Cancer Management and Research

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ORIGINAL RESEARCH

Combined Use of Mean Platelet Volume/Platelet Count Ratio and Platelet Distribution Width to Distinguish Between Patients with Nasopharyngeal Carcinoma, Those with Benign Tumors of the Nasopharynx, and Healthy Subjects

This article was published in the following Dove Press journal:
Cancer Management and Research

Xuan Zhang
Yuan-yuan Qin
Min Chen
Yang-yang Wu
Fa-quan Lin

Department of Clinical Laboratory, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, People's Republic of China

Purpose: For the diagnosis of nasopharyngeal carcinoma (NPC), reliable early indicators with sensitivity and specificity should be sought. This study evaluated the effect of the combined use of mean platelet volume/platelet count ratio (MPV/PC ratio) and platelet distribution width (PDW) for differential diagnosis of NPC. In this study, MPV/PC ratio was used for the first time to diagnostically evaluate NPC.

Patients and methods: We retrospectively analyzed various hematological indices of three subject groups (208, 185, and 162 patients with NPC, benign tumors of the nasopharynx, and healthy subjects, respectively) and evaluated the value of combined use of MPV/PC ratio and PDW for differential diagnosis of the three groups using the one-way analysis of variance.

Results: Comparison of laboratory variables between the three groups showed a significant difference in MPV/PC ratio and PDW ($P<0.001$, all). The MPV/PC ratio in the NPC group was significantly lower than the other two groups ($P<0.001$); MPV/PC ratio also showed a statistically significant difference in different stages ($P=0.034$) and serosal invasions ($P<0.001$) of the NPC group. Receiver operating characteristic curve (ROC) analysis showed that areas under the curve (AUC) of either patients with benign tumors of the nasopharynx ($AUC_{MPV/PCratio+PDW}$: 0.708) or healthy subjects ($AUC_{MPV/PCratio+PDW}$: 0.909) were larger than those of MPV/PC ratio ($AUC_{MPV/PCratio}$: 0.665, 0.869, respectively) and PDW (AUC_{PDW}:0.614, 0.716, respectively) use alone ($P<0.05$, all).

Conclusion: MPV/PC ratio and PDW may be used as indexes of NPC. MPV/PC ratio combined with PDW could be considered as meaningful laboratory indexes for differential diagnosis of NPC, benign tumors of the nasopharynx, and healthy subjects. This finding could enhance the detection of NPC.

Keywords: mean platelet volume/platelet count ratio, platelet distribution width, nasopharyngeal carcinoma

Correspondence: Fa-quan Lin
Department of Clinical Laboratory, The First Affiliated Hospital of Guangxi Medical University, No.6 Shuang Yong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, People's Republic of China
Tel +86 13877118318
Email fqlin1998@163.com

Introduction

Although cancer-related mortality has declined since the 1990s, it still remains a significant cause of death.[1] Nasopharyngeal carcinoma (NPC) is a common head and neck malignant tumor, and a poorly differentiated carcinoma of the nasopharyngeal mucosa. NPC has an incidence rate of approximately 1 in 100,000 individuals, with ethnic and geographical variations, and is relatively common in East and Southeast

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http://doi.org/10.2147/CMAR.S226050

Asia.[2] It also has a high incidence in southern China, accounting for 15–18% of malignant tumors.[3] There are approximately 60,000 new cases, and more than half die every year in China.[4] One of the causes of death is metastasis of the cancer.

It was reported that 90% of patients had lymph node metastasis when NPC was first diagnosed; of these, 5–10% already had distant metastasis.[5] Therefore, most patients with NPC already show middle and advanced stages of the disease when NPC diagnosis was confirmed. As a result, it is essential to identify early diagnostic indicators with reliable sensitivity and specificity. Platelets are the smallest cells in the blood and are a key source of circulating angiogenesis-related proteins. Platelets accelerate the growth and metastasis of tumor cells by regulating tumor cell growth and angiogenesis.[6] It is reported that thrombocytopenia is closely related to the progression of ovarian cancer[7] and gastrointestinal cancer,[8] which may be the mechanism by which platelets participate in the regulation of cancer-associated inflammation. Mean platelet volume/platelet count ratio (MPV/PC ratio) and platelet distribution width (PDW) as platelet-related index have the advantage of ease of collection, low cost, and high repeatability, and are associated with the prognosis of laryngeal cancer, colorectal cancer, and breast cancer.[9–11] Therefore, we intended to explore the value of MPV/PC ratio and PDW to distinguish between patients with NPC, those with benign tumors of the nasopharynx, and healthy subjects.

