Can Platelet and Leukocyte Indicators Give Us an Idea about Distant Metastasis in Nasopharyngeal Cancer?

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Abstract: This study aimes to evaluate platelet and leucocyte indicators, such as the mean platelet volume, platelet distribution width, plateletcrit, white blood cell count, neutrophil to lymphocyte ratio in nasopharyngeal cancer patients and also to evaluate the relationship between these indicators and nasopharyngeal cancer with distant metastasis. The medical records of 118 patients diagnosed with nasopharyngeal cancer in our hospital between January 2006 and August 2015 were reviewed. The nasopharyngeal cancer group was further sub grouped according to the presence or absence of distant metastasis and TNM (tumour – T, node – N, metastasis – M) classification. A control group consisted of 120 healthy patients. The platelet and leucocyte values at the time of the initial diagnosis were recorded. Neutrophil to lymphocyte ratio and platelet distribution width values were significantly higher in the nasopharyngeal cancer group. But only platelet distribution width values were significantly higher in the nasopharyngeal cancer group with distant metastasis compared to the nasopharyngeal cancer group without distant metastasis. Neutrophil to lymphocyte ratio and platelet distribution width values may increase in nasopharyngeal cancer. But only the platelet distribution width values may give us an idea about the distant metastasis in nasopharyngeal cancer.

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Introduction

Nasopharyngeal cancer (NPC) is associated with a particular ethnic and geographic distribution. The incidence rates of NPC have a distinct distribution (Breda et al., 2010). Although its prevalence is quite low (1/100 000), in some endemic areas, such as Southern China, it can be higher, with a prevalence of 80/100 000 (Breda et al., 2010). Its epidemiology, clinical signs, biological markers, carcinogenic risk factors, and prognostic factors are different from those of other head and neck cancers (Adham et al., 2012). Currently, the primary treatment is radiotherapy. However, residue tumours resistant to radiotherapy and distant metastasis have proved to be significant factors that limit the success of the treatment (Chang et al., 2013).

The use of hematologic parameters shed light on the prognosis and it becomes popular recently for both NPC and cancers of other regions (Chang et al., 2013; Eryilmaz et al., 2015). The platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) are the main parameters used to show platelet function. White blood cell (WBC), neutrophil and lymphocyte counts, in addition to the neutrophil to lymphocyte ratio (NLR), are frequently used parameters of leucocyte values (Gao et al., 2013; Eryilmaz et al., 2015; Karateke et al., 2015; Luo et al., 2015).

The MPV provides information only on the average platelet size in blood. It cannot be used to infer microscopic changes in platelet size. The coefficient of variation in the mean platelet volume is used to calculate the PDW. A high PDW signifies unusually high changes in the MPV and can denote high platelet production and destruction. Some automated haematology analysers utilize the MPV and number of platelets to calculate the PTC. The PTC is then used to evaluate the mass of the platelets, an analogy of haematocrit, which usually indicates the red cell mass. The platelet mass is responsible for platelet plaque formation rather than platelet. PCT can provide additional information for a better evaluation of primary hemostasis in the presence of high MPV values (Mahdavi-Zafarghandi et al., 2014; Schwartz et al., 2014).

Leucocytes are one of the clearest indicators of inflammation and tissue injury. The NLR is obtained by calculating the average of the absolute neutrophil count and absolute lymphocyte count in blood (Kum et al., 2014). An increase in this ratio is an important indicator of elevated systemic inflammation. Previous research reported that a high NLR value was a poor prognostic factor in various cancers (Kum et al., 2014).

In recent years, platelet and leucocyte indicators, apart from their use as inflammatory, thromboembolic, cerebrovascular, and cardiac disease markers, have been employed as markers of inflammation and prognosis in some cancers (Muscari et al., 2009; Yüksel et al., 2009; Berger et al., 2010; Braekkan et al., 2010; Chang et al., 2013).

The aim of this study was to evaluate platelet and leucocyte indicators, such as the MPV, PDW, PTC, PLT, WBC, and NLR, in NPC patients and then analyse the relationship between these parameters and NPC with distant metastasis.

Material and Methods

This study was carried out retrospectively and was approved by the Ethical Committee and Intuitional Review Board of Necmettin Erbakan University Faculty of Medicine (no. 2016-503).

