**Research**

# Correlation of changes in mean platelet volume with clinical stage of undifferentiated nasopharyngeal carcinoma

**I Gede Wahyu Adi Raditya*, I Ketut Suanda**, Jessica Filbertine****
*Department of Otorhinolaryngology – Head and Neck Surgery, Faculty of Medicine, Udayana University/ Udayana University Hospital, Bali
**Department of Otorhinolaryngology – Head and Neck Surgery, Faculty of Medicine, Udayana University/ Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali

## ABSTRACT

**Background:** The mean platelet volume (MPV) is known to serve as a platelet activation assessment system for cancer prognosis evaluation. However, its role in nasopharyngeal carcinoma (NPC) has not been studied. **Purpose:** To determine the correlation between MPV changes and stage progression, in undifferentiated-type NPC. **Method:** A retrospective cross-sectional study was conducted in Ear, Nose, Throat-Head and Neck Surgery (ENT-HNS) clinic of Sanglah General Hospital, Denpasar, from May to June 2020. Patients with undifferentiated-type NPC meeting inclusion and exclusion criteria were included. The mean MPV values were determined by calculating the difference in MPV from complete blood count tests after six chemotherapy sessions, compared to before chemotherapy. Changes in NPC staging were assessed using TNM classification pre- and post-chemotherapy. Logistic regression analysis was performed to examine the correlation between MPV changes and clinical stage changes, considering the confounding factors. **Result:** A total of 30 subjects were participated in this study, with mean age of 50.70±12.55 years. A significant correlation was observed between MPV changes and changes in clinical stages T ($p=0.021$, $r=0.419$), N ($p=0.025$, $r=0.408$), and M ($p=0.048$, $r=0.364$). Linear regression analysis showed a significant correlation between MPV changes and clinical stage T ($p<0.001$, $r=0.268$), clinical stage N ($p=0.042$, $r=0.039$), and clinical stage M ($p=0.003$, $r=0.059$) after adjusting for age and sex as confounding factors. **Conclusion:** There was a significant correlation between changes in MPV and clinical stage progression (T, N, M), in patients with undifferentiated-type nasopharyngeal carcinoma.

**Keywords:** nasopharyngeal carcinoma, mean platelet volume, staging, prognosis

## *ABSTRAK*

***Latar belakang:*** *Nilai* mean platelet volume (MPV) *diketahui dapat menjadi suatu sistem penilaian aktivasi platelet untuk evaluasi prognosis kanker. Akan tetapi, penilaiannya dalam kanker nasofaring belum pernah diteliti.* ***Tujuan:*** *Meneliti hubungan perubahan nilai* MPV *dengan perubahan stadium karsinoma nasofaring (KNF) tipe tidak berdiferensiasi.* ***Metode:*** *Studi retrospektif dengan desain potong-lintang ini dilakukan di poliklinik Telinga Hidung Tenggorok-Bedah Kepala Leher, Rumah Sakit Sanglah, Denpasar, pada Mei-Juni 2020. Subjek adalah pasien dengan KNF tipe tidak berdiferensiasi, yang memenuhi kriteria inklusi dan eksklusi. Nilai rerata* MPV *diambil dengan menghitung selisih nilai MPV pada pemeriksaan darah lengkap, setelah kemoterapi 6 kali dan sebelum menjalani kemoterapi. Perubahan stadium KNF dinilai dengan klasifikasi TNM sebelum dan sesudah kemoterapi. Dilakukan analisis uji regresi logistik untuk mengetahui hubungan perubahan nilai MPV dan perubahan stadium klinis, dengan mempertimbangkan faktor perancu.* ***Hasil:*** *Didapatkan total 30 subjek dalam studi ini. Rerata usia dalam studi ini adalah 50,70±12,55 tahun. Terdapat hubungan signifikan antara perubahan nilai MPV dengan perubahan stadium klinis T ($p=0,021$, $r=0,419$), N ($p=0,025$, $r=0,408$), dan M ($p=0,048$, $r=0,364$). Uji regresi linear menunjukkan bahwa terdapat korelasi antara perubahan nilai MPV dengan stadium klinis T ($p<0,001$, $r=0,268$), dengan stadium klinis N ($p=0,042$, $r=0,039$), dan dengan stadium klinis M ($p=0,003$, $r=0,059$) setelah pertimbangan faktor perancu umur dan jenis kelamin.* ***Kesimpulan:*** *Terdapat hubungan bermakna antara perubahan nilai MPV dengan perubahan stadium klinis T, N, dan M pada pasien dengan karsinoma nasofaring tipe tidak berdiferensiasi.*

***Kata kunci:*** *karsinoma nasofaring,* mean platelet volume*,* staging*, prognosis*

**Correspondence address:** I Gede Wahyu Adi Raditya. Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Udayana University/ Udayana University Hospital, Bali, Indonesia. Email: dr.wahyuraditya@gmail.com