Materials and Methods

Patients

The data of patients who were initially diagnosed with NPC by postoperative pathology from January 2012 to February 2019 in the First Affiliated Hospital of Guangxi Medical University, China, were retrospectively analyzed. The following were the exclusion criteria: patients who (1) underwent treatment for NPC; (2) had other malignancies; (3) had infection; (4) had cardiovascular disease, hypertension, and diabetes mellitus; (5) had blood disease and anemia; or (6) were using antiplatelet drugs. All patients were clinically staged in accordance with the seventh edition of the American Joint Committee on Cancer (AJCC)/TNM tumor stage. Patients initially pathological diagnosed with benign tumors of the nasopharynx in our hospital during the same period as well as healthy subjects were included. There was no statistically significant difference in sex and age between the three groups (P=0.999, P=0.402, respectively). The Ethics Committee of the first Affiliated Hospital of Guangxi Medical University approved the study.

Methods

Preoperative hematology was performed at the initial diagnosis of patients with NPC and those with benign tumors of the nasopharynx by postoperative pathology. Fasting venous blood was collected from healthy subjects, in ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes in the morning. All the blood parameters were tested using Beckman Coulter LH780 hematology analyzer (Beckman Coulter, Brea, CA, USA), including white blood cells (WBC), platelets (PLT), mean platelet volume (MPV), neutrophils (N), lymphocytes (L), monocytes (M), PDW, and red blood cells (RBC). MPV/PC ratio was calculated from the mean platelet volume and the platelet count. The instrument has been quality controlled prior to sample testing. Quality control uses the Westgard multi-rule quality control method. When the two quality control values are within the limits of X±2S, they are judged to be in control.

There are 208, 185, and 162 patients with NPC, benign tumors of the nasopharynx, and healthy subjects, respectively. A total of 191 males and 17 females were included in the NPC group. According to the seventh edition of the AJCC/TNM tumor stage, there were 43 cases of stage I, 47 cases of stage II, 108 cases of stage III, and 10 cases of stage IV. According to the degree of serosal infiltration, there were 62 cases of T_1+T_2 and 146 cases of T_3+T_4. In accordance with the degree of lymph node metastasis, 90 cases were N0 and 118 cases were N1–N3. In the light of the situation of distant metastasis, M_0 was 198 cases and M_1 was 10 cases. The diagnosis of nasopharyngeal carcinoma and benign tumors of the nasopharynx was confirmed by postoperative pathology.

Statistical Analysis

In this study, data were analyzed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). Hematological indices were presented as mean±standard deviation (SD), and categorical data were presented as number or rate. The Chi-square test was used to compare the rates. Graphs were drawn using GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA). Differences in blood parameters between the three groups (patients with NPC, those with benign tumors of the nasopharynx, and healthy subjects) were analyzed using one-way analysis of variance (ANOVA). Differences in blood parameters were carried out to compare the three groups in pairs, using

Tukey's test. Mann–Whitney *U*-test and Kruskal–Wallis rank sum test were used to assess the difference in blood parameters between pathological stages. MedCalc version 15.0 (MedCalc Software, Mariakerke, Belgium) was used to draw the ROC curve, in order to assess the sensitivity, specificity, optimal cutoff values as well as the area under the ROC curves of MPV/PC ratio in combined with PDW. $P<0.05$ was considered statistically significant.

