



# MEAN PLATELET VOLUME: AN OVERLOOKED HERALD OF MALIGNANT THYROID NODULES

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**SUMMARY** – Physicians and surgeons pay much attention to evaluating thyroid nodules due to the malignant potential of these growths. Inflammation has a crucial role in the development of cancer. Increase in the mean platelet volume (MPV) has been described in various inflammatory conditions. Since some of thyroid nodules are malignant, we aimed to compare MPV values between patients with malignant and benign thyroid nodules after precise pathologic diagnosis. We retrospectively analyzed hemograms of patients having undergone thyroid surgery for thyroid nodule between January 2013 and January 2015, and compared them to those recorded in healthy subjects. MPV was higher in the malignant thyroid nodule group than in the benign nodule group ( $9.1 \pm 1$  fL *vs.*  $7.8 \pm 0.8$  fL). The difference was statistically significant ( $p < 0.001$ ). Increased MPV should be considered as an assistive diagnostic tool in differentiating malignant and benign thyroid nodules. However, further prospective studies are required to confirm its usefulness in this population.

**Key words:** *Thyroid nodule; Neoplasms; Inflammation; Mean platelet volume; Blood cell count*

## Introduction

Physicians and surgeons pay much attention to evaluating thyroid nodules due to the malignant potential of these growths. Women are more likely to develop thyroid nodules, and in iodine deficient countries, its prevalence may reach 5%<sup>1</sup>. Advances in imaging modalities such as ultrasound scan have increased the rate of nodule detection in the gland. The prevalence of thyroid nodules on ultrasound may be as high as 67%<sup>2</sup>. Since an important proportion of thyroid nodules include malignant cells, clinicians should search for possible malignancy, especially in suspected nodules. Ultrasound scan and scintigraphy features help discriminate these nodules, especially in cases with a history of exposure to radiation.

Inflammation has a crucial role in the development of cancer<sup>3,4</sup>. Association between neoplasm and many

inflammatory markers has been studied recently<sup>5</sup>. One of these markers is the hemogram derived mean platelet volume (MPV). It is an index of routine hemogram tests and reflects platelet size. Activation of platelets is associated with an increase in MPV value<sup>6</sup>. An increase in MPV has been described in various inflammatory conditions<sup>7-9</sup>. Not only inflammatory diseases with a high inflammatory burden, but also neoplastic disorders have been associated with MPV. Elevated MPV is reported in gastric<sup>10</sup> and colon cancer<sup>11</sup>. Moreover, increased MPV has been proposed as a prognostic factor in critically ill patients<sup>12</sup>.

Since some of thyroid nodules are malignant, we aimed to compare MPV values in patients with malignant and benign thyroid nodules after precise pathologic diagnosis.

## Materials and Methods

### *Patient selection*

The subjects having undergone surgery for thyroid nodule at our surgery departments between January

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2013 and January 2015 were included in the study. Based on pathologic examination of thyroid gland surgical specimens, these patients were divided into two groups of malignant nodules and benign nodules. The study was approved by the institutional Ethics Committee. Demographic and laboratory data were obtained from the hospital computerized database. Pre-operative hemogram values of thyroid nodule patients, white blood cell count (WBC), hemoglobin (Hb), hematocrit (Htc), mean corpuscular volume (MCV), platelet count (PLT), thyroid stimulating hormone (TSH) and MPV were recorded.

Active infection, diabetes mellitus, thyroiditis, any other type of malignancy, inflammatory diseases were set as exclusion criteria. Patients on corticosteroid or aspirin treatment were also excluded.

The Beckman Coulter LH 780 autoanalyzer (Beckman Coulter Inc., Brea, CA, USA) was used to perform hemogram tests. Hemogram and other biochemical and pathological assays were conducted at laboratories of our university hospital.

### Statistical analysis

Statistical analysis was conducted by use of SPSS software (SPSS15.0; SPSS Inc., Chicago, IL, USA). Data were expressed as mean  $\pm$  SD or median (min-max). Student's t-test or Mann-Whitney U test was used to compare variables between the study groups. The level of statistical significance was set at  $p < 0.05$ .

### Results

A total of 199 subjects, 101 patients with malignant and 98 patients with benign thyroid nodules, were included in the study. Median age of the malignant and benign thyroid nodule patients was 43 (25-77) and 45 (26-60) years, respectively. Age was not significantly different between malignant and benign thyroid nodule groups ( $p = 0.79$ ).

