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# Platelet/Monocyte Ratio Before Treatment Predicts Prognosis in Solid Childhood Cancers

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**Abstract:** The prognostic value of thrombocytosis and inflammatory biomarkers in adult cancer patients has been the subject of many studies. This study investigated the role of platelet count and other inflammatory biomarkers in the prognosis of solid childhood tumours. The data of 176 pediatric patients diagnosed with solid tumours were evaluated retrospectively; 150 patients still under follow-up were included in the study. We examined the relationship between platelet count, platelet/neutrophil ratio (PNR), platelet/lymphocyte ratio (PLR) and platelet/monocyte ratio (PMR) at the time of diagnosis on survival. The mean age of diagnosis was 7.91 ± 5.75 years, and 60.7% were male. The mean platelet count of the patients was 424.326 ± 167197.32. The median (range) follow-up was 13 (1-68) months. Relapse was seen in 18% of the patients, and 9.3% died. The relationship between PMR and overall survival (OS) and event-free survival times (EFS) was statistically significant (p=0.002 and p=0.016, respectively). However, no statistically significant association was found for PLR or PNR. Overall survival and EFS were significantly poorer in this cohort in patients with high pretreatment PMR.
**Keywords:** Cancer; child; monocyte; mortality; thrombocyte.

## INTRODUCTION

Interactions between platelets and cancer cells are essential in tumour angiogenesis and, therefore, in tumour growth and metastasis (Buergy et al., 2012; Cui et al., 2017; Goubran et al., 2014). Riess et al. reported a relationship between high platelet count and malignant tumours as far back as 1872 (Riess L., 1872). In many recent studies, it has been reported that thrombocytosis at the time of diagnosis is a prognostic indicator in solid tumours of the lung, liver, pancreas, breast, and ovary in adults (Ikeda et al., 2002; Shimada et al., 2004; Suzuki et al., 2004; Lu et al., 2007; Ye et al., 2019).

Oncogenic changes in malignant cells are associated with the inflammatory tumour microenvironment (Crusz et al., 2015). As a result of tissue damage, inflammation is triggered to eliminate dangerous stimuli and initiates regenerative processes (Steinman RM. 2012). Excessive or irregular inflammatory responses increase the risk of metaplasia and cancer (Kundu et al., 2008). Recently, platelet-lymphocyte ratio (PLR) has been reported as a beneficial prognostic factor in tumour types, including lung cancer, colorectal cancer and esophageal cancer in the adult age group (Tan et al., 2016; Yodying et al., 2019; Zhao et al., 2016). Studies of other markers of inflammation, such as platelet/neutrophil ratio (PNR) and platelet/monocyte ratio (PMR), may also be of prognostic value and are of great interest as they can be evaluated with a simple, low-cost complete blood count (CBC).

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Cancer is one of the most important causes of morbidity and mortality worldwide (Siegel et al., 2018). Despite the advances in chemotherapy protocols, diagnostic tools, surgical methods, and supportive care, the survival rates of most solid tumours are still disappointing (Siegel et al., 2018). Therefore, searching for effective and appropriate indicators to predict cancer prognosis is clinically essential (Xia et al., 2015). This study aimed to investigate the prognostic value of a range of blood count-derived biomarkers based on the platelet count in pediatric patients diagnosed with solid tumours. This study showed that high PMR during diagnosis might be a prognostic marker in children with solid tumours. To the best of our knowledge, this is new information for the literature.

## MATERIALS AND METHODS

The hospital ethics committee approved this study of Başakşehir Çam and Sakura City Hospital Ethical Committee. A total of 176 pediatric patients who were diagnosed and treated for solid tumours were retrospectively investigated between August 2021 and April 2022 at the Pediatric Hematology and Oncology Clinic Istambul Turkey.

