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Differences of Mean Platelet Volume (MPV) value based on clinical stage of undifferentiated type nasopharyngeal carcinoma patient

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is a head and neck malignancy that is endemic in southern China and Southeast Asia, including Indonesia. Biomarkers that are clinically proven in the prognosis of NPC therapy are still less effective. Measurement of the mean platelet volume (MPV) is a simple, inexpensive, useful, easy to apply test without additional costs. Increased MPV value can be a significant biomarker of head and neck malignancies as well as a warning of the risk of thrombosis in malignancy. Objective: to investigate the differences of mean platelet volume (MPV) value based on clinical stage of undifferentiated type nasopharyngeal carcinoma (NPC) patient. Methods: A cross-sectional study with 30 undifferentiated types of NPC patient. The sample was selected by systematic random sampling. The analysis used the ANOVA difference test to determine the difference in MPV values based on the clinical stage of the undifferentiated type of NPC patient. Results: The mean of MPV value was 12.40 with a standard deviation of 1.27. The highest distribution of undifferentiated types NPC patients based on the clinical stage, at stage III and IVA, with 12 patients (40%). The MPV values based on clinical stage in patients with undifferentiated type of NPC is significantly different with p = 0.012. Conclusion: In this study there was a significant difference between the MPV value based on the clinical stage of the undifferentiated type of NPC in ORL-HNS Outpatient, Ngoerah General Hospital with p = 0.012

Keywords: NPC; MPV; Clinical stage; ANOVA; Undifferentiated type

1. Introduction

Head and neck malignancies are diagnosed worldwide every year and are the 8th most common malignancy[1]. Nasopharyngeal carcinoma (NPC) is a head and neck malignancy that is endemic in southern China and Southeast Asia with an incidence of 50 cases per 100,000 people and a low survival rate for sufferers[2].

Although it is the most common malignancy found in the head and neck, biomarkers that are clinically proven in the prognosis of NPC therapy are still less effective[3]. Thus, it is important to identify effective and easily available biomarkers for prognosis NPC patients.

Measurement of the mean platelet volume (MPV) is a simple, inexpensive, useful, easy to apply test without additional costs. In addition, MPV provides information on platelet function and diameter, as well as a good indicator of platelet activation. A high MPV value indicates the presence of large and active platelets in the peripheral blood vessels. These platelets express platelet-derived growth factor (PDGF), thromboxane A2, glycoprotein Ib and IIb/IIIa receptors in excess. The production of these substances, especially PDGF, can increase the occurrence of thrombosis in cancer patients and is associated with the growth rate and invasion of malignant tumors. MPV is reported as a prognostic factor and therapeutic evaluation for several types of cancer[4].

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Increased MPV value can be a significant biomarker of head and neck malignancies as well as a warning of the risk of thrombosis in malignancy. Increased thrombosis in head and neck malignancies has been reported in several studies[5]. Zhang et al. Using MPV as a platelet activation scoring system to evaluate the prognosis of cancer patients, they evaluated the relationship between several clinical variables and overall survival and disease-free survival where it was found that MPV had the best discriminatory ability as lymph node metastasis status. This study proved that MPV biomarkers had prognostic value in 468 esophageal carcinoma patients with histopathological squamous cell type compared to undifferentiated type. In addition, MPV predictive ability is effective in both early stage (TNM I and II) and advanced stage (TNM III and IV) patient groups[6].

2. Material and methods

The research design used in this study was a cross-sectional design by taking retrospective data from the medical records of patients with undifferentiated types of NPC in ORL-HNS outpatient at Ngoerah General Hospital Denpasar. The sample was selected by systematic random sampling with 30 samples. The selected sample met the inclusion criteria, namely NPC patients with undifferentiated types and had performed laboratory supporting examinations, CT-scans and chest radiographs for clinical stage enforcement, with exclusion criteria, namely NPC patients with a history of cardiovascular disease, hematology disease, history of consumption of antiplatelet drugs in the last 3 months, and incomplete medical records.

Patients who met the inclusion and exclusion criteria were included in the study samples and data was recorded. Data recording includes clinical information in the form of name, sex, age, registration number, telephone number, medical history and drug consumption history, clinical stage and MPV value. Data from the results of the examination were recorded in a data collection sheet then tabulated and analyzed.

The data analysis conducted in this study was univariate and bivariate analysis. Univariate analysis aims to describe the characteristics of research subjects and research variables. Variables that are scaled to numeric data are shown as means and standard deviation. Variables that were of a categorical scale were displayed using numbers and percentages (relative frequency). The results of the univariate analysis will be displayed in the form of a single distribution table. The bivariate analysis used the ANOVA difference test to determine the difference in MPV values based on the clinical stage of the undifferentiated type of NPC.

