



Can Mean Platelet Volume be Used as a Thrombosis Marker in Subjective Tinnitus?

Deniz Avcı 

ABSTRACT

Objective: To investigate the relationship between subjective tinnitus and red cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) levels.

Materials and Methods: This retrospective research included a total of 91 patients with subjective tinnitus and a control group of gender- and age-matched 65 healthy volunteers. Ear, nose, throat examination followed by pure tone audiometry, tympanometry, complete blood count, and magnetic resonance imaging of the temporal bone was performed. The clinical features and duration of tinnitus were recorded for each patient. The MPV, NLR, PDW, PLR and RDW levels were compared between tinnitus and control groups.

Results: Mean RDW was $15.49 \pm 2.43\%$ in the patient group and $15.42 \pm 2.04\%$ in the control group ($p=0.831$). Mean PDW was $16.13 \pm 2.51\%$ in the patient group and $15.99 \pm 9.94\%$ in the control group ($p=0.901$). Mean MPV was 8.95 ± 0.77 fL in the patient group and 8.55 ± 0.75 fL in the control group ($p=0.002$). Mean NLR was 1.89 ± 0.63 in the patient group and 1.88 ± 0.75 in the control group ($p=0.916$). Mean PLR was 113.93 ± 33.91 in the patient group and 120.90 ± 33.23 in the control group ($p=0.204$). Only MPV established a significant difference between tinnitus and control groups.

Conclusion: Only MPV was found to have an important role in the clinical prognosis and diagnosis of tinnitus. Elevated MPV indicates a possible role of thrombosis and vascular diseases in the etiology of subjective tinnitus, so increased MPV can be used as a thrombosis marker in subjective tinnitus.

Keywords: Complete blood count, lymphocyte, mean platelet volume, neutrophil, subjective tinnitus

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INTRODUCTION

Tinnitus is an inconvenience of the ear characterized by the perception of sounds that cannot be attributed to an external source. Tinnitus is not a stand-alone clinical entity and has unclear pathophysiology although it has been attributed to anatomical and/or functional alterations in the auditory system. The prevalence of tinnitus in both genders has been reported to be 10.1–14.6%, and the prevalence has been shown to increase with age. In young adults, tinnitus has been associated with anxiety, depression, sleep deprivation, and decreased quality of life (1). Tinnitus can be subjective or objective and pulsatile or non-pulsatile based on its clinical features. Idiopathic subjective tinnitus is the most common form of tinnitus (2).

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are new inflammatory indicators that can be easily calculated from complete blood count (CBC). In otolaryngological practice, NLR and PLR have been shown to be associated with the prognosis and diagnosis of several pathological conditions, including vestibular neuritis, sudden sensorineural hearing loss (SSHL), and peripheral facial palsy (3–5). Red cell distribution width (RDW), platelet distribution width (PDW), and mean platelet volume (MPV) are some other parameters that can also be calculated from CBC. Both MPV and PDW are indicators of thrombocyte function and activation. PDW indicates the heterogeneity in thrombocyte morphology, variability in thrombocyte size and the changes with thrombocyte activation. MPV indicates the average size of platelets (6). RDW indicates variability in the size differences of erythrocytes. RDW plays a role in differentiating the false-negative of mean corpuscular volume in the measure of erythrocyte morphological changes (7).

This research purposed to assess the relationship between subjective tinnitus and NLR, MPV, PDW, RDW, and PLR levels and to compare the findings with those of other studies, which are highly rare in the literature. Accordingly, to our knowledge, the present study is a rare report in the literature to analyze 5 CBC parameters in an integrated fashion in subjective tinnitus.

MATERIALS and METHODS

This retrospective case-control study contained 91 patients with subjective tinnitus and 65 healthy volunteers that

Department of
Otorhinolaryngology,
Nevşehir State Hospital,
Nevşehir, Turkey

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Correspondence
Deniz Avcı,
Department of
Otorhinolaryngology,
Nevşehir State Hospital,
50130 Nevşehir, Turkey
Phone: +90 506 584 95 67
e-mail:
deniz.avci@hotmail.com

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Table 1. Tinnitus Handicap Inventory Questionnaire (Turkish version was used for the patients)