Data including age, gender, underlying diagnosis, platelet, lymphocyte, neutrophil, and monocyte counts at the time of diagnosis, treatment response rates, relapse/refractory disease, and death were collected and evaluated. Twenty-six (14.8%) of 176 patients were excluded because they were lost to follow-up, and there was no factual information about their survival. Overall survival (OS) was defined as the duration of time from diagnosis until death. Event Free survival (EFS) was defined as the time from diagnosis to treatment failure, relapse, death, or last follow-up. All haematological analyzes assessed for the study were performed within seven days of starting treatment. In particular, platelet, lymphocytes, neutrophils, monocytes counts and platelet-lymphocyte ratio (PLR), platelet/neutrophil ratio (PNR), platelet/monocyte ratio (PMR) at the time of diagnosis of the patients were examined in complete blood count (CBC). Since thrombocytosis is defined as a platelet count between 350000 and 450000/μL in different sources in the literature, the cohort was divided twice for analysis purposes into two sets of two groups based on these differing limits, once using a platelet cut-off of ≥350000/μL and a cut-off of ≥450000/μL (Riesco, 1970 & Riess L., 1872). The OS and EFS of the patients in these groups were compared with platelet count, PLR, PNR and PMR, and the value of these different biomarkers as prognostic indicators was assessed.

Data were analyzed with Statistic Computing Application. Log Rank (Mantel-Cox) test was used to compare total and disease-free survival times according to platelet groups. Risk factors affecting OS and EFS were analyzed by Cox regression analysis. Receiver Operator Curve (ROC) analysis was used to determine the cut-off value for platelet count. The level of statistical significance was set at $p<0.05$.

## RESULTS AND DISCUSSION

The median age of the patients at diagnosis was eight years (range: 0-18 years), and 60.7% were male. The median follow-up period was 13 months (1-68 months). Of the 150 patients included in the study, neuroblastoma, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumour, and Ewing sarcoma were the most common five solid tumours, accounting for 70.6% of all patients. Patient characteristics and underlying diagnoses of the patients are presented in Table 1. The median platelet count of the patients was 421.000/μL (min-max 10.000-1123000/μL). Median counts of leukocyte, thrombocyte, neutrophil, lymphocyte, and monocyte and the values for

hemoglobin and lactate dehydrogenase (LDH) concentrations of the patients at the time of diagnosis are presented in Table 2.

The platelet count of >350000/μL or>450000/μL was not associated with patient mortality that was assessed by ROC analysis (p=0.920). Chemotherapy (CT) treatment was completed in 50.7%, while 9.3% of the patients died. Disease recurrence was observed in 18%. There was no statistically significant difference between OS and EFS when the two groups were compared using a platelet cut-off value of 450000/μL (p=0.367 and p=0.440, respectively) and 350000/μL (p=0.742 and p=0.932, respectively), respectively (Table 3) (Figure 1- 2).

Univariate and multivariate risk factor analysis for OS revealed a significant association between PMR and mortality (p=0.008 and p=0.002, respectively). Platelet-lymphocyte ratio and platelet/neutrophil ratio was not found to be significant. Furthermore, when the risk factors affecting EFS were examined in the univariate and multivariate analysis, the PMR was again significantly associated with EFS (p=0.049 and p=0.016, respectively) (Table 4).

Table 1. Patients Characteristics

| | | |
|---|---|---|
| Age at diagnosis, median, years | 8 (0-18 years) | |
| Follow-up time, median, months | 13 (1-68 months) | |
| | Frequency (n) | Percent (%) |
| Gender | | |
| Female | 59 | 39.3 |
| Male | 91 | 60.7 |
| Underlying Diagnosis | | |
| Neuroblastoma | 30 | 20 |
| Hodgkin Lymphoma | 28 | 18.7 |
| Non-Hodgkin Lymphoma | 17 | 11.3 |
| Wilms tumour | 16 | 10.7 |
| Ewing sarcoma | 15 | 10 |
| Rhabdomyosarcoma | 10 | 6.7 |
| Osteosarcoma | 9 | 6 |
| Langerhans Cell Histiocytosis | 9 | 6 |
| Germ Cell Tumor | 7 | 4.7 |
| Hepatoblastoma | 4 | 2.7 |
| Brain Tumors | 4 | 2 |
| Adrenocortical Carcinoma | 1 | 0.7 |

As far as we know, the effect of the ratio of neutrophil, platelet and monocyte values to lymphocyte count on the prognosis in children with Hodgkin lymphoma has been published only once. Apart from this, there are no studies on this subject in childhood cancers. There is no published study about PMR in tumour progression. Our study found PMR levels to be a statistically significant marker for cancer prognosis (Table 4).