## INTRODUCTION

Head and neck malignancies rank as the 8th most diagnosed cancers worldwide.[1] Nasopharyngeal carcinoma (NPC) is an endemic malignancy in Southern China and Southeast Asia, with an incidence of 50 cases per 100,000 people, and low survival rates. The Tumor, Nodes and Metastasis (TNM) classification by the American Joint Committee on Cancer (AJCC) is the most widely used staging system for NPC, and serves as a prognosis predictor. However, clinical outcomes vary widely among patients with the same stage and treatment strategy, suggesting the staging system may not fully reflect the biological heterogeneity of NPC.[2]

Despite its prevalence, clinically proven biomarkers for NPC prognosis and treatment evaluation remain insufficient.[3] Identifying an effective and accessible biomarker is crucial for NPC prognosis and therapy evaluation.

Mean platelet volume (MPV) measurement is a simple, low-cost, and practical test that provides insights into platelet function and size, and serves as a marker of platelet activation. Platelets express excess platelet-derived growth factor (PDGF), thromboxane A2, and glycoprotein Ib and IIb/IIIa receptors. These substances, particularly PDGF, promote thrombosis in cancer patients, and correlate with tumor growth and invasion. MPV has been reported as a prognostic factor and a tool for therapy evaluation in several cancers.[4]

Studies such as Zhang et al.[5] demonstrated MPV's potential as a platelet activation marker for cancer prognosis, showing its discriminative ability for lymph node metastasis. Another study by Earnesty et al.[6] reported a positive correlation between MPV and clinical stage in NPC patients, though this was limited to pre-treatment patients. Thus, the potential of MPV as a predictor of prognosis and treatment evaluation for NPC remains unexplored.

Therefore, this study aimed to evaluate the correlation between MPV changes and clinical stage progression in undifferentiated-type NPC.

## METHOD

This retrospective cross-sectional study was conducted at the ENT clinic of Prof. Dr. I.G.N.G. Ngoerah Hospital Denpasar, a type-A Tertiary Hospital, from January 2023 –December 2024, using secondary data from medical records. Systematic random sampling was used to select patients with undifferentiated-type NPC who had undergone six cycles of chemotherapy and have undergone laboratory support examinations, CT scan and chest X-ray in preparation for radiotherapy. Exclusion criteria included cardiovascular or hematologic diseases, antiplatelet use within the last three months, concomitant chemoradiotherapy, supportive examination less than three months post-chemotherapy, or incomplete data.

There were 103 NPC patients who had undergone 6 cycles of chemotherapy from January 2023-December 2024. After applying the inclusion and exclusion criteria, 87 patients remained. Random sampling was conducted using the formula with n as the minimum number of subjects, α as the type I error set at 5%, then $Z\alpha=1.96$, β as the type II error set at 20%, then $Z\beta=0.842$ and r as

the correlation coefficient value. The number 0.5 is used because there had been no similar research before. Based on these calculations, a minimum sample was 29.02≈30 samples.

$$n = \left[\frac{(Z_\alpha + Z_\beta)}{0.5ln[(1+r)/(1-r)]}\right]^2 + 3$$

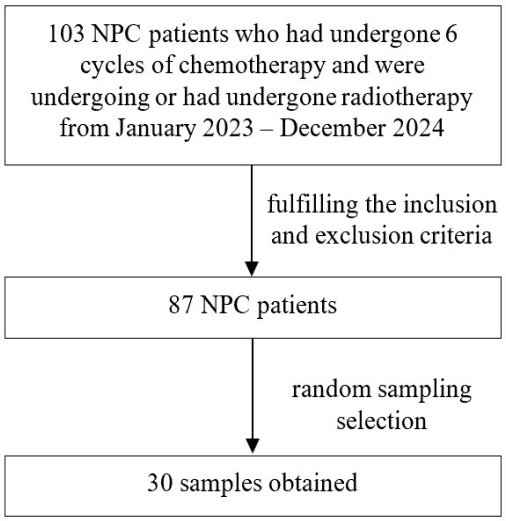


**Figure 1. Sample selection**

Data collected included demographics, MPV values, NPC clinical stage progression, histopathological type, medical history, and antiplatelet drug use. MPV changes were calculated as the difference between MPV values pre- and post-chemotherapy. TNM classification was an ordinal data, used to assess stage progression pre- and post-chemotherapy. Measurement using CT scan results and other supporting examinations, so that clinical stages T (T0-T4), N (N0-N3) and M (M0-M1) were obtained.