The medical records of 118 patients diagnosed with NPC in our hospital between January 2006 and August 2015 were retrospectively reviewed. Patients with hypertension, diabetes mellitus, autoimmune disease or chronic infection, heart failure, acute chronic infection, other known malignancies, myeloproliferative disorders, hepatorenal disorders, and patients taking anticoagulation medication were excluded from the study.

The study consisted of two groups: an NPC group (n=118) and a healthy control group (n=120). The NPC patient group was further subdivided according to the presence or absence of distant metastasis and clinical staging. In the NPC group, 94 (79.6%) patients did not have distant metastasis, and 24 (20.4%) had distant metastasis. When they were classified according to the TNM (tumour – T, node – N, metastasis – M) stage, 75 (63.5%) were stage 3 and 4 (advanced stage), and 43 (36.5%) were stage 1 and 2 (early stage). Thirty-three patients who met the exclusion criteria and 14 patients with missing data were not included in the study.

The medical records were reviewed, and data on NPC, with or without distant metastasis, TNM stage, and platelet and leucocyte values at the time of the initial diagnosis were recorded. The hematologic values were measured in our laboratory within the first 20 min after venous puncture (bloods keep in potassium EDTA tubes) and then analysed using Sysmex XP-300 (Sysmex Corporation, Japan). MPV, PDW, platelet count, PCT, WBC, neutrophil and lymphocyte count, NLR was included as hemogram parameters in the present study.

Statistical analysis

The SPSS 13.0 program (USA) was used for the statistical analysis of the data. In the descriptive statistics, the average ± standard deviation and percentage distribution were used. In the analysis of categorical variables, a chi-square test was used. In the analysis of continuous variables with a normal distribution, a *t*-test and Mann-Whitney U test were used. The ROC curve was used to calculate the PDW cut-offs and specificity and sensitivity values. A value of $P<0.05$ was accepted as statistically significant.

Results

The study consisted of 118 NPC cases. Of those, 90 (76.3%) were males, and 28 (23.7%) were females. The average age in this group was 49.22 (18–70). The

Table 1 – Demographic features and hematologic parameters of nasopharyngeal cancer and control groups

Features	Nasopharyngeal cancer group (n=118) (mean ± SD)	Control group (n=120) (mean ± SD)	P-value
Age (year)	49.22 ± 14.5	50 ± 9.2	0.790
Sex (male %/female %)	76.3/23.7	73.3/26.7	0.761
Mean platelet volume (fL)	7.72 ± 1.44	10.27 ± 1.15	0.001
Platelet count	233.656 ± 67.951	248.233 ± 48.885	0.299
Platelet distribution width 10 (GSD)	26.381 ± 14.000	14.020 ± 2.330	0.001
Plateletcrit (%)	0.523 ± 0.790	0.824 ± 0.950	0.126
White blood cell (10^3/µl)	6.762 ± 2.630	6.763 ± 1.475	0.999
Lymphocyte count	1.421 ± 0.778	2.213 ± 0.480	0.001
Neutrophil count	4.534 ± 2.278	3.870 ± 1.058	0.134
Neutrophil/lymphocyte ratio	4.293 ± 3.320	1.793 ± 0.500	0.001

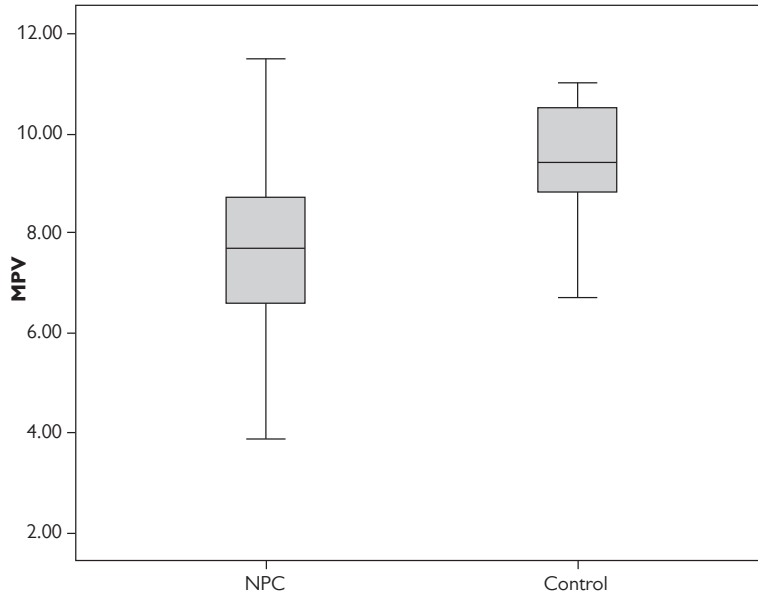

Figure 1 – Median MPV (mean platelet volume) values in nasopharyngeal cancer and control groups.