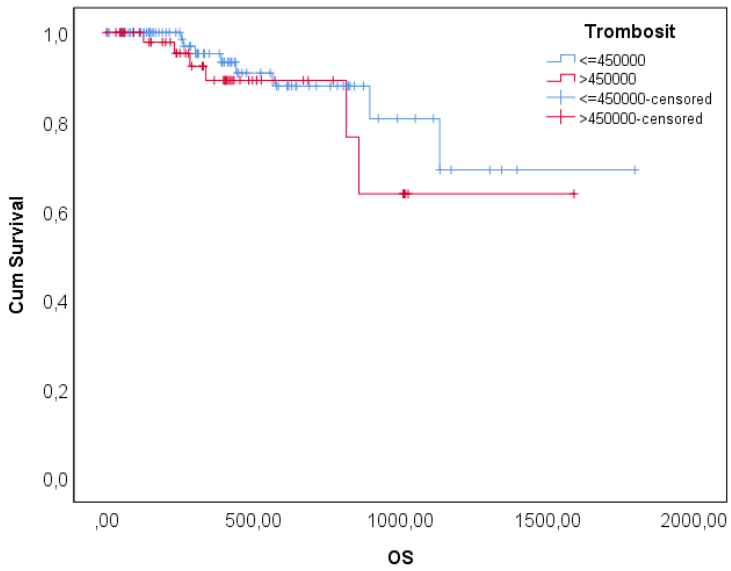
Table 2. Complete Blood Count Variables of the Patients at Diagnosis

| | Median (minimum-maximum) |
|---|---|
| Leukocyte count (x103/µl) | 9660 (1320-33820) |
| Hemoglobin (gr/dl) | 10,85 (6.6–15.7) |
| Platelets count (x103/µl) | 421.000 (10000–1123000) |
| Neutrophil count (x103/µl) | 4730 (120–62020) |
| Lymphocyte count (x103/µl) | 2660 (320-21870) |
| Monocyte count (x103/µl) | 760 (50–7400) |
| Lactate Dehydrogenase (U/l) | 367 (129–6825) |
| PNR | 83.82 (1.28–2116.67) |
| PLR | 148.16 (3.01–1787.5) |
| PMR | 531.34 (2.15–11540) |

Table 3. Comparison of Overall Survival and Event-Free Survival Based on Two Different Cut-Off Values of Thrombocyte Count

| Platelet Count ($x10^3$/µl) | Frequency (%) | **OS** | | **EFS** | |
|---|---|---|---|---|---|
| | | Mean (95% CI) | ***p**** | Mean (95% CI) | ***p**** |
| <=450.000 | 95 (63.3) | 1486.8 (1275.5–1698.1) | **0.367** | 1515.4 (1320.2–1710.7) | **0.440** |
| >450.000 | 55 (36.7) | 1255.2 (1003.6–1506.9) | | 1278.1 (1031.6–1524.6) | |
| <=350.000 | 38 (25.3) | 1190.0 (1019.6–1360.5) | **0.742** | 1185.9 (1006.7–1365.2) | **0.932** |
| >350.000 | 112 (74.7) | 1477.6 (1271.9–1683.2) | | 1530.8 (1360.8–1700.8) | |

*Log-rank test.