Results

Comparison of laboratory variables between the three groups (patients with NPC, patients with benign tumors of the nasopharynx, and healthy subjects) showed a significant difference in MPV/PC ratio ($P<0.001$, Figure 1A) and PDW ($P<0.001$, Figure 1B). The MPV/PC ratio in the NPC group was significantly lower compared to those with benign tumors of the nasopharynx or healthy subjects. The PDW among patients with benign tumors of the nasopharynx was significantly lower than in the other two groups (NPC group vs. benign tumor group, $P<0.001$; NPC group vs. healthy subjects group, $P<0.001$; benign tumors of the nasopharynx group vs. healthy subjects group, $P<0.001$). The data from the three groups are summarized in Table 1.

The characteristics of the clinicopathologic staging of MPV/PC ratio and PDW in 208 patients with NPC are shown in Table 2. MPV/PC ratio showed statistically significant difference in different stages ($P=0.034$, Figure 2A), and serosal invasion between the T_1+T_2 and T_3+T_4 groups ($P<0.001$, Figure 2B), and in no difference was observed with PDW. Moreover, the value of MPV/PC ratio declined from early to late stages; on the contrary, the value of PDW increased in the late stage (Table 2).

The data of correlation analysis of laboratory variables of 208 patients with nasopharyngeal carcinoma were presented in Table 3. Correlation analysis demonstrated that MPV/PC ratio was positively correlated with MPV ($P<0.001$, r=0.572), and negatively correlated with WBC ($P<0.001$, r=−0.317), M ($P=0.005$, r=−0.196), N ($P<0.001$, r=−0.345), PLT ($P<0.001$, r=−0.842), and serosal invasion ($P<0.001$, r=−0.288); PDW was negatively correlated with MPV ($P<0.001$, r=−0.505).

In ROC curve analysis, the AUC was between 0.5 and 1; and AUC between 0.5 and 0.7; between 0.7 and 0.9; and above 0.9, showed low, certain, and high accuracy, respectively. To distinguish between NPC and benign tumors of the nasopharynx, combined use of MPV/PC ratio and PDW ($AUC_{MPV/PC\ ratio+PDW}$:0.708, 95% confidence