healthy control group (n=60) included 88 (73.3%) males and 32 (26.7%) females. The average age was 50 (18–80). There was no statistically significant difference in the age and sex of the two groups. The demographic data and hematologic parameters of both groups are shown in Table 1.

The MPV, lymphocyte number, PDW, and NLR values of the NPC and control groups were significantly different (P<0.05). The MPV and lymphocyte counts

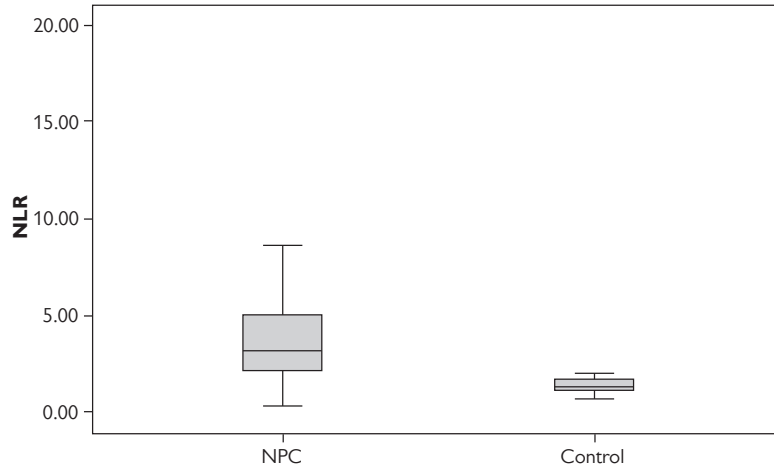

Figure 2 – Median NLR (neutrophil to lymphocyte ratio) values in nasopharyngeal cancer and control groups.

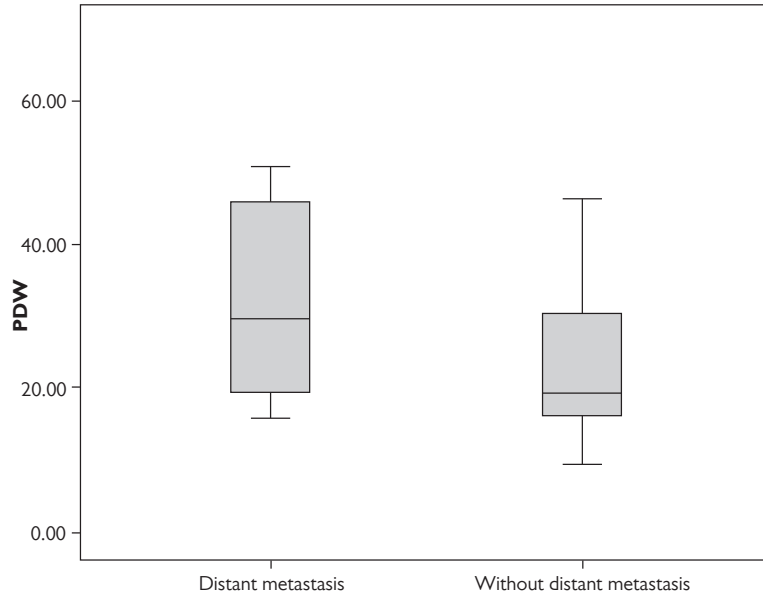

Figure 3 – Median PDW (platelet distribution width) values in nasopharyngeal cancer groups with and without distant metastasis.

in the control group were significantly higher than NPC group, whereas the PDW and NLR in the NPC group were significantly higher than control group (Figures 1 and 2). The PDW value was significantly higher in the NPC group with distant metastasis compared to the NPC group without distant metastasis ($P<0.05$; Figure 3). With regard to the other blood parameters tested, there were

Table 2 – Demographic features and hematologic parameters of nasopharyngeal cancer groups with and without distant metastasis

