinoblastoma classification, and treatment modalities. High-risk retinoblastoma is defined as 1) bilateral Rb, regardless of the stage, 2) trilateral Rb, 3) group D-E in the intraocular tumor classification based on the International Classification of Retinoblastoma (ICRB), 4) stage III-IV in the extraocular tumor classification based on the International Staging System for Retinoblastoma (ISSRB), or 5) unfavorable histological findings, including seeding to the anterior vitreous, iris infiltration, and ciliary body, tumor invasion beyond the lamina cribrosa (nerve parenchyma, CSF, and blood vessels), optic nerve involvement, massive choroidal infiltration (>3 mm), scleral infiltration, and extra scleral extension [7]. Events are subjects who have died, experienced deterioration, or recurrence. Censored is the state where the subject does not experience an event, or is alive, or there is no deterioration, or is lost to follow-up [12]. Survival assessment includes overall survival (OS), defined as the time from diagnosis to death, and event-free survival (EFS), which measures the time from diagnosis to disease progression (including stage advancement based on ICRB, ISSRB, or TNM-WHO-AJCC), recurrence, or therapy (thermotherapy/transpupillary thermotherapy, cryotherapy, laser photocoagulation), 2) chemotherapy (intravenous, intra-arterial, intravitreal, periocular), 3) radiation (External Beam Radiotherapy (EBRT), Proton Therapy), and 4) surgery (enucleation) [7].

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics, version 31. Survival analysis was conducted using the Kaplan-Meier method, which illustrates cumulative survival, survival rate, median or mean survival, and the proportional hazard (PH) assumption. Bivariate analysis was performed to obtain the hazard ratio (HR) and to identify potential confounding variables. Cox regression analysis was conducted for variables that meet the PH assumption, while those that do not meet the PH assumption were analyzed using Cox regression with time-dependent covariates. Extended multivariate Cox regression analysis, using the backward LR method, was conducted on theoretically relevant confounding variables and variables with $p < 0.25$ in bivariate analysis to obtain the adjusted Hazard ratio (aHR) [12-14]. To address potential confounding by indication related to treatment modality, propensity scores were estimated and inverse probability of treatment weighting (IPTW) was applied to achieve covariate balance [15]. Covariate balance was evaluated using standardized mean differences (SMD), with a threshold of <0.1 indicating adequate balance. If adequate balance could not be achieved, multivariable adjustment and sensitivity analyses were prioritized to ensure the robustness of the findings [16,17].

Results

Since 2016, 304 high-risk retinoblastoma (Rb) patients have been registered in the Rb registry. Of these, 176 patients met the inclusion criteria. Nineteen patients were excluded: nine due to infection (including hepatitis C, pulmonary tuberculosis, COVID-19, pneumonia, or dengue fever) and ten due to a history of transfusion. The final analysis included 157 subjects.

The proportion of high-risk Rb subjects was as follows: 1) bilateral Rb: 25 (15.9%) subjects, 2) trilateral Rb: 11 (7.0%) subjects, 3) ICRB classification group D and E: 7 (4.5%) subjects and 28 (17.8%) subjects respectively, and 4) ISSRB classification stage III and IV: 26 (16.6%) subjects and 60 (38.2%) subjects respectively.

The characteristics of 157 research subjects were displayed in Table 1. The median age at diagnosis of high-risk retinoblastoma (Rb) was 29 months, with 65.6% of cases diagnosed at ≥24 months. Most subjects were male, and the majority were well-nourished. The majority of high-risk Rb cases were extraocular, consisting of unilateral ISSRB stage III and IV Rb in 8 (8.2%) and 44 (45.4%) subjects, respectively; bilateral ISSRB stage III and IV Rb in 16 (16.5%) and 11 (11.3%) subjects, respectively; and trilateral Rb in 11 (11.3%) subjects. The most common treatment modality was chemotherapy, followed by a combination of chemotherapy with other modalities, including surgery (such as enucleation), focal therapy, and radiation. Of the 61 patients who received chemotherapy as the sole modality, 43 had extraocular Rb, including 23 with unilateral ISSRB stage IV, 7 with unilateral ISSRB stage III, 6 with bilateral ISSRB stage IV, 6 with trilateral Rb, and 1 with unilateral ICRB group E. The median systemic immune-inflammation (SII) index among high-risk Rb subjects in this study was 334.86.