The malignant thyroid nodule group consisted of 77 women and 24 men, whereas the benign nodule group included 75 women and 23 men. Gender distribution was not significantly different between the groups ( $p = 0.96$ ).

White blood cell count, Hb, Htc, MCV, PLT and TSH levels were not different between the malignant thyroid nodule group and benign nodule group ( $p > 0.05$

Table 1. General characteristics and laboratory data of study groups

		Group		p
		Malignant nodule	Benign nodule	
Gender	Men (n)	24	23	0.96
	Women (n)	77	75	
		Mean $\pm$ SD		
WBC (K/mm <sup>3</sup> )		6.9 $\pm$ 1.7	7.2 $\pm$ 1.9	0.13
Hb (g/dL)		13.5 $\pm$ 1.2	13.6 $\pm$ 1.1	0.79
Htc (%)		40 $\pm$ 3.5	40.5 $\pm$ 3	0.33
MCV (fL)		86.8 $\pm$ 3.7	87.3 $\pm$ 4.2	0.34
PLT (K/mm <sup>3</sup> )		249 $\pm$ 63	260 $\pm$ 58	0.19
MPV (fL)		9.1 $\pm$ 1	7.8 $\pm$ 0.8	<b>&lt;0.001</b>
		Median (min-max)		
Age (years)		43 (25-77)	45 (26-60)	0.79
TSH (uIU/mL)		1.21 (0.01-5.7)	0.93 (0.01-4.4)	0.60

WBC = white blood cell count; Hb = hemoglobin; Htc = hematocrit; MCV = mean corpuscular volume; PLT = platelet count; MPV = mean platelet volume; TSH = thyroid stimulating hormone

all). General characteristics and laboratory data of the study groups are summarized in Table 1.

The MPV was higher in the malignant thyroid nodule group as compared with the benign nodule group (9.1 $\pm$ 1 fL *vs.* 7.8 $\pm$ 0.8 fL), yielding a statistically significant difference ( $p < 0.001$ ).

The receiver operating characteristic curve (ROC) analysis was performed to define the sensitivity and specificity of MPV in detecting malignant nodules. The MPV cut-off value of 8.25 had 81% sensitivity and 66% specificity in determining malignant nodules ( $p < 0.001$ ; area under the curve (AUC) 0.84; lower bound 0.78; upper bound 0.89).

### Discussion

The main finding of the present study was that elevated MPV might indicate malignancy in patients with thyroid nodules. MPV is considered to be associated with certain malignancies. Elevated MPV values have been reported in various types of cancer at the time of diagnosis<sup>13</sup>. Another study reports on increased MPV in patients with colon cancer, which was reduced after surgery<sup>11</sup>. Increased MPV has also been reported in gastric<sup>10</sup> and epithelial ovarian tumors<sup>14</sup>.

We will discuss the rationale for MPV elevation in cancer at this point. Inflammation causes an increase in the levels of circulating cytokines. These cytokines, especially interleukin (IL)-6, may interfere with megakaryopoiesis in bone marrow and cause production of larger platelets. This may be the underlying reason for increased MPV in cancer patients. Cancer is also associated with chronic inflammation, thus such a causal relationship may be present.

Various diagnostic tools are available to differentiate malignant from benign thyroid nodules. Ultrasonography characteristics of malignant thyroid nodules, vertical rather than horizontal shape, spiculated borders, hypoechogenicity and microcalcifications all have about 40%-48% sensitivity in detecting malignancy<sup>15</sup>. Leenhardt *et al.* report on sonography sensitivity and specificity for thyroid nodule malignancy of 75% and 61%, respectively<sup>16</sup>.

Cold thyroid nodules on thyroid scintigraphy require further evaluation for suspicious malignancy. However, Kountakis *et al.* report that only 27.5% of hypofunctional (cold) thyroid nodules were malignant on scintigraphy<sup>17</sup>. Although hot nodules in scintigraphy are considered almost always benign<sup>18</sup>, malignancy was detected in 6% of hyperfunctioning hot nodules<sup>17</sup>. Diagnostic accuracy of a combination of sonography and scintigraphy is not excellent either. Only about 35% of sonographic solid and scintigraphically cold nodules were reported as malignant by fine needle aspiration cytology (FNAC)<sup>19</sup>.