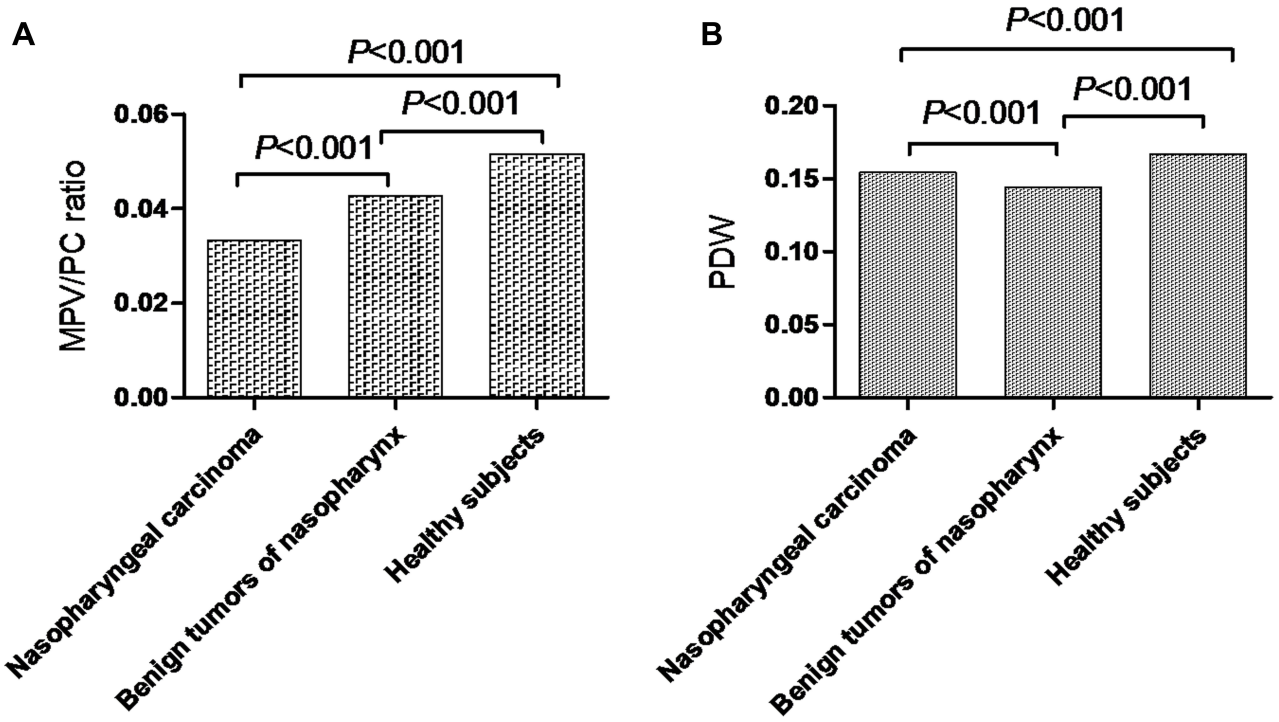

Figure 1 (**A**) MPV/PC ratio in patients with NPC, those with benign tumors of the nasopharynx, and healthy subjects. (**B**) PDW in patients with NPC, those with benign tumors of the nasopharynx, and healthy subjects.

Abbreviations: MPV/PC ratio, mean platelet volume/platelet count ratio; PDW, platelet distribution width; NPC, nasopharyngeal carcinoma.

Table 1 Comparison of Demographics and Laboratory Variables Between Patients with Nasopharyngeal Carcinoma, Those with Benign Tumors of Nasopharynx, and Healthy Subjects

Variables	Nasopharyngeal Carcinoma Group	Benign Tumors of Nasopharynx Group	Healthy Subjects Group	*P* Value
Number	208	185	162	
Sex (Male: Female)	191:17	170:15	149:13	0.999
Age (years)	54.57±11.03	53.03±12.09	53.94±10.73[c]	0.402
WBC (10^9/L)	8.22±3.09[a]	7.09±1.91[b]	6.46±1.16[c]	<0.001
RBC (10^{12}/L)	4.61±0.58[a]	4.84±0.66[b]	4.97±0.08[c]	<0.001
M (10^9/L)	0.74±0.31[a]	0.63±0.27[b]	0.45±0.10[c]	<0.001
L (10^9/L)	1.94±0.85[a]	2.35±0.72[b]	2.13±0.47[c]	<0.001
N (10^9/L)	5.21±2.61[a]	3.82±1.54[b]	3.62±0.92	<0.001
PLT (10^9/L)	275.33±75.55[a]	240.98±60.66[b]	195.83±34.70[c]	<0.001
MPV (fl)	8.42±1.21[a]	9.32±1.59[b]	9.74±0.73[c]	<0.001
MPV/PC ratio	0.0333±0.0116[a]	0.0427±0.0236[b]	0.0516±0.0116[c]	<0.001
PDW	0.1541±0.0214[a]	0.1441±0.0297[b]	0.1669±0.0067[c]	<0.001

Notes: Data are expressed as mean±standard deviation; *P* value was determined by one-way ANOVA tests or Tukey's test; [a]Indicates patients with NPC vs. those with benign tumors of the nasopharynx: $P<0.05$ (Tukey's test); [b]Indicates patients with benign tumors of the nasopharynx vs. healthy subjects: $P<0.05$ (Tukey's test); [c]Indicates patients with NPC vs. healthy subjects; $P<0.05$ (Tukey's test).

Abbreviations: WBC, white blood cells; RBC, red blood cells; M, monocytes; L, lymphocytes; N, neutrophils; PLT, platelets; MPV, mean platelet volumes; MPV/PC ratio, mean platelet volume/platelet count ratio; PDW, platelet distribution width.

interval [CI]: 0.660–0.752), showed a larger AUC than those of MPV/PC ratio ($AUC_{MPV/PC\ ratio}$: 0.665, 95% CI: 0.616–0.712) or PDW (AUC_{PDW}: 0.614, 95% CI: 0.564–0.663) use alone ($P=0.0165$, $P=0.0019$, respectively, Figure 3). The results showed increased specificity and accuracy (specificity: 83.24%, Table 4). To distinguish between patients with NPC and healthy subjects, the combined use of MPV/PC ratio and PDW ($AUC_{MPV/PC\ ratio+PDW}$: 0.909, 95% CI: 0.875–0.936) showed a larger AUC than those of MPV/PC ratio