Table 1. Subject Characteristics

Characteristics	n = 157
Age at diagnosis, median (range), months	29 (2–116)
Age at diagnosis, ≥24 months, n (%)	103 (65.6)
Gender, male, n (%)	82 (52.2)
Nutritional status, n (%)	
Severe malnutrition	13 (8.3)
Moderate malnutrition	14 (8.9)
Well-nourished	127 (80.9)
Overweight	2 (1.3)
Obesity	1 (0.6)
Retinoblastoma classification, extraocular, n (%)	97 (61.8)
Treatment, n (%)	
Chemotherapy	61 (38.9)
Surgery	4 (2.5)
Chemotherapy and focal therapy	2 (1.3)
Chemotherapy and radiation	10 (6.4)
Chemotherapy and surgery	54 (34.4)
Chemotherapy, focal therapy, and surgery	15 (9.6)
Chemotherapy, surgery, and radiation	10 (6.4)
Chemotherapy, focal therapy, surgery, and radiation	1 (0.6)
Hematology profile, (x 103 /mm^3), median (range)	
Neutrophil	3.76 (0.06–25.16)
Platelet	413.00 (16–1 400)
Lymphocyte	4.51 (0.61–13.86)
SII, median (range)	334.86 (3.05–9 193.74)
Events, n (%)	79 (50.3)

Table 2 presents the relationship between various variables based on censored categories and events. Survival data were obtained from 109 subjects through telephone contact with family members, medical records, or registries. Censoring was applied to 48 subjects for whom no event was recorded because they were lost to follow-up or could not be contacted during the follow-up period.. The causes of death and deterioration were identified in 55 subjects, including 33 due to intracranial metastasis, 4 due to recurrence, 8 due to pneumonia, 8 due to sepsis, 1 due to COVID-19, and 1 due to meningitis. Among the censored group, three subjects experienced health complications within 60 months, including tumor mass infection, tuberculous meningitis, and COVID-19. Additionally, two subjects in the censored group experienced relapse. Three subjects temporarily discontinued chemotherapy, two of whom subsequently died.

The 60-month OS and EFS survival rates are shown in Figure 1. The median overall survival (OS) was 17 months (SE ± 3.57; 95% CI: 10.01–23.99), with a five-year OS rate of 35.9% (SE ± 4.8%). The median EFS was 16 months (SE ± 3.28; 95% CI: 9.57–22.43), with a five-year EFS rate of 32.1% (SE ± 4.8%). The Area Under the Curve (AUC) for the Systemic Immune-Inflammation Index (SII) was 71.9% (95% CI: 63.8–80.0), indicating a moderate discrimination ability in predicting the survival of high-risk retinoblastoma (Rb)[11]. The optimal cut-off point for SII was 351.72.

Figure 1 illustrates the Kaplan-Meier curves for each variable, while Table 3 summarizes the Cox regression analysis. An SII value of ≥351.72 predicts a median survival of 11 months (SE ± 9.38; 95% CI: 9.16–12.84). The 60-month survival rate for high-risk Rb patients with SII ≥351.72 was 14.5% (SE ± 4.7%), compared to 58.8% (SE ± 7.2%) for those with SII <351.72.

The median survival for patients diagnosed at ≥24 months was 12 months (SE ± 1.02; 95% CI: 10.00–13.99). The 60-month OS for patients diagnosed at ≥24 months was 25.7% (SE ± 5.2%), compared to 53.6% (SE ± 8.5%) for those diagnosed at <24 months.