Features	NPC with distant metastasis (n=24) (mean ± SD)	NPC without distant metastasis (n=94) (mean ± SD)	P-value
Age (year)	46.27 ± 17.939	49.6 ± 12.143	0.224
Sex (male %/female %)	66.7/33.3	78.7/21.3	0.768
Mean platelet volume (fL)	7.587 ± 1.010	7.575 ± 1.324	0.451
Platelet count	266.1 ± 64.347	236.7 ± 65.637	0.142
Platelet distribution width 10 (GSD)	31.87 ± 15.138	25.619 ± 14.265	0.042
Plateletcrit (%)	0.202 ± 0.680	0.586 ± 0.861	0.796
White blood cell (10^3/µl)	7.598 ± 3.052	6.939 ± 2.774	0.480
Lymphocyte count	1.335 ± 0.695	1.551 ± 0.886	0.142
Neutrophil count	5.544 ± 2.446	4.630 ± 2.394	0.318
Neutrophil/lymphocyte ratio	4.819 ± 2.358	4.362 ± 3.911	0.309

NPC – nasopharyngeal cancer

Table 3 – Demographic features and hematologic parameters of early and late stage nasopharyngeal cancer groups

Features	Early stage 1–2 NPC (n=34) (mean ± SD)	Late stage 3–4 NPC (n=84) (mean ± SD)	P-value
Age (year)	44.28 ± 18.935	46.5 ± 11.173	0.221
Sex (male %/female %)	64.4/35.6	71.7/28.3	0.809
Mean platelet volume (fL)	7.805 ± 1.866	7.685 ± 1.254	0.164
Platelet count	243.235 ± 75.449	231.233 ± 65.277	0.570
Platelet distribution width 10 (GSD)	2 6.911 ± 14.958	14.958 ± 13.776	0.855
Plateletcrit (%)	0.323 ± 0.580	0.651 ± 0.853	0.156
White blood cell (10^3/µl)	7.024 ± 3.452	6.994 ± 2.675	0.094
Lymphocyte count	1.262 ± 0.604	1.485 ± 0.863	0.259
Neutrophil count	3.999 ± 1.551	4.750 ± 2.554	0.169
Neutrophil/lymphocyte ratio	4.103 ± 2.731	4.372 ± 3.574	0.782

NPC – nasopharyngeal cancer

no significant differences between the NPC groups, with and without distant metastasis. Table 2 shows the significant and no significant parameters in the NPC groups, with and without distant metastasis. There were no statistically significant differences in any of the parameters in the early-versus advanced-stage NPC groups (Table 3). The cut-off value of PDW was 19.95 10(GSD) (76% sensitivity and 78% specificity).

Discussion

Current studies done on MPV have revealed that MPV is high in some groups of cancer and it is considered as a negative prognostic factor (Gu et al., 2015). The size of platelets is associated with their function. Large platelets contain more granules and respond faster to endogenous and exogenous stimuli, eventually leading to thrombosis and tumour progression. Previous studies revealed that the MPV was increased in some types of cancers, such as hepatocellular carcinoma, colon cancer, gastric cancer, pancreatic cancer, and non small cell lung cancer (Karaman et al., 2011; Kurt et al., 2012; Matowicka-Karna et al., 2013; Inagaki et al., 2014; Li et al., 2014). Research also showed that increased platelet count in NPC was associated with a poor prognosis (Chen et al., 2015). In the present study, the MPV values of the NPC group and control group differed, with higher values recorded in the latter. In contrast, there was no difference in the MPV values in the NPC group, according to the presence or absence of distant metastasis. Even though studies analysing the relationship between MPV and the other types of cancer have been done we still have little information about the relationship between NPC and MPV.

Many studies have analysed the relationship between the MPV and cancer (Aksoy et al., 2008; Kumagai et al., 2015; Oncel et al., 2015). One study reported a considerable decrease in the MPV values in some types of cancer (Oncel et al., 2015). Others reported that a significant decrease in the MPV was associated with bone marrow metastasis and increased cell death in advanced-stage cancer (Aksoy et al., 2008; Kumagai et al., 2015). However, there have not been any studies on the relationship between the MPV and NPC. In the present study, there were 24 NPC patients with distant metastasis. Eight of these patients showed bone marrow involvement on radiographic imaging. However, there was no statistically significant difference between those with distant metastasis and those without distant metastasis in the NPC group. In the NPC group (n=118), 75 patients had advanced-stage disease (TNM classification; stage 3/4). However, there was no statistically significant difference in the MPV of the early- versus advanced-stage patients.