Table 2 MPV/PC Ratio and PDW in Serosal Invasion, Lymph Node Metastasis, and Distant metastasis of 208 Patients with Nasopharyngeal Carcinoma

Variables	N	MPV/PC Ratio	*P* Value	PDW	*P* Value
Stage					
Ⅰ	43	0.0367±0.0101	0.034	0.1493±0.0237	0.642
Ⅱ	47	0.0317±0.0115		0.1566±0.0181	
Ⅲ	108	0.0326±0.0121		0.1544±0.0221	
Ⅳ	10	0.0333±0.0106		0.1600±0.0156	
Serosal invasion					
T_1+T_2	62	0.0373±0.0102	<0.001	0.1492±0.0242	0.187
T_3+T_4	146	0.0315±0.0117		0.1562±0.0198	
Lymph node metastasis					
N_0	90	0.0340±0.0111	0.223	0.1536±0.0209	0.700
N_1-N_3	118	0.0326±0.0120		0.1546±0.0218	
Distant metastasis					
M_0	198	0.0333±0.0116	0.792	0.1538±0.0216	0.427
M_1	10	0.0333±0.0106		0.1600±0.0156	

Notes: *P* value was analyzed by Kruskal–Wallis *H*-test or Wilcoxon rank sum test.

Abbreviations: MPV/PC ratio, mean platelet volume/platelet count ratio; PDW, platelet distribution width.

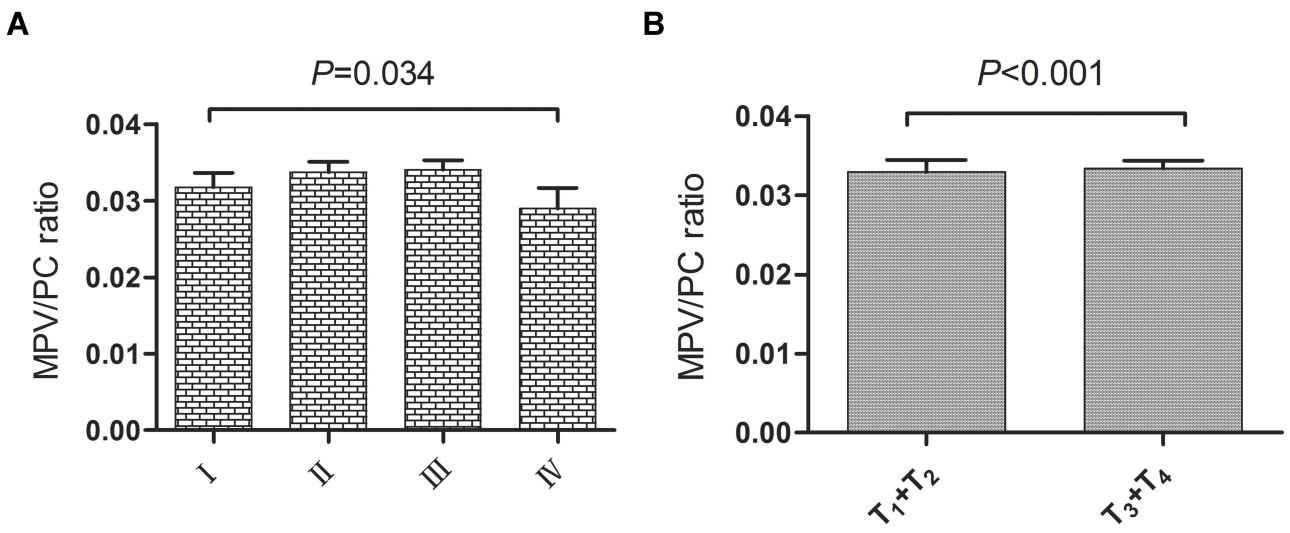

Figure 2 (**A**) MPV/PC ratio between the different stages of the nasopharyngeal carcinoma. (**B**) MPV/PC ratio between the different serosal invasions of the nasopharyngeal carcinoma.
Abbreviation: MPV/PC ratio, mean platelet volume/platelet count ratio.