The median survival by gender was 15 months for females (SE ± 1.63; 95% CI: 11.8–18.20) and 24 months for males (SE ± 9.97; 95% CI: 4.45–43.55). The 60-month OS for females and males was 31.5% (SE ± 7.0%) and 40.5% (SE ± 6.5%), respectively.

The median survival for extraocular Rb was 13 months (SE ± 1.55; 95% CI: 9.97–16.03). The 60-month OS for extraocular and intraocular Rb was 19.9% (SE ± 5.1%) and 65.6% (SE ± 7.8%), respectively.

Patients undergoing chemotherapy as a single modality had a median survival of 9 months (SE ± 1.60; 95% CI: 5.87–12.13). At 60 months, no patients who received chemotherapy alone survived, whereas the OS for those receiving other or combined modalities was 51.6% (SE ± 5.7%).

Multivariable analysis was performed using extended Cox regression (Table 3). Variables meeting the proportional hazards (PH) assumption were analyzed using standard Cox regression, whereas those violating the PH assumption were modeled as time-dependent covariates. In the multivariable model, baseline SII ≥351.72 remained independently associated with overall survival (aHR 1.94; 95% CI, 1.11–3.40; p=0.02). Sensitivity analysis across treatment subgroups showed a numerically stronger association in the combined/other treatment group (aHR 2.86; 95% CI, 1.35–6.07; p<0.01), whereas no significant association was observed in the chemotherapy-only group.

To further evaluate changes in SII during treatment, serial SII was analyzed using a time-dependent approach. Propensity score–based IPTW did not achieve adequate covariate balance (standardized mean differences >0.1); therefore, weighted analyses were not further interpreted. Serial SII (Table 4) was significantly associated with overall survival. In the fully adjusted model, high SII (≥351.72) was associated with poorer survival (aHR 3.59; 95% CI, 2.49–5.19; p<0.01). Subgroup analyses demonstrated consistent findings across treatment modalities, with a stronger effect observed in the combined/other treatment group (aHR 5.37; 95% CI, 3.26–8.84; p<0.01) compared with the chemotherapy-only group (aHR 2.26; 95% CI, 1.30–3.92; p<0.01). Other covariates, including age ≥24 months, extraocular disease, and sex, were not consistently associated with survival across models.

Table 2. The Relationship of Various Variables to 60-Month Survival of High-Risk Rb

Variables	Censored (N = 80)	Events (N = 77)	p
Age at diagnosis, median (range), months	24.5 (2–162)	30 (4–94)	<0.01[a]
<24 months, n	35	19	<0.01[b]
≥24 months, n	43	60	
Gender, n			0.47[b]
Male	43	39	
Female	35	40	
Nutritional status, n (%)			0.42[a]
Severe malnutrition	5	8	
Moderate malnutrition	6	8	
Well-nourished	66	61	
Overweight	1	1	
Obesity	0	1	
Retinoblastoma classification			<0.01[b]
Intraocular	45	15	
Extraocular	33	64	
Treatment, n			0.01[a]
Chemotherapy	22	39	
Surgery	3	1	
Chemotherapy and focal therapy	1	1	
Chemotherapy and radiation	2	8	
Chemotherapy and surgery	35	19	
Chemotherapy, focal therapy, and surgery	13	2	
Chemotherapy, surgery, and radiation	1	9	
Chemotherapy, focal therapy, surgery, and radiation	1	0	
Hematology profile, (x 10^3 /mm^3), median (range)			
Neutrophil	3.24 (0.53–9.54)	4,49 (0.60–25.16)	<0.01[a]
Platelet	404.00 (39–1 082)	417.00 (16–1 400)	0.75[a]
Lymphocyte	5.25 (1.34–13.86)	4.09 (0.61–10.14)	<0.01[c]
SII, median (range)	254.05 (11.03–1 710.74)	490.89 (3.05–9 193.74)	<0.01[a]

[a], Mann-Whitney, [b], Pearson Chi-Square, [c], Independent sample T-test.