Questions	4 points	0 point	2 points
1. Because of your tinnitus, is it difficult for you to concentrate?	Yes	No	Sometimes
2. Does the loudness of your tinnitus make it difficult for you to hear people?	Yes	No	Sometimes
3. Does your tinnitus make you angry?	Yes	No	Sometimes
4. Does your tinnitus make you feel confused?	Yes	No	Sometimes
5. Because of your tinnitus, do you feel desperate?	Yes	No	Sometimes
6. Do you complain a great deal about your tinnitus?	Yes	No	Sometimes
7. Because of your tinnitus, do you have trouble falling to sleep at night?	Yes	No	Sometimes
8. Do you feel as though you cannot escape your tinnitus?	Yes	No	Sometimes
9. Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)?	Yes	No	Sometimes
10. Because of your tinnitus, do you feel frustrated?	Yes	No	Sometimes
11. Because of your tinnitus, do you feel that you have a terrible disease?	Yes	No	Sometimes
12. Does your tinnitus make it difficult for you to enjoy life?	Yes	No	Sometimes
13. Does your tinnitus interfere with your job or household responsibilities?	Yes	No	Sometimes
14. Because of your tinnitus, do you find that you are often irritable?	Yes	No	Sometimes
15. Because of your tinnitus, is it difficult for you to read?	Yes	No	Sometimes
16. Does your tinnitus make you upset?	Yes	No	Sometimes
17. Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends?	Yes	No	Sometimes
18. Do you find it difficult to focus your attention away from your tinnitus and on other things?	Yes	No	Sometimes
19. Do you feel that you have no control over your tinnitus?	Yes	No	Sometimes
20. Because of your tinnitus, do you often feel tired?	Yes	No	Sometimes
21. Because of your tinnitus, do you feel depressed?	Yes	No	Sometimes
22. Does your tinnitus make you feel anxious?	Yes	No	Sometimes
23. Do you feel that you can no longer cope with your tinnitus?	Yes	No	Sometimes
24. Does your tinnitus get worse when you are under stress?	Yes	No	Sometimes
25. Does your tinnitus make you feel insecure?	Yes	No	Sometimes

presented to Otorhinolaryngology Department between October 2018 and May 2019. Healthy volunteers were selected from patients who applied to our hospital for general health screening without any disease. The patients had a history of tinnitus for at least one month. This study was confirmed by the Scientific Research Board and was conducted in accordance with the Helsinki Declaration.

A detailed ear, nose, throat examination followed by pure tone audiometry (PTA), tympanometry, CBC, and magnetic resonance imaging (MRI) of the temporal bone was performed for all patients in this study. The clinical features and duration of tinnitus were registered for all patients. Subjective tinnitus severity was assessed using the Turkish version of the Tinnitus Handicap Inventory (THI) in this study (8). The 25 Turkish questions of the THI were asked to patients with subjective tinnitus (Table 1). Patients were divided into five groups according to THI scores (Table 2).

CBC was performed using a hematology analyzer (Sysmex XE 2100; Sysmex, Kobe, Japan) and the following parameters were recorded: white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute platelet count (APC), MPV, RDW, and PDW. The NLR and PLR were determined as follows: $NLR=ANC/ALC$, $PLR=APC/ALC$.

Patients and healthy volunteers with an outer, middle, or inner ear disease (such as Meniere's disease, chronic otitis media, otosclerosis, autoimmune diseases, and other middle ear diseases), any form of hearing loss, uncontrolled systemic diseases, malignancies, acute and chronic inflammatory diseases, history of acoustic trauma, aged below 18 or over 70 years, and abnormal laboratory parameters were excluded from the study. Patients who had non-pulsatile, subjective tinnitus graded as slight, mild, moderate, severe, or catastrophic based on the THI scores. Patients with normal air and bone thresholds, MRI, laboratory and physical examination findings were included in this study. Healthy volunteers with normal laboratory and physical examination findings were included in this study. We eliminate differential diagnosis by MRI in all patients. All the PTA and tympanometric assessments were applied by the same audiometry team using an Interacoustics AC-40 clinical audiometer (Assens, Denmark) and 226 Hz Maico tympanometer (Berlin, Germany). PTA was assessed air thresholds at 250, 500, 1000, 2000, 4000, and 8000 Hz. and bone thresholds at 500, 1000, 2000, and 4000 Hz. Pure tone average was accepted as the sill averaged across 0.5, 1, 2, and 4 kHz. Patients with Type A tympanometry (ranging from +50 daPa to -50 daPa) were included in this study.

