Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2023; 2(5)

Association between Coagulation Profile and Platelet Lymphocyte Ratio with Karnofsky Performance Status Scale In Brain Tumor Patients

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ARTICLE INFO

Article history:
Received
4 April 2023

Accepted
31 May 2023

Manuscript ID:
JSOCMED-040423-25-2

Checked for Plagiarism: Yes

Language Editor:
Rebecca

Editor-Chief:
Prof. Aznan Lelo, PhD

ABSTRACT

Introduction: Patients with tumor usually show abnormal laboratory coagulation tests, indicating a subclinical hypercoagulable state that contributes to morbidity and mortality. Hematologic markers such as the platelet-lymphocyte ratio (PLR) can be used as an index of tumor progression, high PLR is associated with morbidity and mortality in patients with primary or metastatic tumors. KPS is a method that is widely used to assess the functional status of a patient. The aim of this study is to determine the relationship between coagulation profile and platelet-lymphocyte with Karnofsky Performance Status Scale in Brain Tumor Patients.

Method: This study was an observational analytic study with a cross-sectional design using primary data sources taken consecutively from all brain tumor patients who were hospitalized in Inpatient Room at Haji Adam Malik General Hospital Medan who met the inclusion criteria. The parameters analyzed were Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), D dimer (DD), and PLR. Clinical outcome of brain tumor patients was assessed using KPS. To assess the relationship between coagulation marker factors and the ratio of platelets to lymphocytes to KPS, the Spearman and Gamma tests were used.

Results: Of the 30 research subjects analyzed, the number of female subjects was comparable to that of males (50%). The highest age is in the age range of 61-70 years by 30%. The highest level of education was high school at 40%, the most research subjects were housewives at 33.3% and the most types of brain tumors were primary brain tumors at 56.7%. The highest KPS score during treatment was found in the <70 group of 76.7%. From the correlation test, it was found that there was a strong, significant relationship between the values of PT ($p<0.02$ $r = -0.731$), APTT ($p<0.013$ $r = -0.761$), D-dimer ($p<0.001$ $r = -0.737$) and PLR ($p<0.001$ $r = 0.78$) on the clinical outcome of brain tumor patients assessed by KPS.

Conclusion: There is a strong relationship between PT, APTT, D-dimer and PLR values on KPS in patients with brain tumor.

Keywords

Brain tumor, Coagulation profile, Karnofsky performance status scale, Platelet-lymphocyte ratio

How to cite: Salsabila K, Sinurat PPO, Nasution IK. Association between Coagulation Profile and Platelet Lymphocyte Ratio with Karnofsky Performance Status Scale In Brain Tumor Patients. *Journal of Society Medicine*. 2023; 2 (5): 155-163. **DOI: https://doi.org/10.47353/jsocmed.v2i5.50**

INTRODUCTION

Tumors in the central nervous system (CNS) can be found at all ages and are included in the 10 biggest causes of death from systemic malignancies. CNS tumors can originate from cells lining the meninges (meningioma), brain tissue (glioma, neuronal tumor, choroid plexus tumor), from other CNS cells (primary CNS lymphoma), or the result of systemic cancer cell metastases [1].

Globally, the incidence of primary malignant brain tumors is 3.7 per 100,000 for men and 2.6 per 100,000 for women with a higher incidence in developed countries (men, 5.8 and women, 4.1 per 100,000). from developing countries (3.0 men and 2.1 women per 100,000). Worldwide mortality for primary malignant brain tumors is 2.8 for men and 2.0 for women per 100,000 population. The incidence of malignant and benign brain tumors in the United States is 14.8/100,000/year [2]. In Indonesia, data collected by the Department of Neurology at Dr Cipto Mangunkusumo National General Hospital shows that the majority of primary brain tumors are astrocytoma (47%) followed by meningioma (26%) [1]. In the profile of brain tumor patients undergoing treatment at 10 hospitals in North Sumatra, the number of male patients was comparable to that of female patients with almost the same proportion (50.7% : 49.3%) and mean age 51.45 (11 – 87 years) [3].