Discussion

This study uses the term high-risk Rb according to national guidelines. Singh in 2018 used the term advanced stage, to describe cases that includes subjects classified under the International Intraocular Retinoblastoma Classification (IIRC) group D and E categories as well as all extraocular Rb [18]. The majority of the study participants were extraocular Rb (61.8%), with ISSRB stage IV classification (38.2%). This finding aligns with Radhakrisnan statement in 2012, which noted that extraocular Rb accounts for up to 50% of all Rb cases in developing countries in Southeast Asia and Africa. Factor contributing to the advanced stages at presentation include delayed diagnosis, socio-cultural practices, economic factors, and disparities in healthcare provision [6].

Table 3. Univariable and Multivariable Analysis of Prognostic Factors for 60-Month Overall Survival and Sensitivity Analysis of baseline SII Across Treatment Subgroups

Analysis Model	Bivariate Analysis			Multivariate Analysis			Sensitivity Analysis on Treatment Modality					
							Chemotherapy only (n=61)			Other/Combined (n=96)		
	HR	p	95% CI	aHR	p	95% CI	aHR	p	95% CI	aHR	p	95% CI
SII ≥351.72 (baseline)	3.44	<0.01	2.11–5.61	1.94	0.02	1.11–3.40	1.29	0.56	0.55–3.05	2.86	<0.01	1.35–6.07
Treatment modality (chemotherapy only)	3.61	<0.01	2.29–5.70	2.56	<0.01	1.60–4.10	–	–	–	–	–	–
Age ≥24 months	3.04	<0.01	1.80–5.14	1.74	0.07	0.96–3.17	2.77	0.08	0.90–8.56	1.65	0.21	0.76–3.57
Extraocular Rb*	1.09	<0.01	1.04–1.14	1.06	0.02	1.01–1.10	0.96	0.30	0.89–1.04	1.10	<0.01	1.03–1.17
Female*	1.02	0.27	0.99–1.05	1.01	0.42	0.98–1.05	1.02	0.60	0.95–1.09	1.02	0.31	0.98–1.06