Univariate analysis described subject characteristics. Data on changes in T, N and M stages were displayed on a categorical scale, while changes in MPV values were displayed on a numeric scale and data normality tests were performed to determine data distribution. Data normality tests were performed using the Kolmogorov-Smirnoff test, and obtained a p value of 0.239 (p>0.05) which indicated that all data were normally distributed. Therefore, a Pearson correlation test was performed to determine the correlation between changes in clinical stages T, N and M with changes in MPV values. Logistic regression assessed the correlation between MPV changes and TNM stage progression, considering confounding factors such as age and sex. Data analysis was performed using SPSS version 21.0.

## RESULT

A total of 30 subjects with a mean age of 50.70±12.55 years were included. The majority were aged over 50 years (50%), and in stages III and IVA (40%). Table 1 showed the characteristics data.

MPV values pre-chemotherapy averaged 12.40±1.27, post-chemotherapy 8.35±2.46, with an average MPV change of 4.03±2.80. Significant differences in MPV values were noted across clinical stages (p=0.012).

**Table 1. Characteristics of the subjects**

| Characteristics | n = 30 |
|---|---|
| Age (year) | |
| Mean ± SD | 50.70±12.55 |
| Min – Max | 20-73 |
| Age group | |
| <20 year-old | 1 (3.3%) |
| 21-30 year-old | 0 (0%) |
| 31-40 year-old | 4 (13.3%) |
| 41-50 year-old | 10 (33.3%) |
| >50 year-old | 15 (50%) |
| Gender | |
| Male | 19 (63.3%) |
| Female | 11 (36.7%) |
| Clinical Staging | |
| Stage I | 0 (0.0%) |
| Stage II | 4 (13.3%) |
| Stage III | 12 (40.0%) |
| Stage IVA | 12 (40.0%) |
| Stage IVB | 2 (6.7%) |

**Table 2. The correlation between MPV changes and TNM clinical staging**

| The correlation between MPV changes and TNM clinical staging | r (correlation coefficient) | p-value |
|---|---|---|
| T changes | 0.419 | 0.021* |
| N changes | 0.408 | 0.025* |
| M changes | 0.364 | 0.048* |

*Pearson test, statistically significant.

**Table 3. Multivariate analysis showing the correlation between MPV changes**

| Variable | B | 95% CI | p-value |
|---|---|---|---|
| Stage T | 0.268 | 0.143-0.393 | <0.001* |
| Stage N | 0.039 | 0.059-0.138 | 0.042* |
| Stage M | 0.059 | 0.022-0.096 | 0.003* |

Table 2 showed the correlation between MPV changes and TNM progression. The Pearson correlation test was used after the Kolmogorov-Smirnoff test showed normally distributed data (p>0.05). A significant correlation was found between changes in MPV values and changes in clinical stages T and N, with correlation coefficients (r) of 0.419 and 0.408, and p-values of 0.021 and 0.025, respectively. These results indicated a moderate positive correlation that was statistically significant. For clinical stage M, a weak but significant positive correlation was observed (p=0.048; r=0.364). Figures 1, 2, and 3 below displayed scatter plots for changes in stages T, N, and M, respectively.

Table 3 showed the results of a multivariate analysis using linear regression to evaluate the correlation between MPV changes and clinical stage progression. The analysis revealed significant correlation between MPV changes and clinical stages T (p<0.001, r=0.268), N (p=0.042, r=0.039), and M (p=0.003, r=0.059).

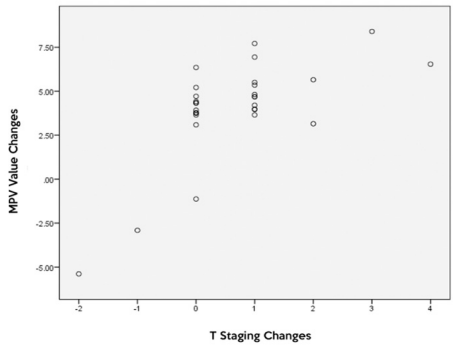


**Figure 2. Scatter plot for MPV changes and T staging changes. Showing T staging changes on the x-axis and MPV value changes on the y-axis**

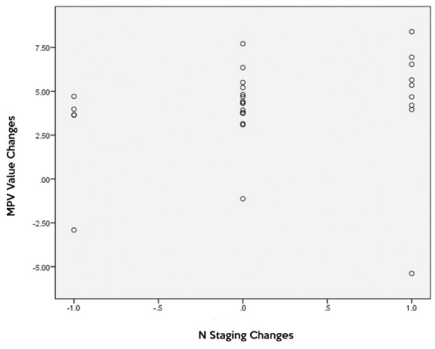


**Figure 3. Scatter plot for MPV changes and N staging changes. Showing N staging changes on the x-axis and MPV value changes on the y-axis**