As many as 50% of primary tumor patients and 90% of metastatic tumor patients will experience coagulation disorders in the form of a prothrombotic state, hypercoagulability of various degrees and compensation. The most common abnormalities are thrombocytosis, increased levels of fibrinogen and fibrinopeptide A [4]. The coagulation system is an important aspect of the unique vascular microenvironment in which primary and metastatic brain tumors continue to develop. Patients with tumor usually show abnormal laboratory coagulation tests, indicating a subclinical hypercoagulable state that contributes to morbidity and mortality [5].

Inflammation has been accepted as a hallmark of tumors. The role of inflammation in the initiation, development and progression of both solid brain tumors such as gliomas and metastatic brain tumors has been demonstrated. Lymphocyte infiltration around the tumor has been associated with a good prognosis, but neutrophil infiltration around the tumor is associated with a poor prognosis. As the tumor progresses, the levels of neutrophils, platelets and monocytes change. Previous studies have shown that preoperative inflammatory markers such as the neutrophil lymphocyte ratio (RNL), lymphocyte monocyte ratio (RLM) or platelet lymphocyte ratio (PLR) can be used as an index of tumor progression [6].

Platelets play an important role in tumor growth. Platelets can promote tumor development by increasing angiogenesis through Vascular Endothelial Growth Factor (VEGF) cytokines. There is a direct correlation between the number of circulating platelets and the serum VEGF level. Tumor cells tend to aggregate to form circulating clumps with homotypic adhesions between the tumor cells themselves and heterotypic adhesions between tumor cells and platelets. Platelet aggregation with tumor cells promotes tumor cells to live longer [7]. In the previous study, high PLR was associated with morbidity and mortality in patients with primary and metastatic tumors, it was also stated that high PLR was associated with the degree and progression of gliomas and predicted a poor prognosis [8].

Various instruments can be used to assess the neurological outcome of cancer patients, one of them is the Karnofsky Performance Status Scale (KPS). KPS is a widely used method for assessing a patient's functional status. The Karnofsky Performance Status Scale describes a patient's functional status in 11 correlation scales with percentage values ranging from 100% (no evidence of disease or symptoms) to 0% (death). In clinical trials KPS is used as a selection criterion and for certification in patient groups as a prognostic factor test in tumor patients and assessing the patient's quality of life [9].

Recently, there has been increasing interest in the host inflammatory response to neoplasms. Inflammatory cells that surround cancer cells play an important role in the patient's prognosis [10]. Haematological biomarkers can potentially stratify patient prognoses and require only blood tests that are inexpensive, simple, and relatively harmless [11]. Based on the description above, the researchers wanted to know the relationship between the Coagulation Profile and the Platelet-Lymphocyte Ratio with the Karnofsky Performance Status Scale in Brain Tumor Patients.

METHOD

This was an observational analytic study with a cross sectional design using primary data sources taken consecutively from all brain tumor patients who were hospitalized in Inpatient Room at Haji Adam Malik General Hospital Medan in August to December 2023 with the aim of finding the association between

coagulation profile and platelet lymphocyte ratio with Karnofsky Performance Status Scale in brain tumor patients.

Subjects who participated in the study were patients who met the inclusion criteria, which are Brain tumor patients based on medical history, physical examination, neurological examination, laboratory examination and CT-scan examination and agreed to participate in this study by signing informed consent. The exclusion criteria in this study were patients with factors that could affect the coagulation profile and lymphocyte level such as the history previous medication with antiplatelet, anticoagulant, injected corticosteroid and chemotherapy, and also some factors that could affect KPS such as patients with metabolic encephalopathy and history of sedative medication.

CT scan examination in this study used X-Ray CT System, Hitachi brand W 450 series. Coagulation profile measured was Prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer levels, also thrombocyte and lymphocyte levels were measured using SYSMEC XN-1000. After the blood sample was taken, clinical outcome was assessed using the KPS score.