* Time–dependent variable

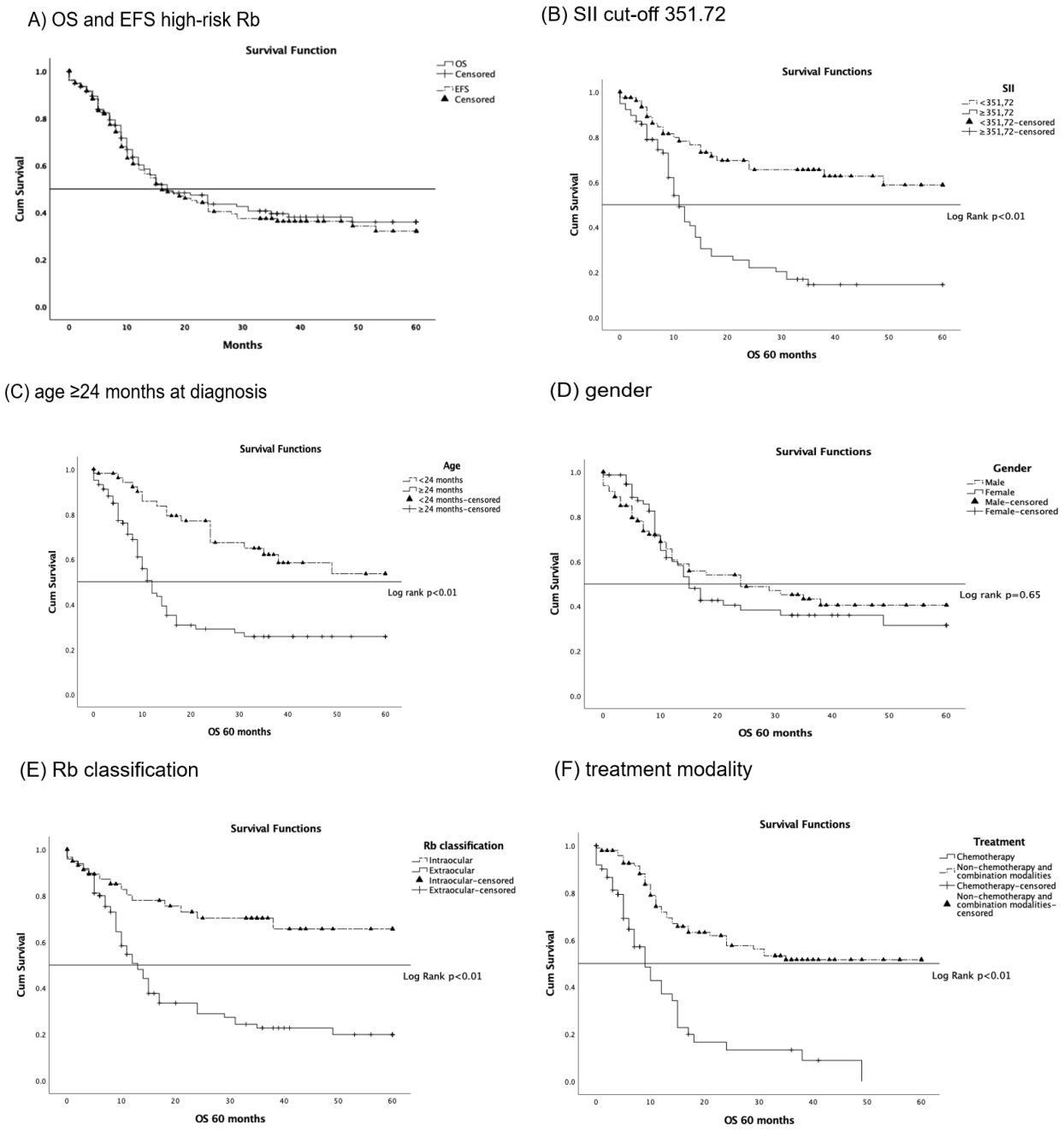

Figure 1. Kaplan-Meier Curve of A) OS and EFS high-risk Rb, and based on variables (B) SII cut-off 351.72, (C) age ≥24 months at diagnosis, (D) gender, (E) Rb classification, (F) treatment modality

This study identified hematological profiles, including median neutrophil and lymphocyte counts, statistically associated with survival outcomes. The event group exhibited higher median neutrophils and platelets counts, along with lower median lymphocytes counts, compared to the censored group. A study conducted at a tertiary hospital

Table 4. Sensitivity Analysis of Serial SII Measurements in Relation to 60–Month Overall Survival Across Treatment Subgroups

Analysis Model	Full Adjusted Model			Sensitivity Analysis on Treatment Modality					
				Chemotherapy only (n=61)			Other/Combined (n=96)		
	aHR	p	95% CI	aHR	p	95% CI	aHR	p	95% CI
SII ≥351.72 (serial)	3.59	< 0.01	2.49–5.19	2.26	< 0.01	1.30–3.92	5.37	<0.01	3.26–8.84
Treatment modality (chemotherapy only)	1.66	0.05	1.01–2.71	–	–	–	–	–	–
Age ≥24 months	1.78	0.05	1.01–3.13	2.26	0.13	0.79–6.42	2.07	0.06	0.97–4.41
Extraocular Rb*	1.04	0.06	1.00–1.08	0.99	0.72	0.91–1.07	1.06	0.05	1.00–1.12
Female*	0.98	0.29	0.95–1.02	0.96	0.35	0.89–1.04	1.00	0.88	0.96–1.05