3. Results

In this study, the mean age of NPC patients was 50.70 with a standard deviation of 12.55, the youngest was 20 years old and the oldest was 73 years old. In the age category, the most NPC patients were found to be at the age of more than 50 years, as many as 15 patients or 50%. The proportion of NPC patients based on sex was found more in men, 19 patients (63.3%) and 11 women (36.7%). The mean of MPV value was 12.40 with a standard deviation of 1.27.

In this study, the highest distribution of undifferentiated types NPC patients based on the clinical stage based on AJCC 2018, at stage III and IVA, with 12 patients or 40%, followed by stage II with 4 patients (13.3%) and stage IVB as many as 2 patients (6.7%). The distribution of undifferentiated types of NPC patients based on clinical stage is shown in Table 2.

Table 3 shows the difference in MPV values based on clinical stage in patients with undifferentiated type of NPC. It can be seen that the mean MPV value based on clinical stage is significantly different with $p = 0.012$

Table 1 The characteristics of research subjects

Characteristics	**n = 30**
Age (year)	
Mean ± SD	50.70 ± 12.55
Min – Max	20 – 73
Age category	
<20 years old	1 (3.3%)
21 – 30 years old	0 (0%)
31 – 40 years old	4 (13.3%)
41 – 50 years old	10 (33.3%)
>50 years old	15 (50%)
Sex	
Male	19 (63.3%)
Female	11 (36.7%)
Mean Platelet Volume (MPV)	
Mean ± SD	12.40 ± 1.27
Min – Max	10.51 – 15.40

Table 2 The distribution of undifferentiated type of NPC patients based on clinical stage

Clinical stage	**(n=30) n (%)**
Stage I	0 (0.0%)
Stage II	4 (13.3%)
Stage III	14 (40.0%)
Stage IVA	14 (40.0%)
Stage IVB	2 (6.7%)

Table 3 Differences in MPV values based on clinical stage in patients with undifferentiated type of NPC

Stage	***Mean***	**95% CI**	**p**
Stage II	11.21	7.14 – 15.27	0.012
Stage III	12.00	11.47 – 12.52	
Stage IVA	12.65	11.74 – 13.56	
Stage IVB	13.45	10.93 – 15.96	

4. Discussion

In this study, it was found that the sex of NPC patients with the highest frequency was male as many as 19 people (63.3%). This result is in accordance with previous research conducted at Ngoerah General Hospital[7]. Several studies in various countries also show that there are more male NPC patients than women with an average ratio of 2-3:1[8]. NPC

patients were more often found in men than women reported in almost all studies, this is thought to be related to life and work habits that cause men to be frequently exposed to carcinogens that cause NPC. Exposure to smoke, dust fumes and chemical gases in the workplace increases the risk of NPC 2 – 6 times, while exposure to formaldehyde increases the risk 2 – 4 times[7].

In this study it was also seen that the age distribution of NPC patients with the highest frequency was >50 years as many as 15 people (50.0%), while the lowest frequency was found to be the same in the 21-30 year age group, where there were no patients at that age (0.0%). This finding is in accordance with Earnesty's research in 2018. Although not exactly the same, it is in line with other researchers who get the most NPC patients in the 36-60 year age group[7,9]. The 41-60 year age group is the highest proportion of the population according to the research Puspitasari (2011) at RSUP H. Adam Malik Medan and Pua (2008) in Malaysia. Hasibuan, et al., (2014) also found that the most age group of NPC sufferers was the 41-60 year group. This is because the DNA repair mechanism system that has mutated is not functioning properly and the body's immune system decreases at the age of more than 40 years so that patients with malignancy are more likely to occur in old age[9].

In this study, it was found that the distribution of clinical stage of NPC patients with the highest frequency was at stage III and IV A as many as 14 patients (40.0%), while the lowest frequency was found in the stage I group of 0 patients (0%). This is in accordance with previous research conducted by Danastri (2019) at Ngoerah General Denpasar Hospital. Research conducted by Earnesty (2018) and Hasibuan, et al. (2014) at RSUP H. Adam Malik Medan also got a similar result. Early symptoms of NPC are not typical, similar to an upper respiratory tract infection so that they don't get enough attention from the patient or the examining doctor. In addition, the location of the tumor hidden in the nasopharynx, inadequate equipment, inadequate knowledge, trust in non-medical treatment, fear of seeing a doctor and the patient's weak socio-economic condition often become obstacles in making a diagnosis of this disease. Therefore, early symptoms of NPC are often overlooked and patients are diagnosed after the size of the tumor and enlarged large lymph nodes at an advanced stage so that patients often come for treatment when they are at an advanced stage[9].