Univariate analysis in this study was conducted to analyze the demographic characteristics of subjects. Numerical variables are presented by displaying the mean, standard deviation, median, (minimum-maximum). Bivariate analysis in this study was conducted to analyze the relationship between the research variables, in this case to determine the association between coagulation profile and platelet lymphocyte ratio with Karnofsky Performance Status Scale, the Spearman and Gamma correlation test was used.

RESULT

Characteristics of Study Subjects

Table 1. Characteristics of research subjects

Characteristics	n=30	Percentage (%)
Age, median (min-max)	55,5(18-71)*	
18-20	1	3,3
21-30	4	13,3
31-40	1	3,3
41-50	8	26,7
51-60	6	20,0
61-70	9	30
71-80	1	3,3
Sex		
Male	15	50
Female	15	50
Education		
Elementary School	6	20
Junior High School	3	10
High School	12	40
Bachelor Degree	9	30
Occupation		
Housewife	10	33,3
Farmer	5	16,7
Retiree	5	16,7
Civil Servant	5	16,7
Self-employed	4	13,3
Student	1	3,3
Tumor Type		
Primary	17	56,7
Metastatic	13	43,3
KPS		
<70	23	76,7
≥70	7	23,3

*Data is not normally distributed

Correlation between Coagulation Profile and Karnofsky Performance Status Scale in Brain Tumor Patients. In this study, the coagulation factors assessed were PT, aPTT, D-dimer. The value of each coagulation factor is then grouped into hypocoagulation, normal and hypercoagulation based on its normal value. The PT values were grouped into hypercoagulation (<11 seconds), normal (11-18 seconds) and hypocoagulation (≥18 seconds). From the results of the study, 16 subjects had a shortened PT (53.3%), 13 normal subjects (43.3%) and 1 subject had a prolonged PT (3.3%). Based on the Gamma test, it was found that there was a significant relationship with a p value <0.02 with a negative correlation direction and a strength correlation with r = -0.731. aPTT values were grouped into hypercoagulable (<27 seconds), normal (27-42 seconds) and hypocoagulable (≥42 seconds). Based on the Gamma test, it was found that there was a significant relationship with a p value <0.013 with a negative correlation direction and a strength correlation with r = -0.761. D-dimer values were grouped into normal (<500ng/l), and hypercoagulable (≥500ng/l). From the results of the study, there were 8 subjects with normal D-dimer values (26.7%) and 22 subjects with increased D-dimer values (73.3%). Based on the Spearman test, a significant relationship was obtained with a value of p <0.001 with a negative correlation direction and a strength correlation with r = -0.737. For complete data regarding the relationship between the Coagulation Profile and the Karnofsky Performance Status Scale, it is presented in table 2 below.

Table 2. Correlation between Coagulation Profile and Karnofsky Performance Status Scale in Brain Tumor Patients

Coagulation Marker Factors	KPS		Total (%)	p	r
	≥70	<70			
PT					
Hypercoagulable	1	15	16(53,3%)	0,02*	-0,731*
Normal	6	7	13(43,3%)		
Hypocoagulable	0	1	1(3,3%)		
aPTT					
Hypercoagulable	1	16	17(56,6%)	0,013*	-0,761*
Normal	6	6	12(40%)		
Hypocoagulable	0	1	1(3,3%)		
D-dimer					
Normal	6	2	8(26,7%)	0,001**	-0,737**
Hypercoagulable	1	21	22(73,3%)		

Note: *Gamma test, **Spearman test

Based on table 3, the Platelet-Lymphocyte Ratio in patients with brain tumors in this study was grouped into two categories, namely <200 and ≥200. Based on the Spearman test, a significant relationship was obtained with a value of p <0.001 with a positive correlation direction and a strength correlation with r = 0.78.