* Time–dependent variable

reported a higher median neutrophil count in cases of bilateral Rb compared to unilateral Rb; however, it did not explore the relationship between neutrophil count and survival in Rb patients. The finding of elevated median platelet counts in the bilateral Rb group and in patients who died has also been documented in various studies conducted at tertiary referral hospitals [19, 20]. The event group showed a significantly lower median lymphocyte count, which is consistent with the literature suggesting that a low peripheral blood lymphocyte count is associated with poor prognosis in several cancer types [21-23]. Platelets and neutrophils exhibit protumor activity by promoting angiogenesis and cellular proliferation, thereby increasing the risk of invasion and metastasis. In the case of Rb, interactions with the tumor microenvironment, neutrophils, and platelets resulting in immunosuppression, contribute to a reduction in lymphocyte antitumor activity. As the mass of the Rb tumor increases, more platelets and neutrophils are recruited to the tumor site, which in turn enhances immunosuppression against lymphocytes in the tumor microenvironment. This ultimately facilitates increased angiogenesis, cellular proliferation, invasion, and metastasis of Rb [21, 24, 25]. These findings support the role of systemic inflammation in tumor progression and its interaction with host immunity [26]. The interaction of the number of platelets, neutrophils, and lymphocytes is further illustrated in the SII.

At 60 months, high-risk Rb had an OS rate of 39.5% and an EFS rate of 38.11%. This survival rate is lower than the total survival rate of children from low-income countries (57.3% (52.1–63.0)) [9]. Handayani in Yogyakarta also observed low survival rates in this study, with OS and EFS rates of 37% and 17%, respectively [27]. However, these rates were higher than those reported by Malabanan-Cabebe in Davao (28%), and Atima in Nigeria (20%) [5, 27 ,28]. One contributing factor to the low OS rate in this study is that the analysis focused on high-risk Rb cases rather than all Rb cases. Both OS and EFS in this study tend to decline particularly within the first 12 months after diagnosis, indicating that mortality and progression of high-risk Rb primarily occur during this period. This is consistent with findings from Fabian, who reported that children with stage cT4 tumors (more advanced or severe) experienced a significant drop in survival rates to 55% in the first year and 31.9% at 3 years [9].

This study reports a median OS and EFS of 60 months for high-risk Rb, with median survival times of 17 months and 16 months, respectively. Malabanan-Cabebe in 2024, Dunkel in 2022, and Handayani in 2022 reported a lower median survival rate, which below than 12 months [27-29]. The median OS of these studies is better compared to previous reports. Leal et al. in 2006 reported a median OS of 6.1 months for extraorbital metastatic Rb [30]. Wong noted a significant improvement in Rb OS over the past four decades, with an increase from 79% to 88% ($p = 0.017$) from 1980 to 2020, although disparities remain between high-income and lower-middle or low-income countries [31].

SII research as a survival marker in children with Rb has not yet been conducted, although it has been explored in several other solid tumors, including osteosarcoma, neuroblastoma, and medulloblastoma. This study supports previous research, which found that subjects with higher SII values had an increased risk of mortality and poorer survival outcomes. The approach of determining the cutoff point using the Youden index in this study is consistent with prior studies, although the cutoff point in this study differs [2-4]. This suggests that each solid tumor type has its own optimal SII cutoff point. Multivariate analysis in this study confirmed that SII significantly influences the five-year survival rate of high-risk Rb.

The median age at diagnosis of high-risk Rb in this study was 29 months. This is consistent with Supartoto's findings in 2020, which the average age was 29.44 months. However, this study used cutoff point of 24 months according to the literature [27, 32]. Subjects diagnosed at ≥24 months had a lower OS rate. Handayani in 2021 reported that children diagnosed at the age of two years or older had a lower 5-year OS (24%). The age at diagnosis reflects delays in Rb patients seeking healthcare, delays in referral to specialized centers, and delays in diagnosis [27]. Bilbeisi in 2023, Tomar in 2022, and Aschero in 2021, also found that older age at diagnosis was associated with poorer survival outcomes [33-35]. Age is associated with an increasing number of copy number alterations (CNAs), which are indicators of rising genomic instability. The older the age at diagnosis, the higher the risk of developing high-risk genomic features [34].