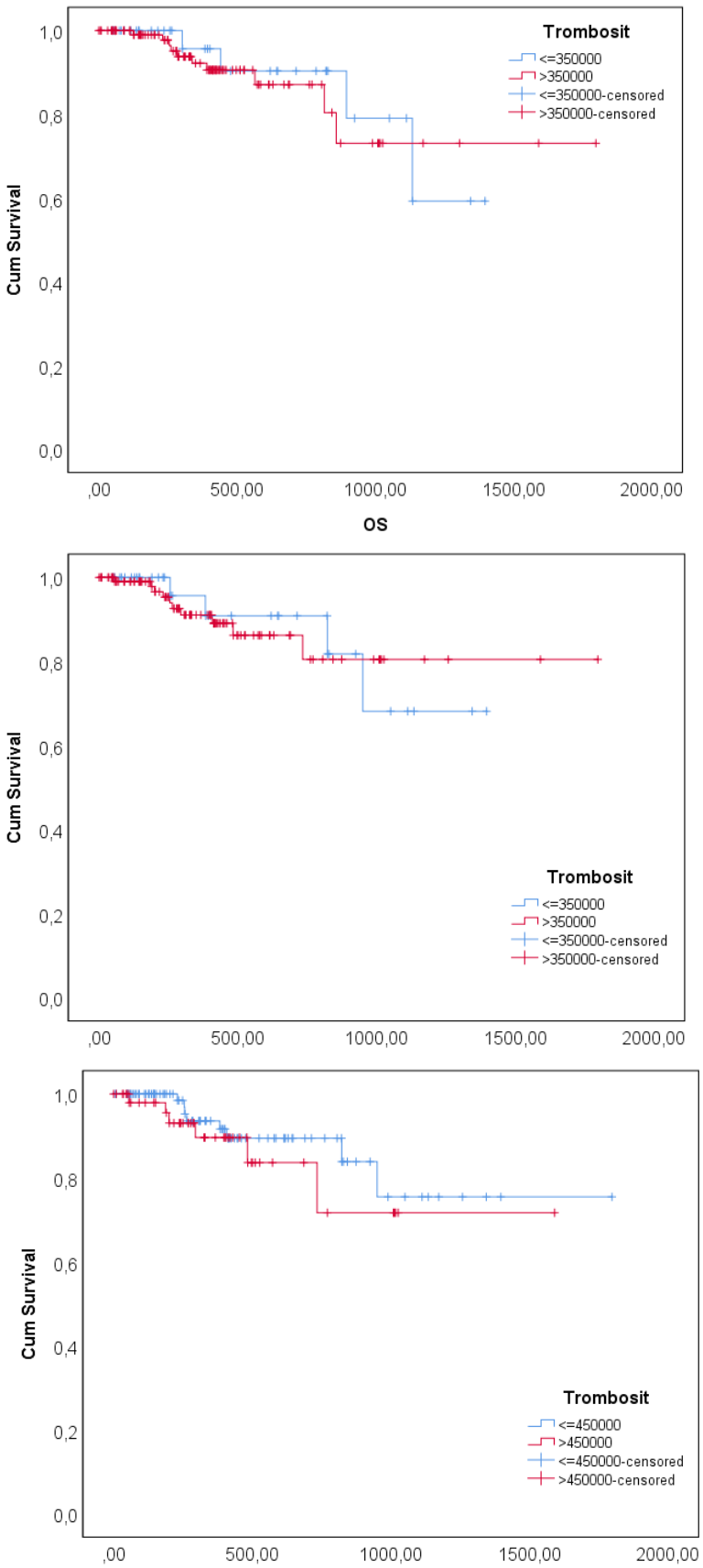



Figure 1. Total Survival Curve (OS) and Event-Free Survival (EFS) Curve for Platelet Counts Below and Above 450.000 and 350.000, Respectively.

Table 4. Examination of Risk Factors Affecting OS and EFS

| | **OS** | | | | **EFS** | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | | Multivariate | | Univariate | | Multivariate | |
| | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *P* |
| Platelet count ≤450000 | 1.63 (0.56-4.75) | 0.372 | | | 1.516 (0.52 – 4.38) | 0.443 | | |
| Platelet count ≤350000 | 1.219 (0.37-3.97) | 0.743 | | | 1.053 (0.32 – 3.41) | 0.932 | | |
| PLR | 1 (0.99 – 1.00) | 0.764 | | | 1 (0.99 – 1.00) | 0.827 | | |
| PMR | 1.008 (1.00 – 1.01) | **0.008** | 1.01 (1.00 – 1.01) | **0.002** | 1.004 (1 – 1.00) | **0.049** | 1.005 (1.00 - 1.00) | **0.016** |
| PNR | 0.999 (0.99 – 1.00) | 0.562 | | | 0.998 (0.99 – 1.00) | 0.508 | | |