Table 3. Correlation Between Platelet-Lymphocyte Ratio with Karnofsky Performance Status Scale in Brain Tumor Patients

Rasio Trombosit-Limfosit	KPS		Total (%)	Nilai p	Nilai r
	≥70	<70			
<200	7	3	10(33,3%)	0,001*	0,78*
≥200	0	20	20(66,7)		

Note: *Spearman test

DISCUSSION

Characteristics of Brain Tumor Patients

Based on demographic data, This study was attended by 30 research subjects who met the inclusion and exclusion criteria, the largest age group of research subjects, namely 61-70 years, as many as 9 subjects (30%) with a median value of 55.5 years, the youngest age was 18 years and the oldest was 71 years. . These results are in line with previous research by Youlpi et al (2021) with an average age of intracranial tumor patients of

50.12 ± 12.7[12] as well as research by Mariska et al (2020) who found an average age of intracranial tumor patients of 51.36 ± 2.85 year [13]. Research by Ritarwan et al (2018) in patients with metastatic brain tumors also found that the average age of the patients was 51.74 ± 11.17 years [14]. When compared with the results of the studies above, it can be seen that the majority of tumor cases occur in the age group > 40 years, so these results are in accordance with the results of other studies where the age factor does have an effect on the incidence of intracranial tumor disease [15].

The number of brain tumor patients in this study was the same for male gender as many as 15 subjects (50%) and women as many as 15 subjects (50%). This is also in line with previous research conducted by Mariska (2020) where the incidence of intracranial tumors was found to be the same between males and females, namely as many as 15 subjects (50%) [13]. In a study conducted by Rambe et al (2013), it was found that there were more brain tumor sufferers in men (60.47%) than women (39.26%) [3].

Previous study by Aninditha et al (2019) said that women have a higher incidence of CNS tumors than men, which may be due to the high incidence of meningioma in women. This is thought to be due to the role of sex hormones in women [9]. Malignant brain tumors such as gliomas, lymphomas, embryonal tumors and germ cell tumors are more common in men. Meningiomas and pituitary tumors, on the other hand, are more common in women [16].

In this study, the highest educational level of brain tumor patients was High School, with 12 subjects (40%). This result is relevant to Youlpi et al (2021) who also found that the education level of the research subjects was mostly high school, which was 35% [12]. Mariska et al (2020) also found that the education level of the most research subjects was high school, which was 56.7% [13]. In a study by Oemiati et al (2011) stated that people with higher education, exposure to information about tumor disease will be greater than people with low education and the need for health services is also increasing [17].

The occupational characteristics of brain tumor patients in this study were mostly housewives with 10 subjects (33.3%). The results of this study are relevant to previous research conducted by Rambe et al (2013) which stated that most of the work of research subjects was housewives as much as 34.7%[3]. Research conducted by Youlpi et al (2021) stated that the most occupations in intracranial tumor patients were housewives with 14 subjects (35%) [12]. Research conducted by Mariska et al (2020) states that the most occupations in intracranial tumor patients are housewives as much as 36.7%[13]. Research by Oemiati et al (2011) reports that employment status is an aspect related to physical activity. Physical activity is necessary to maintain health. Physical activity will reduce the risk of cancer [17].

In this study, the characteristics of the most types of intracranial tumors were primary brain tumors in 17 subjects (52.5%) and metastatic brain tumors in 13 subjects (47.5%). This is relevant to the study of Rambe et al (2013) who reported that subjects with primary brain tumors were 74.7% and secondary brain tumors were 25.3% [3].

In this study, it was found that the patients present with KPS <70 were 23 subjects (76.7%) and KPS >70 were 7 subjects (23.3%). This is relevant to research by Laila et al (2019) where it was found that the majority of subjects had a low performance status, namely KPS <70 during hospitalization, both in primary intracranial tumors (67.7%) and secondary (71.4%) [18].

The KPS value <70 causes a low survival rate [19]. Jang et al (2014) stated that the lower the KPS, the lower the survival rate in patients [20]. In a study by Alexiou et al (2013) reported that glioblastoma patients with KPS values > 80 could be predicted to have better survival [21].