Even though gender is not statistically associated with survival, most of the subjects in this study were male. Retinoblastoma is more prevalent in boys, and the risk of metastasis is higher in males with Rb. This may be related with the involvement of the X chromosome in familial and sporadic Rb, which typically presents as bilateral Rb [32]. Although not clinically or statistically significant, female subjects in this study had a 1.02 times higher risk of mortality and a lower five-year OS. In 2024, Berry reported that females with Rb are at a 1.98 times higher risk of death, a finding that may be influenced by unequal access to healthcare in certain countries where males are prioritized, as opposed to biological mechanisms [36]. Fabian in 2022 revealed that besides gender discrimination favoring boys, non-compliance with treatment also occurs more frequently in girls compared to boys (64% vs. 36%; $p = 0.02$) [37].

In this study, most subjects were diagnosed with extraocular Rb, which is commonly found in various tertiary referral hospitals [38-40]. Although extraocular Rb marginally increased HR, other studies have reported that it carries nearly a ten-fold higher risk of death compared to early-stage intraocular Rb [9]. Extraocular Rb was associated with poorer five-year OS compared to intraocular Rb. Dunkel (2022) also reported that extraocular Rb, including stages IVa and IVb/trilateral, had a 3-year OS of 76.7% and 12.3%, respectively [29]. The more progressive and extensive the tumor, the lower the survival rate. Tumors that invade the optic nerve (groups D and E in the intraocular tumor classification based on ICRB) have an HR 8.98 times higher compared to group A ICRB [7, 41].

Most subjects in this study were treated with

systemic chemotherapy alone. This may be related to the advanced stage at diagnosis, age restrictions on radiation, or palliative treatment options [7]. The Global Retinoblastoma Study reported that 1937 (47.9%) of 4043 patients received intravenous chemotherapy as their primary treatment [9]. Subjects treated with chemotherapy alone had lower OS compared to those receiving other treatment modalities or combinations of treatments. However, treatment modality is a confounding factor, a common bias in non-experimental studies. Indication bias occurs when predicted risks influence the choice of therapy, making it challenging to determine whether observed outcomes are due to the treatment itself or the underlying risk factors [42].

The prognostic value of baseline SII remained significant after adjustment, suggesting that SII provides additional information beyond conventional clinical factors. Consistent associations across treatment subgroups further support the robustness of SII, with stronger effects observed in patients receiving combined or alternative treatments. The inability to achieve adequate covariate balance using IPTW underscores the challenges of observational data and supports the use of multivariable and sensitivity analyses [15,43].

From a clinical perspective, SII is a simple and cost-effective biomarker derived from routine blood tests, making it particularly relevant for resource-limited settings. Serial measurement of SII may provide additional value for monitoring disease progression and treatment response. This study has limitations, including its retrospective design, relatively small sample size, and potential residual confounding. However, the use of time-dependent modeling strengthens the validity of the findings.

In conclusion, 60-month OS and EFS for high-risk Rb at Dr. Cipto Mangunkusumo Hospital were 35.9% (SE ± 4.8%) and 32.1% (SE ± 4.8%), respectively. High SII (SII ≥351.72), both baseline and serial, was identified as an independent variable associated with poorer survival in high-risk. Further studies are needed to evaluate the performance of SII in assessing therapy response and progression in both Rb and other solid tumors. SII may serve as a practical prognostic tool, although further prospective studies are needed to validate its role in clinical decision-making.

Author Contribution Statement

YM is responsible for Conceptualization; Formal analysis; Funding acquisition; Data curation; Validation; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. NAC, MK, AHP, HAS is responsible for conceptualization, methodology, and supervision. ES is responsible for supervision.

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Ethical declaration

This study was conducted after obtaining ethical approval with reference number: KET-952/UN2.F1/ETIK/PPM.00.02/2024 from the Health Research Ethics Committee of Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine, Universitas Indonesia, and after securing a site permit at Dr. Cipto Mangunkusumo National General Hospital, Jakarta, with official memo number: YR.02.01/D.IX.2.3/877/2024. This study did not involve any interventional procedures. All data used throughout the study were kept confidential.

Data availability

The datasets generated and analyzed during the current study are not publicly available because of privacy and ethical restrictions. The data is available as request to authors.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Registration

This observational study was not registered in any clinical trial registry.

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