A decrease in the MPV plays a key role in the relationship between coagulation and cancer (Thomas et al., 2009). Recent studies have shown that P-selection, a tissue factor activator, produced by tumorous tissues can cause thrombus formation of platelets in the systemic circulation (Falanga et al., 2009; Thomas et al., 2009). Furthermore, studies demonstrated that tumour necrosis factor alpha, interleukin 1 beta, vascular endothelial growth factor, and basic fibroblast growth factors released from various cells stimulated the formation of vascular endothelial thrombus and increased the destruction of larger sized platelets (Mutlu et al., 2013). Another study suggested that increased thrombotic activity in metastatic colon cancer led to a decrease in the MPV (Mutlu et al., 2012). MPV values of cancer patients were found to be lower, compared to control group in our study. There may be some possible reasons for the lower MPV values of cancer patients.

The lower MPV of NPC patients in our study may have been due to increased thrombotic activity. Other reasons, variability of MPV values in cancer patients may be due to different study methods used and effects of EDTA on the results (Dundar et al., 2008). In addition, since one of the factors affecting the value of MPV is the time of analysis, the value of MPV can vary because this variable is not taken into account in retrospective studies (Vagdatli et al., 2010). Consequently, MPV values may vary depending on above reasons. Therefore, MPV values in this study may not give us an idea about distant metastasis.

The PDW is the standard deviation of the logarithmic transformation of platelet data. An increased value of PDW signifies the presence of platelets, both large and small, in the circulation, with consequent thrombocyte destruction (Alsweedan et al., 2008). In healthy individuals, MPV and PDW values are counterbalancing each other. But previous studies of the MPV and PDW showed that this collateral distribution could change in various types of cancer (Okuturlar et al., 2015; Ozaksit et al., 2015). For example, a study of lung cancer patients reported that the MPV was lower and that the PDW was higher (Oncel et al., 2015), similarly to that what was found in the present study. Also, other studies found no statistically significant differences between the PDW value in neoplastic adnexal mass and breast cancer and PDW values in a control group (Ma et al., 2014; Okuturlar et al., 2015). The PDW value in non small cell lung cancer was reported to be lower than that of a control group (Inagaki et al., 2014). These findings contradict those in the current study. Interestingly, in the present study, the PDW value of both NPC groups (with and without distant metastasis) was significantly higher than that of the healthy control group. Thus, PDW value may give us an idea about the distant metastasis in nasopharyngeal cancer.

Inflammation develops in response to tumoral development, resulting in increased angiogenesis, DNA injury and increased cell proliferation. This facilitates tumoral growth and the development of resistance to apoptosis (Jaiswal et al., 2000; Kacan et al., 2014; Kum et al., 2014). The NLR is a well-known marker of inflammation. Recent studies stressed that an elevated NLR increased the risk of recurrence and distant metastasis and that it was therefore associated with a poor prognosis in head, neck, and thyroid cancers (Lang et al., 2014; Haddad et al., 2015; Salim et al., 2015). A previous study suggested that an increased NLR indicated an increased risk of metastasis in NPC (Jin et al., 2015). Another study indicated that an elevated NLR before treatment in NPC patients negatively affected their prognosis (He et al., 2012). The results of these studies partly contradict those of the present study. In the current study, although the NLR value of the NPC group and control group was significantly different, the NLR value of the NPC group with distant metastasis and advanced-stage disease was not significantly different from that of the NPC group without distant metastasis and early-stage disease. Distant metastases have a negative effect on the prognosis. However, in the present study, there was no significant increase in the NLR of the NPC group with distant metastasis and

advanced-stage disease. Consequently, the NLR values may increase in NPC but may not give us an idea about the distant metastasis.

The limited parts of our study are that the number of cases is low and the PDW has less than 80% of specificity and sensitivity.

Conclusion

NLR and PDW values may increase in NPC, but only the PDW may give us an idea in terms of distant metastasis. A study with a larger patient population is required to elucidate the relationship between platelet and leucocyte indicators and NPC and also to determine whether these markers are effective in determining distant metastasis.

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