Correlation between Coagulation Profile and Karnofsky Performance Status Scale in Brain Tumor Patients

Based on the Gamma test in this study, it was found that there was a significant relationship between PT and KPS values in intracranial tumor patients with a significance value of p <0.02, thus it could be interpreted that there was an influence of PT values on the clinical outcome of brain tumor patients. From the correlation test, it was found that the direction of the correlation was negative and the correlation strength was

r=-0.731, thus it can be interpreted that there is a strong relationship between the values of PT and KPS in the opposite direction. The higher the PT value, the lower the KPS value.

This study is in line with research by Brockmann et al (2007) on preoperative predictors of patients with glioblastoma, it was found that the PT value significantly affected the survival rate of patients with glioblastoma (p: 0.016) [22]. Research by Navone et al (2019) showed lower PT values in the GBM group compared to the Meningioma group (p<0.01) and the 1-year cumulative survival rate for GBM with PT ≤0.97 was 11% compared to GBM with PT > 0.98, survival was 40% (P < 0.01). In patients with a shortened PT, overall survival is reduced, possibly due to hypercoagulability. The PT test is a test performed to identify extrinsic disorders of the coagulation cascade that begins at the site of the lesion in response to TF (Tumor Factors). At the tumor cell level, aberrant expression of TF is responsible for triggering excessive coagulation with consequent thrombus formation, which will then result in reduced PT in patients with brain tumors, especially in GBM. At the level of human glioma tumor cells, there is high expression of TF and this expression correlates with tumor aggressiveness [23].

In this study, based on the PT value, there were 16 subjects (53.3%) with hypercoagulation. This is in line with research by Wibowo et al (2019) which found that most subjects experienced hypercoagulation (69.4%). Subjects with hypercoagulation had a relative risk (RR) of 3.97 times more prone to dying after 12 months than controls (p=0.009) [24].

Based on the Gamma test in this study, it was found that there was a significant relationship between the aPTT and KPS values in intracranial tumor patients with a significance value of p<0.013, thus it can be interpreted that there is an influence of the aPTT value on the clinical outcome of brain tumor patients. From the correlation test, it was found that the direction of the correlation was negative and the correlation strength was r=-0.761, thus it can be interpreted that there is a strong relationship between the aPTT and KPS values in the opposite direction. The higher the aPTT value, the lower the KPS value.

This study is in line with research by Brockmann et al (2007) on preoperative predictors of patients with glioblastoma, it was found that the aPTT value significantly affected the survival rate of patients with glioblastoma (p: 0.026) [22]. Research by Navone et al (2019) showed lower aPTT values in the GBM group compared to the Meningioma group (p<0.01) and the 1-year cumulative survival rate for GBM with aPTT ≤0.86 was 14% compared to GBM with PT > The surviving 0.87 was 57% (p<0.01). The aPTT test is primarily used to evaluate intrinsic coagulation disorders, which are initiated when contact between blood and extracellular matrix occurs, in particular with collagen macromolecules. In the study of Navone et al (2019) preoperative aPTT was significantly reduced in GBM compared to Meningioma indicating a state of hypercoagulability, possibly due to high plasma coagulation values [23]. In this study, based on the aPTT value, there were 17 subjects (56.6%) with hypercoagulation, which is also in line with research by Wibowo et al (2019) where most of the subjects experienced hypercoagulation (69.4%) [24].

From the results of the study, there were 8 subjects with normal D-dimer values (26.7%) and 22 subjects with increased D-dimer values (73.3%). Based on the Spearman test, the results showed that there was a relationship between the D-dimer value and KPS in intracranial tumor patients with a significance value of p <0.001, thus it could be interpreted that there was an effect of the D-dimer value on the clinical outcome of brain tumor patients. From the correlation test, it was found that the direction of the correlation was negative and the correlation strength was r=-0.737, thus it can be interpreted that there is a strong relationship between the D-dimer and KPS values in the opposite direction. The higher the D-dimer value, the lower the KPS value. This is in line with the research by Wibowo et al (2019) where 66.7% of subjects experienced an increase in D-dimer [24].