In this study, it was found that the mean MPV value of NPC patients before undergoing chemotherapy was 12.40 ± 1.27 fl with the lowest value of 10.51 fl and the highest was 15.40 fl. This is similar to the study by Earnesty (2018) which found that the mean MPV value of NPC patients before undergoing therapy was 10.28 ± 1.24 fl. The results of this study indicate that in NPC patients there was an increase in the MPV value above normal (6.8 - 10.0 fl)[9].

The increase in MPV value in NPC patients reflects an increase in the size of the platelets circulating in the blood. A large platelet size is a marker of high platelet activity, where platelets are known to play a role in facilitating the formation of circulating tumor cells, protecting tumor cells from attacks originating from the host such as immune attack and apoptosis and regulating intravasation/extravasation of circulating tumor cells. Cytokines and receptors derived from platelets are involved in this cascade[10].

In this study it was proven that the mean MPV value in NPC patients increased significantly with the increasing stage of NPC patients before undergoing chemotherapy ($p = 0.012$). It appears that patients with stage IV B have the highest mean MPV value, with 13.45 fl. This finding is in accordance with the research of Earnesty (2018) which found that there were significant differences in mean MPV values between clinical stages of undifferentiated type of NPC. This study obtained the highest mean MPV value in patients with NPC stage IV, namely 10.49 with $p < 0.01$.9

This study found that the mean MPV value in patients with NPC stage IV B (metastasis) was higher than other stages. Metastasis is the leading cause of death from malignancy. During this process, some cancer cells, also known as circulating tumor cells, regardless of the primary location, invade through the surrounding tissue, enter the circulating bloodstream, extravasate and proliferate at the site of metastasis. The presence of circulating tumor cells in malignant patients is associated with a poor prognosis because these cells are able to reach secondary organs before the onset of clinical symptoms. Thrombocytosis is frequently observed in patients with metastatic malignancy, indicating the important role of platelets in metastasis. So that in patients with metastatic NPC, there will be an increase in platelet activity, which is further illustrated by an increase in the MPV value[10].

Sehitoglu et al., (2016) reported that increasing the MPV value is not only important in the process of invasion and recurrence of Kaposi's sarcoma, but also important for therapeutic response. They reported an increase in the MPV value in Kaposi sarcoma patients and the MPV value increased according to the stage, as well as a higher MPV value in Kaposi sarcoma patients who had relapsed. In addition, Keles, et al. (2014) in their study of 104 patients with renal cell carcinoma found an increase in the mean MPV value along with the higher stage of kidney cancer, where the lowest MPV mean value was found at stage I and the highest at stage IV[4].

Evidence of the relationship between MPV value and cancer stage also emerged, such as colon cancer, blood cancer, kidney cancer, liver cancer, stomach cancer, and endometrial cancer. The underlying mechanism is also very clear, whereby the platelet activation process, which is stimulated by inflammatory factors such as IL-6, tends to produce platelets with massive and giant characteristics. Therefore, it can be estimated that the number and volume of platelets will increase compared to more benign disease conditions[6].

Epithelial-mesenchymal transitions, or mesenchymal-epithelial transitions, play an important role in increasing migration capacity, increasing invasion capacity, increasing resistance to apoptosis and increasing production of extracellular matrix components. Lou et al., (2015) showed the expression of proteins related to epithelial-mesenchymal transitions, such as E-cadherin, cytokeratin (CK), vimentin and N-cadherin. Tumor cell-induced platelet aggregation triggers platelets to release alpha granules, which contain TGF-β and platelet-derived growth factor (PDGF) at concentrations several times higher than most cell types. Platelet-derived TGF-β activates the SMADs signaling pathway and the trans-differentiation of circulating tumor cells into mesenchyme-like phenotypes. PDGF is a motor of epithelial-mesenchymal transition that contributes to cancer invasion and angiogenesis. In addition, TGF-β was shown to increase the expression of PDGF and PDGF receptors through β-catenin activation and signal transducer and activator of transcription 3 (STAT3)[10].