($AUC_{MPV/PC\ ratio}$: 0.869, 95% CI: 0.830–0.902) or PDW (AUC_{PDW}: 0.716, 95% CI: 0.667–0.761) use alone (*P*=0.0016, *P*<0.001, respectively, Figure 4). The results also showed increased sensitivity and high accuracy (specificity: 95.06%, Table 4).

Table 3 Correlation Analysis of Laboratory Variables of 208 Patients with Nasopharyngeal Carcinoma

Variables	MPV/PC Ratio (*P* Value/*r*)	PDW (*P* Value/*r*)
MPV/PC ratio	*	0.663/-0.030
PDW	0.663/-0.030	*
Age	0.738/0.023	0.242/-0.082
WBC	0.000/-0.317	0.275/0.076
RBC	0.324/0.069	0.341/-0.066
M	0.005/-0.196	0.326/0.069
L	0.731/0.024	0.793/0.018
N	0.000/-0.345	0.307/0.071
PLT	0.000/-0.842	0.057/-0.132
MPV	0.000/0.572	0.000/-0.505
Stage (Ⅰ–Ⅳ)	0.079/-0.122	0.348/0.065
Serosal invasion (T_1+T_2, T_3+T_4)	0.000/-0.288	0.187/0.092
Lymph node metastasis (N_0, N_1-N_3)	0.224/-0.085	0.701/0.027
Distant metastasis (M_0, M_1)	0.793/0.018	0.428/0.055

Notes: *P* value and *r* were determined by Pearson correlation or Spearman correlation analysis, *r* was correlation coefficient. *Indicates that there is no correlation between the two indicators.
Abbreviations: WBC, white blood cells; RBC, red blood cells; M, monocytes; L, lymphocytes; N, neutrophils; PLT, platelets; MPV, mean platelet volumes; MPV/PC ratio, mean platelet volume/platelet count ratio; PDW, platelet distribution width.

Discussion

It has been reported that inflammation is closely related to the development of tumors.[12,13] PLT serves as one of the inflammatory markers with great importance in thrombosis, a factor in tumor development.[14,15] A previous study has found that an increased level of PLT was associated with a poor overall survival in NPC patients.[16] However, PLT count does not accurately reflect abnormalities in PLT functional status. Under the effective compensation mechanism, hypercoagulability and inflammation may occur within the body even if PLT is normal.[17] Thus, two PLT-related indicators, MPV (an indicator of platelet activation) and PDW (an indicator of reflecting variations in platelet volume), can be derived. MPV and PDW are often used in the preliminary diagnosis and prognostic assessment of malignant tumors. Studies have shown that an inverse relationship exists between PLT and MPV, suggesting the combination of the two variables as a ratio.[18–20]

MPV/PC ratio is used for the postmortem evaluation in patients with non-elevation myocardial infarction,[21] as well as for prognosis and diagnosis in non-small cell gastric cancer cases and lung cancer.[22,23] Low MPV/PC ratio serves as a reference index for cirrhosis with ascites, infection, and some immune diseases.[24,25] Our study showed that MPV/PC ratio was the lowest in the NPC group compared with the other two groups (patients with benign tumors of the nasopharynx and healthy subjects), which is similar to the results of the study by Pietrzyk et al.[22] Moreover, MPV/PC ratio also showed statistically significant differences in different stages and serosal