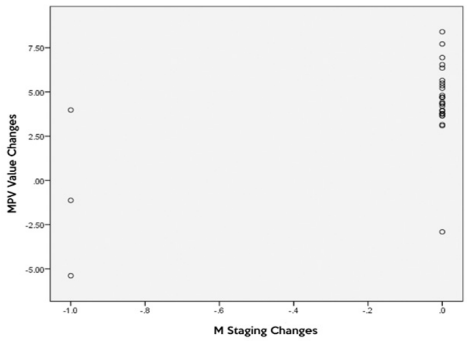


**Figure 4. Scatter plot for MPV changes and M staging changes. Showing M staging changes on the x-axis and MPV value changes on the y-axis**

## DISCUSSION

In this study, it was found that the most common gender among NPC (nasopharyngeal carcinoma) patients was male, accounting for 19 cases (63.3%). Studies in various countries have similarly shown that NPC was more prevalent in males than females, with an average ratio of 2–3:1.[7]

The age distribution of NPC patients in this study showed that the highest frequency was in the >50 years age group, with 15 patients (50.0%). This finding aligned with Earnesty's study, which found the highest incidence of NPC in the 36–60 years age group.[6]

The mean MPV (mean platelet volume) of NPC patients before undergoing chemotherapy in this study was 12.40±1.27 fl, comparable to Earnesty's findings, which reported a mean MPV of 10.28±1.24 fl before therapy. This study demonstrated an elevated MPV above normal levels (6.8–10.0 fl) in NPC patients. Furthermore, a significant increase in MPV levels was observed with advancing clinical stages of NPC prior to chemotherapy (p=0.012).[6] Stage IVB NPC patients had the highest mean MPV of 13.45 fl, consistent with Earnesty's findings showing significant differences in mean MPV among clinical stages of undifferentiated NPC.[6]

This study revealed a moderate positive correlation between changes in MPV values and changes in clinical stages T and N, and a weak positive correlation with changes in clinical stage M. These findings indicated that changes in MPV values, whether increasing or decreasing, reflected changes in the size and invasion of the primary tumor, as well as lymph node size, and invasion in undifferentiated NPC patients. No prior studies had evaluated the correlation between changes in MPV values and clinical stage progression in NPC. Most existing studies focused on differences in MPV levels across clinical stages before chemotherapy. A study by Sehitoglu et al.[4] on other cancer types reported that increased MPV levels played a role not only in invasion and recurrence in Kaposi's sarcoma, but also in therapy response. They observed elevated MPV levels in Kaposi's sarcoma patients, with higher levels corresponding to more advanced stages and recurrence. Similarly, Keles et al. quoted by Sehitoglu et al.[4], found that mean MPV levels increased with higher stages of renal cell carcinoma, with the lowest levels in stage I and the highest in stage IV.

Multivariate analysis in this study showed that, even after adjusting for confounding variables, there was a significant correlation between changes in MPV values and changes in clinical stages T, N, and M. No similar studies had performed linear regression analyses to assess these correlations in undifferentiated NPC patients. Existing studies had explored MPV changes in other cancers. Baldane et al.[8] reported elevated MPV levels in papillary thyroid carcinoma patients compared to benign goiter patients and controls, with MPV levels decreasing postoperatively. Cihan et al.[3] found elevated MPV levels in basal cell carcinoma and squamous cell carcinoma patients compared to controls. Ulutas et al.[9] and Yilmas et al.[10] suggested that increased MPV levels in newly diagnosed pancreatic cancer patients reflected

ongoing inflammation and may correlate with elevated cytokine levels, particularly IL-6, supporting MPV as a marker for pancreatic cancer detection.

This study underscored the importance of elevated MPV levels in NPC patients, which indicated larger and more reactive platelets in peripheral vessels, contributing to increased prothrombotic factors and micro- and macrovascular pathologies associated with malignancy.[3] High MPV values correlated with characteristics of malignancy, such as excessive expression of PDGF, thromboxane A2, glycoprotein receptors Ib and IIb/IIIa, which promoted thrombosis, tumor growth, invasion, angiogenesis, metastasis, and proteolysis during malignant inflammation, making MPV a prognostic marker.[4,11]

This study had limitations due to secondary data derived from medical records. The cross- sectional design assessing NPC staging prior to radiotherapy resulted in limited and homogenous changes in clinical stages T, N, and M, as radiotherapy was the primary treatment modality for NPC. This led to less variability in the data, and narrower stage progression. Future studies should utilize primary data to reduce bias, and to adopt a cohort design to evaluate clinical stage progression and MPV changes after radiotherapy for continuous observation.

In conclusion, there was a significant correlation between changes in MPV values and changes in clinical stages T, N, and M in undifferentiated NPC patients.

## ACKNOWLEDGEMENT

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