Research by Navone et al (2019) in the GBM patient group, D-dimer values (median, 324 ng/mL; IQR, 216-796 ng/mL) were significantly higher compared to the Meningioma group with an average D-dimer level of 165 ng/mL (IQR, 82–206 ng/mL) (p < 0.001). Previous evidence has shown that, in patients with cancer, increased D-dimer values are associated with poor clinical outcomes. High D-dimer levels are prognostic for

an unfavorable clinical outcome in patients with brain tumors leading to reduced overall survival and increased risk of thromboembolic events [24].

In this study, 1 subject (3.33%) was found to be hypocoagulable. There are no studies that examine the relationship between hypocoagulation and KPS values in patients with intracranial tumors. However, based on the research of Sugiyanto et al (2019) the APTT value shows a significant positive relationship with the amount of bleeding (r = 0.428) which is a medium correlation. This is related to the hypothesis of previous studies which stated that large tumors can actually cause a hypocoagulable state that triggers bleeding, one of which is due to disseminated intravascular coagulopathy [25].

Correlation Between Platelet-Lymphocyte Ratio with Karnofsky Performance Status Scale in Brain Tumor Patients

Based on the Spearman test, it is known that there is a relationship between the platelet-lymphocyte ratio value and the KPS value with a significance value of p = 0.001 with a positive correlation direction and the correlation strength is r = 0.78, so it can be said that there is a strong relationship between the platelet-lymphocyte ratio and clinical outcome of brain tumor patients. This is in line with the study of Li et al (2019) where an increase in PLR (platelet-to-lymphocyte ratio, p = 0.003) predicts a poor prognosis in patients with Medullablastoma with an PLR cut-off value of > 147.5 [24]. Research by Karadag et al (2021) found an increase in PLR showed a negative prognostic effect on overall survival in patients with Brain Metastases (p=0.014) [25]. According to Wang et al's research (2018), KPS <70 together with PLR<200 is a parameter significantly to the survival rate of patients with Glioma, with PLR≥ 200 had significantly shorter overall survival than patients with PLR < 200 (p = 0.007) [26].

As platelet-mediated inflammation contributes to cancer progression, several investigators have tested various PLR-based markers in several types of cancer. In glioblastoma patients, platelets induce tumor endothelial cell angiogenesis and VGEF secretion, aiding the progression of glioma. Platelet-derived inflammatory factors contribute to oncogenic transformation and tumorigenesis [26].

The mechanisms underlying the association of high RTL and poor clinical outcome in patients with cancer are poorly understood. Inflammatory cytokines and chemokines can be produced by tumor and host-associated cells such as leukocytes and platelets, contributing to the progression of malignant cells. Although various cytokines are involved in the systemic inflammatory response, IL6 acts to increase the synthesis of acute phase proteins, including CRP, IL6 also stimulates the differentiation of megakaryocytes into platelets and is involved in neutrophil recruitment. Several studies have shown that IL6 can stimulate thrombopoietin production and can cause an increase in platelets in patients with cancer. Furthermore, serum concentrations of IL6 have been shown to be increased in 13 different types of cancer and have been associated with tumor stage and disease progression [8].

LIMITATIONS

This study did not analyze factors such as tumor type, tumor location and comorbidities that influence clinical outcomes in intracranial tumor patients. Other factors such as the type and duration of treatment that affect hemostasis have not been investigated. Age, smoking status, and medication status which affect hemostasis play a role in patient survival have not been analyzed in this study.

CONCLUSION

There is a strong, significant relationship between coagulation profile measured by the values of PT (p<0.02 r = -0.731), APTT (p<0.013 r = -0.761), D-dimer (p<0.001 r = -0.737) and also PLR (p<0.001 r = 0.78) on the clinical outcome of brain tumor patients assessed by KPS.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and H. Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

FUNDING

This research has received no external funding.

COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

None

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