This research is important because most people with NPC often experience an increase in MPV levels, which indicates the presence of large and reactive platelets in peripheral blood vessels, which causes an increase in the number of prothrombic factors and their accumulation, which are known to cause microvascular and macrovascular pathologies in malignancies[3]. MPV value correlates with the characteristics of malignant patients where high MPV values express PDGF, thromboxane A2, excessive glycoprotein Ib and IIb / IIIa receptors which can increase the occurrence of thrombosis and growth rate and invasion of malignant tumors, markers of angiogenesis, metastasis and proteolysis in the process of malignant inflammation and be a prognostic factor[4,11]. In addition, the measurement of the MPV value is a simple, inexpensive, useful, easy to apply test, without additional costs, so it is hoped that the MPV value is also used as a predictor of prognosis and therapeutic success biomarkers in patients with undifferentiated types of NPC.

Earnesty (2018) found that the MPV value in NPC patients was found to be more increased in the male sex group, amounting to 137 patients compared to the female sex group[9]. The prevalence of NPC tends to be more prevalent in males than females due to the pattern and lifestyle as well as environmental factors towards carcinogenic exposure which is more dominant in males. In many studies it has been proven that the MPV value in NPC patients is found to be the most increased in the age group> 50 years. Verdoia et al., (2015) found that advancing age was directly related to greater mean platelet volume, but did not contribute to explaining the higher prevalence and rates of coronary artery disease in elderly patients[9].

Meikle et al. (2016) suggested that platelets facilitate cancer development and metastasis by: (1) forming aggregates with tumor cells; (2) induces tumor growth, epithelial-mesenchymal transition and invasion; (3) protects circulating tumor cells from the immune system; (4) facilitates the withdrawal and capture of circulating tumor cells; and (5) inducing angiogenesis and distant tumor cell formation. Platelets activated by tumor cells also predispose cancer patients to thrombotic events. Tumor cells and microparticles originating from tumors cause thrombosis by secreting procoagulant factors, resulting in platelet activation and clotting[12].

Platelets contain both angiogenic and angiostatic factors, where the transition to the angiogenesis phenotype can be triggered by metastatic tumor cells. Tumor cells can function indirectly by binding to von Willebrand factor (vWF) to initiate platelet aggregation, then releasing vascular endothelial growth factor (VEGF), one of the strongest positive regulators of angiogenesis. Protease-activated receptor-1 (PAR-1) ligation can also trigger the release of alpha granules containing VEGF. Conversely, activation of PAR-4 upregulates the secretion of endostatin, an angiogenesis inhibitor derived from platelets[10].

In the literature, MPV is reported as a prognostic factor for several types of cancer[4]. MPV can be used as a marker of angiogenesis in patients with malignancy because of the role of platelets as angiogenic, metastatic and proteolytic in the inflammatory process of malignancy. Tumor cells release procoagulants, fibrinolytic factors, mediators, proteases, cytokines, which have a direct effect on platelet production and activation and directly interact with thrombosis through adhesion molecules[13,14].

Several diseases that affect the platelet count can cause disturbances in platelet volume and function. As platelet reproduction increases, MPV, which is a significant hemostatic physiological variable, also increases. A number of platelets become reactive, causing an increase in the number of prothrombic factors and their easy accumulation. This process is also known to cause microvascular and macrovascular pathologies[3].

Many studies have been conducted to investigate the possible relationship between platelet analysis to several types of disease[3]. Inagaki et al. (2014) stated that the MPV value correlates with the characteristics of patients with various disorders, including malignant tumors[11].

It is well known that the term Trousseau syndrome is used to describe the thromboembolic manifestations that occur in cancer patients. These include venous and arterial thrombosis, nonbacterial thrombotic endocarditis, microangiopathic thrombosis and veno-occlusive disease. Deep vein thrombosis of the lower extremities is the most frequent clinical manifestation followed by deep vein thrombosis of the upper limb, pulmonary embolism, cerebral sinus thrombosis and displaced superficial thrombophlebitis. Large prospective and retrospective population studies show the incidence of venous thromboembolism varies from 0.6% -7.8%[15].

Another clinical manifestation is microangiopathic thrombosis which is a heterogeneous group of diseases characterized by microangiopathic hemolytic anemia, peripheral blood thrombocytopenia and various degrees of organ failure. This group of diseases has been reported in cancers that received certain chemotherapy such as mitomicin, gemsitabin and recently reported on targeted therapies such as monoclonal antibodies and tyrosine kinase inhibitors[16,17].

Veno-occlusive disease is found in severe liver disease characterized by intrahepatic small central venule obstruction by microthrombi and fibrin buildup and is reported in about 50% - 60% of bone marrow transplant patients. Risk factors for this are liver damage, high doses of chemotherapy drugs, abdominal radiation, female sex and differences in human leukocyte antigens. In addition, thrombosis can be an early clinical sign of an undiagnosed cancer. Patients with idiopathic venous thromboembolism have 4-7 times the risk of being diagnosed with cancer within 1 year of known thrombosis. The risk of being diagnosed with cancer in this group is greater if there is recurrent and bilateral venous thromboembolism[17].