In our study, the sensitivity and specificity of MPV at a threshold of 8.25 were better than by ultrasound and scintigraphy.

Fine needle aspiration cytology of thyroid nodule, which is considered as the most important method for detecting malignancy in thyroid nodules, has a sensitivity of 91% in selecting malignant nodules<sup>20</sup>. However, the rate of false-negative and false-positive results of FNAC can be as high as 11% and 7%, respectively<sup>18</sup>. Owing to higher sensitivity and specificity of MPV at 8.25 threshold, we think that it can be used in combination with sonography, scintigraphy and FNAC to establish the nature of thyroid nodules. Such a combination not only increases diagnostic accuracy, but also may improve the cost-effectiveness by reducing repeated expensive techniques (FNAC, etc.) in cases of non-diagnostic test results.

Not only thyroid disease but also metabolic alteration such as obesity, type 2 diabetes mellitus and dia-

betic nephropathy were associated with MPV levels in hemogram tests<sup>21,22</sup>.

There were several limitations to the present study. First, the retrospective design made our results difficult to interpret. Another limitation was the relatively small study population. Finally, we did not compare sonography, cytology and scintigraphy test results of the study population with MPV, which should be the subject of another study in the near future.

In conclusion, increased MPV should be considered as an assistive diagnostic tool in differentiating malignant and benign thyroid nodules. However, further prospective studies are required to confirm its usefulness in this population.

## References

1. Tunbridge W, Evered D, Hall R, Appleton D, Brewis M, Clark F, *et al.* The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol.* 1977;7(6):481-93. DOI: 10.1111/j.1365-2265.1977.tb01340.x
2. Ezzat S, Sarti DA, Cain DR, Braunstein GD. Thyroid incidentalomas: prevalence by palpation and ultrasonography. *Arch Int Med.* 1994;154(16):1838-40. DOI: 10.1001/archinte.154.16.1838
3. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002;420(6917):860-7. DOI: 10.1038/nature01322
4. Grivnennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell.* 2010;140(6):883-99. DOI: 10.1016/j.cell.2010.01.025
5. Solak Mekić M, Pedišić I, Šobat H, Vučićević Boras V, Kirac I, Štefančić L, *et al.* The role of complete blood count parameters in patients with colorectal cancer. *Acta Clin Croat.* 2018 Dec;57(4):624-9. DOI: 10.20471/acc.2018.57.04.03
6. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. *Platelets.* 2002;13(5-6):301-6. DOI: 10.1080/095371002220148332
7. Kapsoritakis AN, Koukourakis MI, Sfīridaki A, Potamianos SP, Kosmadaki MG, Koutroubakis IE, *et al.* Mean platelet volume: a useful marker of inflammatory bowel disease activity. *Am J Gastroenterol.* 2001;96(3):776-81. DOI: 10.1111/j.1572-0241.2001.03621.x
8. Ceylan B, Fincanci M, Yardimci C, Eren G, Tözalgan Ü, Müderrisoglu C, *et al.* Can mean platelet volume determine the severity of liver fibrosis or inflammation in patients with chronic hepatitis B? *Eur J Gastroenterol Hepatol.* 2013;25(5):606-12. DOI: 10.1097/MEG.0b013e32835d08da
9. Polińska B, Matowicka-Karna J, Kemon H. Assessment of the influence of the inflammatory process on the activation of blood platelets and morphological parameters in patients with ulcerative colitis (colitis ulcerosa). *Folia Histochem Cytobiol.* 2011;49(1):119-24.