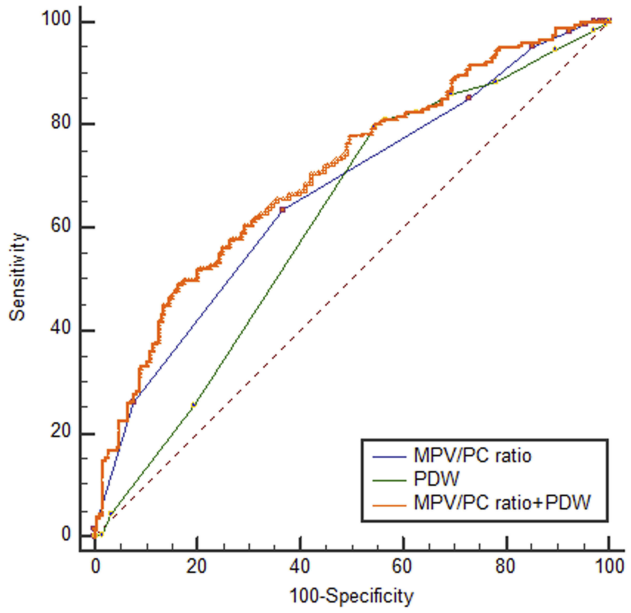

Figure 3 Receiver operating characteristic curves for MPV/PC ratio and PDW alone or combined to distinguish between the diagnoses of nasopharyngeal carcinoma versus benign tumors of the nasopharynx.
Abbreviations: MPV/PC ratio, mean platelet volume/platelet count ratio; PDW, platelet distribution width.

invasions. The value of MPV/PC ratio decreased with increase in NPC pathological stages; all of which may suggest that MPV/PC ratio can be used to distinguish between patients with NPC and those with benign tumors of the nasopharynx or healthy subjects. Currently, it is thought that MPV/PC ratio may indicate the progression and metastasis of malignant tumors through an inflammatory tumor microenvironment. Low MPV/PC ratio is indicative of low MPV and high PLT. MPV is an indicator of PLTs' early activation state, and MPV has significance in the diagnosis of some malignant tumors.[26–28] As shown by our results, MPV and PLT showed the minimum and maximum levels in the NPC group, respectively, compared with the other two groups (patients with benign tumors of the nasopharynx and healthy subjects), which was similar to the findings by Bessman et al.[19] Moreover, MPV/PC ratio was correlated with MPV, WBC, M, N, PLT, and serosal invasion. During the inflammatory phase, increased consumption of a large number of PLT leads to the reduction in MPV.[29] Such reduction may account for high volume of platelets, which are more reactive and are likely to release chemicals with hemostasis and proinflammatory effects, thus participating in the inflammatory response.[30,31] It aggravates endothelial damage, promotes cancer cell invasion, and lymph node metastasis; contributing to the development and metastasis of cancer.[17,32] This better explains the involvement of the MPV/PC ratio in the progression of tumor-associated inflammation.

Changes in PDW level have been reported as a potential marker for the diagnosis and prognosis of laryngeal cancer, colorectal cancer, nasopharyngeal cancer, and liver cancer.[9,28,33,34] Paulus[35] showed in their study that the dysfunction of bone marrow cells could lead to changes in PDW. Bone marrow cell maturation and PLT size are regulated by some cytokines, including interleukin-6 granulocyte colony-stimulating factor and macrophage colony-stimulating factor,[36] which promote tumor angiogenesis and metastasis.[37] Studies have shown that PDW increases in melanoma and gallbladder cancer.[38,39] In our results, PDW showed a statistically significant difference between the three groups (patients with NPC, patients with benign tumors of the nasopharynx, and healthy subjects), with statistically significant differences when the three groups are compared in pairs. Higher the NPC pathological staging the higher the PDW level, suggesting that the increase in PDW could be used to indicate the progression of NPC.