In addition to the clinical manifestations of thrombosis, cancer patients can also find bleeding manifestations. In cancer patients, bleeding disorders are an important cause of mortality, up to 10% in solid tumors and higher in haematological malignancies. Underlying causes of thrombocytopenia, reduced synthesis of coagulation factors due to chronic liver disease or vitamin K deficiency, oral anticoagulants, pre-existing mild coagulation factor disorders, congenital von Willebrand disease, erosion of blood vessel walls, disseminated intravascular coagulation and less frequently disturbances hereditary coagulation factors[17].

The imbalance of the coagulation system in cancer patients is very complex involving various factors, both clinical and biological factors. Clinical risk factors for venous thromboembolism can be grouped into patient-related factors, cancer-related factors and therapy-related risk factors. Old age, African-American race, presence of comorbids (infection, kidney disease, lung disease, obesity, according to the Charlson comorbidity index) have a higher risk. Primary sites for tumors of the brain, pancreas, stomach, kidney, ovaries and lungs are at high risk. Patients with hematological malignancies such as lymphoma and myeloma have a high risk as well. The risk of venous thromboembolism is high in the first 3 months after diagnosis. From the aspect of cancer therapy will increase the risk of venous thromboembolism. Cancer patients who underwent surgery had a two times higher risk of developing postoperative venous thromboembolism than non-cancer patients. This risk persists for more than 7 weeks postoperatively. Use of systemic chemotherapy is associated with a 2-6 times increased risk compared to the general population. Antiangiogenesis group chemotherapy therapy, especially thalidomide and lenalidomide, has a higher risk when combined with dexamethasone or other chemotherapy. The chemotherapy regimen containing bevacizumab increases the risk of arterial thromboembolism. This also applies to sunitinib and sorafenib[15].

Increased MPV value can be a significant biomarker of head and neck malignancies as well as a warning of the risk of thrombosis in malignancy. The incidence of thrombosis in head and neck malignancies has been reported in several studies[5,18].

Several diseases and management such as cardiovascular disease, malignancy, myeloproliferative conditions, splenectomy, rheumatoid arthritis, erythropoietin therapy and thyrotoxicosis are known to cause an increase in MPV values, whereas idiopathic purpuric thrombocytopenia, some types of leukemia, aplastic anemia, pernicious anemia, hypersplenism, thrombocytopenia massive blood pressure, infectious diseases and bone marrow hypoplasia are known to cause a decrease in MPV values[3].

Eryilmaz, Basal and Omurlu (2015) reported an increase in MPV values in head and neck malignancies compared to the control group[19]. Baldane et al. (2015) reported an increase in MPV values in patients with papillary carcinoma of the

thyroid compared to patients with benign goiter and control groups and in their study they also had a decrease in MPV values after surgery[20].

Cihan and Baykan (2015) found a statistically significant difference in mean MPV. An increase in MPV values was found in patients with skin cancer types of basal cell carcinoma and squamous cell carcinoma compared to healthy controls and statistically significant[3]. Osada et al. reported that MPV is an accurate diagnostic parameter in patients with neoplastic disease, especially gastric cancer. Aksoy et al. observed that higher MPV values were predictive of bone marrow metastatics in patients with solid tumors[3].

Ulutas and Sarici (2016) suggest that an increase in the MPV value in a group of patients newly diagnosed with pancreatic cancer is a reflection of an ongoing inflammatory process and can be associated with increased levels of cytokines, especially IL-6, so that the MPV value can be used to detect pancreatic cancer[21]. Several reports have shown that increased MPV values are associated with the prognosis of various cancers. Cho et al. reported that patients with hepatocellular carcinoma had a higher MPV value than the control group. In addition, Kemal et al. found that patients with epithelial ovarian cancer had a significant increase in MPV values compared to the control group. Osada et al., Also found that patients with gastric cancer had a higher MPV value than the control group[22].

5. Conclusion

In this study there was a significant difference between the MPV value based on the clinical stage of the undifferentiated type of NPC in ORL-HNS Outpatient, Ngoerah General Hospital with p = 0.012

Compliance with ethical standards

Statement of ethical approval

The research received ethical clearance from the Ngoerah Hospital. The approval date is May 28th, 2020, with number 1119/UN14.2.2.VII.14/LT/2020

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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