10. Kılınçalp S, Ekiz F, Basar O, Ayte MR, Coban S, Yılmaz B, *et al.* Mean platelet volume could be possible biomarker in early diagnosis and monitoring of gastric cancer. *Platelets*. 2014; 25(8):592-4. DOI: 10.3109/09537104.2013.783689
11. Li J-Y, Li Y, Jiang Z, Wang R-T, Wang X-S. Elevated mean platelet volume is associated with presence of colon cancer. *Asian Pac J Cancer Prev*. 2014;15(23):10501-4. DOI: 10.7314/apjcp.2014.15.23.10501
12. Karagoz I, Aktas G, Yoldas H, Yildiz I, Ogun MN, Bilgi M, *et al.* Association between hemogram parameters and survival of critically ill patients. *J Intensive Care Med*. 2019;34(6):511-3. DOI: 10.1177/0885066617703348
13. Mutlu H, Artis TA, Erden A, Akca Z. Alteration in mean platelet volume and platicrit values in patients with cancer that developed thrombosis. *Clin Appl Thromb Hemost*. 2013; 19(3):331-3. DOI: 10.1177/1076029611433644
14. Kemal Y, Demirag G, Ekiz K, Yucel I. Mean platelet volume could be a useful biomarker for monitoring epithelial ovarian cancer. *J Obstet Gynaecol*. 2014;34(6):515-8. DOI: 10.3109/01443615.2014.912620
15. Moon W-J, Jung SL, Lee JH, Na DG, Baek J-H, Lee YH, *et al.* Benign and malignant thyroid nodules: US differentiation – multicenter retrospective study. *Radiology*. 2008;247(3):762-70. DOI: 10.1148/radiol.2473070944
16. Leenhardt L, Tramalloni J, Aurengo H, Delbot T, Guillausseau C, Aurengo A. Echographie des nodules thyroïdiens: l'échographiste face aux exigences du clinicien. *Presse Med*. 1994; 23(30):1389-92.
17. Kountakis SE, Skoulas IG, Maillard A. The radiologic work-up in thyroid surgery: fine-needle biopsy *versus* scintigraphy and ultrasound. *Ear Nose Throat J*. 2002;81(3):151-4.
18. Maia FF, Zantut-Wittmann DE. Thyroid nodule management: clinical, ultrasound and cytopathological parameters for predicting malignancy. *Clinics*. 2012;67(8):945-54.
19. Fariduddin M, Amin A, Ahmed M, Karim S, Moslem F, Kamal M. Malignancy in solitary solid cold thyroid nodule. *Myensingh Med J*. 2012 Apr;21(2):276-80.
20. Danese D, Sciacchitano S, Farsetti A, Andreoli M, Pontecorvi A. Diagnostic accuracy of conventional *versus* sonography-guided fine-needle aspiration biopsy of thyroid nodules. *Thyroid*. 1998;8(1):15-21. DOI: 10.1089/thy.1998.8.15
21. Aktas G, Kocak MZ, Duman TT, Erkus E, Atak BM, Sit M, *et al.* Mean platelet volume (MPV) as an inflammatory marker in type 2 diabetes mellitus and obesity. *Bali Med J*. 2018;7(3): 650-3. DOI:10.15562/bmj.v7i3.806
22. Kocak MZ, Aktas G, Erkus E, Duman TT, Atak BM, Savli H. Mean platelet volume to lymphocyte ratio as a novel marker for diabetic nephropathy. *J Coll Physicians Surg Pak*. 2018 Nov;28 (11):844-7. DOI: 10.29271/jcpsp.2018.11.844

#### Sažetak

### SREDNJI VOLUMEN TROMBOCITA: PREVIDJELI GLASNIK ZLOĆUDNIH ČVOROVA ŠTITNJAJČE

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Liječnici i kirurzi pridaju veliku pozornost procjeni čvorova štitne žlijezde zbog malignog potencijala ovih novotvorina. Upala ima ključnu ulogu u razvoju raka. Povećani srednji volumen trombocita (*mean platelet volume*, MPV) opisuje se u raznim upalnim stanjima. Kako su neki od čvorova štitne žlijezde zloćudni cilj nam je bio usporediti vrijednosti MPV između bolesnika sa zloćudnim i dobroćudnim čvorovima štitnjače nakon precizne patološke dijagnoze. Retrospektivno su analizirani hemogrami bolesnika podvrgnutih operaciji štitne žlijezde zbog čvorova od siječnja 2013. do siječnja 2015. godine te uspoređeni s vrijednostima dobivenim u zdravih osoba. MPV je bio viši u skupini zloćudnih tireoidnih čvorova nego u skupini dobroćudnih čvorova ( $9,1 \pm 1$  fL prema  $7,8 \pm 0,8$  fL), a razlika je bila statistički značajna ( $p < 0,001$ ). Povišeni MPV može se smatrati pomoćnim dijagnostičkim alatom u razlikovanju zloćudnih i dobroćudnih čvorova štitnjače. Međutim, potrebna su daljnja istraživanja kako bi se potvrdila njegova korist kod ove populacije.

**Ključne riječi:** *Tireoideja, čvor; Neoplazme; Upala; Prosječni volumen trombocita; Krvna slika*