Ultimately, in the ROC curve analysis, the AUC value was from 0.5 to 1; the closer the AUC value was to 1, the

Table 4 Diagnostic Efficiency of MPV/PC Ratio and PDW

Indicator	Optimal Cutoffs	Sensitivity	Specificity	AUC	95% CI
Patients with nasopharyngeal carcinoma vs. those with benign tumors of the nasopharynx					
MPV/PC ratio	≤0.03	63.46	63.24	0.665	0.616–0.712
PDW	>0.15	79.81	45.41	0.614	0.564–0.663
MPV/PC ratio+PDW	>0.64	49.04	83.24	0.708	0.660–0.752
Patients with nasopharyngeal carcinoma vs. healthy subjects					
MPV/PC ratio	≤0.04	85.10	70.99	0.869	0.830–0.902
PDW	≤0.16	74.52	63.58	0.716	0.667–0.761
MPV/PC ratio+PDW	>0.67	76.92	95.06	0.909	0.875–0.936

Abbreviations: MPV/PC ratio, mean platelet volume/platelet count ratio; PDW, platelet distribution width; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

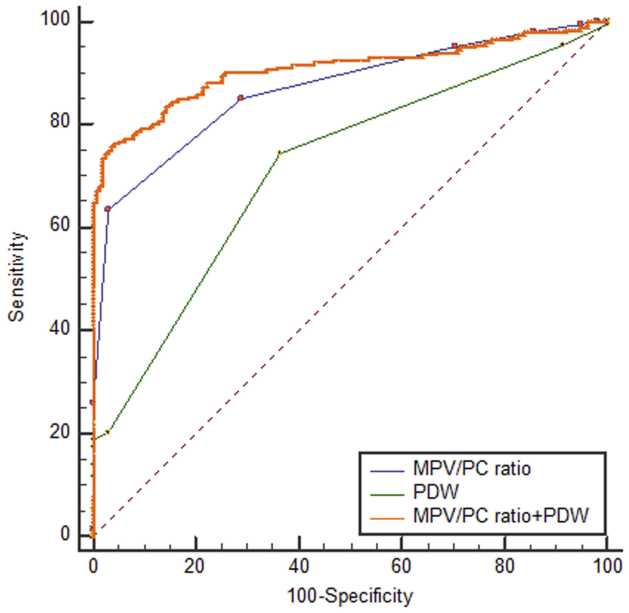

Figure 4 Receiver operating characteristic curves for MPV/PC ratio and PDW alone or combined to distinguish between the diagnoses of nasopharyngeal carcinoma versus healthy subjects.
Abbreviations: MPV/PC ratio, mean platelet volume/platelet count ratio; PDW, platelet distribution width.

better was the diagnostic effect. AUC of between 0.7 and 0.9 and that above 0.9 showed certain and high accuracy, respectively. In our study, the combined use of MPV/PC ratio and PDW to distinguish between patients with NPC and benign tumors of the nasopharynx had a large AUC, increased specificity, and certain accuracy. Furthermore, the combined use of MPV/PC ratio and PDW to distinguish between patients with NPC and healthy subjects showed a large AUC, increased specificity, and high accuracy.

Our study had some limitations. First, this is a retrospective study. Second, this was a single research center study, from China, in a certain population; hence, there is a need for larger prospective studies to clarify how MPV/PC ratio affects the progress and precise mechanism of NPC. Undoubtedly, this study is the first to explore the value of MPV/PC ratio in NPC, and to provide a reference for distinguishing between the diagnosis of NPC and others.

Conclusion

MPV/PC ratio and PDW may be used as indexes of NPC, MPV/PC ratio combined with PDW could be considered as significant laboratory indexes for differential diagnosis of NPC, benign tumors of the nasopharynx, and healthy subjects. This finding could enhance the detection of NPC. However, further large-scale prospective study is suggested.

Abbreviations

AUC, area under the curve; CI, confidence interval; L, lymphocytes; M, monocytes; MPV, mean platelet volumes; MPV/PC ratio, mean platelet volume/platelet count ratio; N, neutrophils; NPC, nasopharyngeal carcinoma; PDW, platelet distribution width; PLT, platelets; RBC, red blood cells; ROC, receiver operating characteristic; WBC, white blood cell.

Ethical Approval

The Ethics Committee of the first Affiliated Hospital of Guangxi Medical University approved the study. This article does not contain any studies with animals performed by any of the authors.

Acknowledgments

We would like to thank the staff at the Department of Clinical Laboratory, the First Affiliated Hospital of Guangxi Medical University, China.

Informed Consent

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

Disclosure

The authors declare that they have no conflict of interest.

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