Platelets play an essential role in the inflammatory response and may affect the tumour microenvironment, possibly promoting tumour growth (Desai et al., 2018). Tumour cells may secrete interleukin-6 outgrowth, which activates matrix metalloproteinases and platelets, supporting the tumour (Lee et al., 2017; Seizer et al., 2013). In addition, it has been shown that activated platelets can release tumour growth factors through degranulation which acts as a vascular endothelial growth factor that leads to abnormal angiogenesis and thus again promotes tumour growth (Matowicka-Karna et al., 2016). Moreover, platelet-derived growth factor has been confirmed to inhibit the cell-killing effects of natural killer (NK) cells (Peterson et al., 2012).

It is essential to identify prognostic markers for pediatric patients with cancer so that clinical decisions about potential treatments and disease outcomes can be made more quickly. In a study conducted in Canada, the blood counts of 3.3 million people were examined, and 53,339 people with a median age of 59.7 years (range 50.2-67.7 years) with a platelet count higher than 450 × 10-9/L were followed. Cancer incidence was found to be 5.5% and 7.5%, respectively, in the two and 5-year follow-ups of these individuals. It was suggested that individuals with unexplained thrombocytosis should be offered screening for various cancers (Giannakeas et al., 2021). In the study by Giannakeas et al.(2022), high platelet count was associated with poor survival for many types of cancer. These authors suggested that the platelet count could potentially be used as a measure of risk stratification for cancer patients (Giannakeas et al., 2022). In contrast, in the study of Ye et al., pretreatment thrombocytosis (>400x103 platelets/mm3) was a good predictor of overall survival regardless of the clinical stage (Qingjian et al., 2020). However, the data in our study showed that thrombocytosis at the time of diagnosis was not a predictor of cancer prognosis (Figure1).

It has been reported that chronic infection contributes to malignancy by over 15% (Ulich et al., 1987). It is well known that the systemic inflammatory response plays a vital role in tumour angiogenesis. Inflammation is manifested by changes in blood

count parameters, especially the different lines of white blood cells; neutrophils, lymphocytes, monocytes and platelets (Riesco, 1970). Therefore, inflammatory biomarkers are potential prognostic factors. Experimental studies have shown that cancer and inflammatory cells interact to promote angiogenesis, the extracellular matrix for remodelling and preparation of the metastatic niche (Mantovani et al., 2008). In addition, cancer-related inflammation promotes cell proliferation, cell survival, epithelial-mesenchymal transition, and angiogenesis and influences tumour-cell migration, metastasis, and a response to chemotherapy (Mantovani et al., 2008; Condeelis et al., 2006).

Zhang et al. stated that high PLR might be a predictive factor for poor prognosis in non-small cell lung cancer (Zhang et al., 2016). In the study of Li et al., elevated PLR was associated with poor overall survival in urologic cancers (Li et al., 2017). Elevated PLR was also associated with the same outcome in malignant colorectal cancer, breast cancer, and hepatocellular cancer (Huang et al., 2017; Zhang et al., 2017; Ma W et al., 2016). In our study, no such association with prognosis was found, nor was there an association with PNR (Table4). However, well-designed experimental research still needs to explore the mechanism underlying this association.

The limitation of the current study was that PMR was evaluated in several pediatric solid cancers as a whole. Thus it is difficult to conclude the results of our study for specific pediatric cancer. Large-scale studies are needed to investigate the prognostic association of PMR in pediatric cancers and should also be investigated in different tumour types.

## CONCLUSION

The relationship between PMR and overall survival (OS) and event-free survival times (EFS) was statistically significant (p=0.002 and p=0.016, respectively). However, no statistically significant association was found for PLR or PNR. This study has shown that PMR may be useful as a prognostic indicator at the time of diagnosis in pediatric patients with solid tumours.

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## CONFLICT OF INTEREST

The authors declared no potential conflicts of interest concerning this article's research, authorship, and publication.

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