Table 2. Grading system for the Tinnitus Handicap Inventory

Total score	Classification	Grade
0–16	Slight (only heard in quiet environments)	1
18–36	Mild (easily masked by environmental sounds and easily forgotten with activities)	2
38–56	Moderate (noticed in the presence of background noise, though daily activities can still be performed)	3
58–76	Severe (almost always heard, leads to disturbed sleep patterns and can interfere with daily activities)	4
78–100	Catastrophic (always heard, disturbed sleep patterns, difficulty with any activities)	5

Table 3. Comparison of the demographic and clinical data of the tinnitus and control groups

Variables	Tinnitus group	Control group	p
Age	48.03±15.12	47.55±17.49	0.855
Gender			
Female	57 (62.6%)	41 (63.1%)	0.956
Male	34 (37.4%)	24 (36.9%)	
White blood cell (WBC) count	6.92±1.56 10 ³ mm ³	6.99±1.89 10 ³ mm ³	0.798
Absolute neutrophil count	4.05±1.14 10 ³ mm ³	4.05±1.45 10 ³ mm ³	0.983
Absolute lymphocyte count	2.22±0.58 10 ³ mm ³	2.27±0.69 10 ³ mm ³	0.658
Absolute platelet count	243.79±62.47 10 ³ mm ³	258.97±60.31 10 ³ mm ³	0.131
Neutrophil-to-lymphocyte ratio (NLR)	1.89±0.63	1.88±0.75	0.916
Platelet-to-lymphocyte ratio (PLR)	113.93±33.91	120.90±33.23	0.204
Mean platelet volume (MPV)	8.95±0.77 fL	8.55±0.75 fL	0.002*
Red cell distribution width (RDW)	15.49±2.43%	15.42±2.04%	0.831
Platelet distribution width (PDW)	16.13±2.51%	15.99±9.94%	0.901

SD: Standard deviation; *Statistically significant; Chi-square test and Independent sample test were used for comparing between groups; significance at p<0.05

Statistical Analysis

Data were evaluated using SPSS for Windows version 22.0 (IBM SPSS Inc., Armonk, NY, USA). Descriptives were expressed as mean and standard deviation (SD) for numerical variables and expressed as frequencies and percentages for categorical variables. Numerical variables that follow parametric assumptions were compared using Independent-samples t-test and categorical variables were compared using the Chi-Square test. Parametric assumptions were controlled using the Shapiro-Wilk test. The MPV, PLR, RDW, PDW, and NLR levels were compared between tinnitus and control groups. P-value of <0.05 was accepted significant.

RESULTS

The tinnitus group included 91 patients, including 57 (62.6%) women and 34 (37.4%) men with a mean age of 48.03±15.1 years. The control group included 65 healthy subjects, 41 (63.1%) women and 24 (36.9%) men with a mean age of 47.55±17.49 years. No significant difference was found between age (p=0.855) and gender (p=0.956) (Table 3). Mean duration of tinnitus was 7.17±10.52 months in the tinnitus group. Of the 91 patients, 32 (35.2%) patients had right ear tinnitus, 35 (38.5%) patients had left ear tinnitus, and 24 (26.3%) patients had bilateral tinnitus. In the tinnitus group, the mean PTA threshold was 17.01±6.57 decibels hearing level (dB HL) in the right ear and 16.05±6.05 dB HL in the left ear and no significant difference was found between the

Table 4. Clinical data of the patients in the tinnitus group (n=91)

Tinnitus side, n (%)	
Right	32 (35.2%)
Left	35 (38.4%)
Bilateral	24 (26.4%)
THI score, Mean±SD	37.29±15.22
PTA (dB HL), Mean±SD	
Right	17.01±6.57
Left	16.05±6.05
Tinnitus duration (month), Mean±SD	7.17±10.52

SD: Standard deviation; THI: Tinnitus Handicap Inventory; PTA: Pure tone average; dB HL: Decibel hearing level

ears in terms of PTA threshold (p=0.058). Mean THI score was 37.29±15.22 in the tinnitus group, which corresponded to Grade 3 moderate tinnitus (Table 4).

No significant difference was observed between tinnitus and control groups concerning WBC, neutrophil, lymphocyte, platelet, and PLR levels. Although the NLR, RDW, and PDW levels were higher in the tinnitus group, no significant difference was observed between tinnitus and control groups (Fig. 1a–d, Table 3). However,

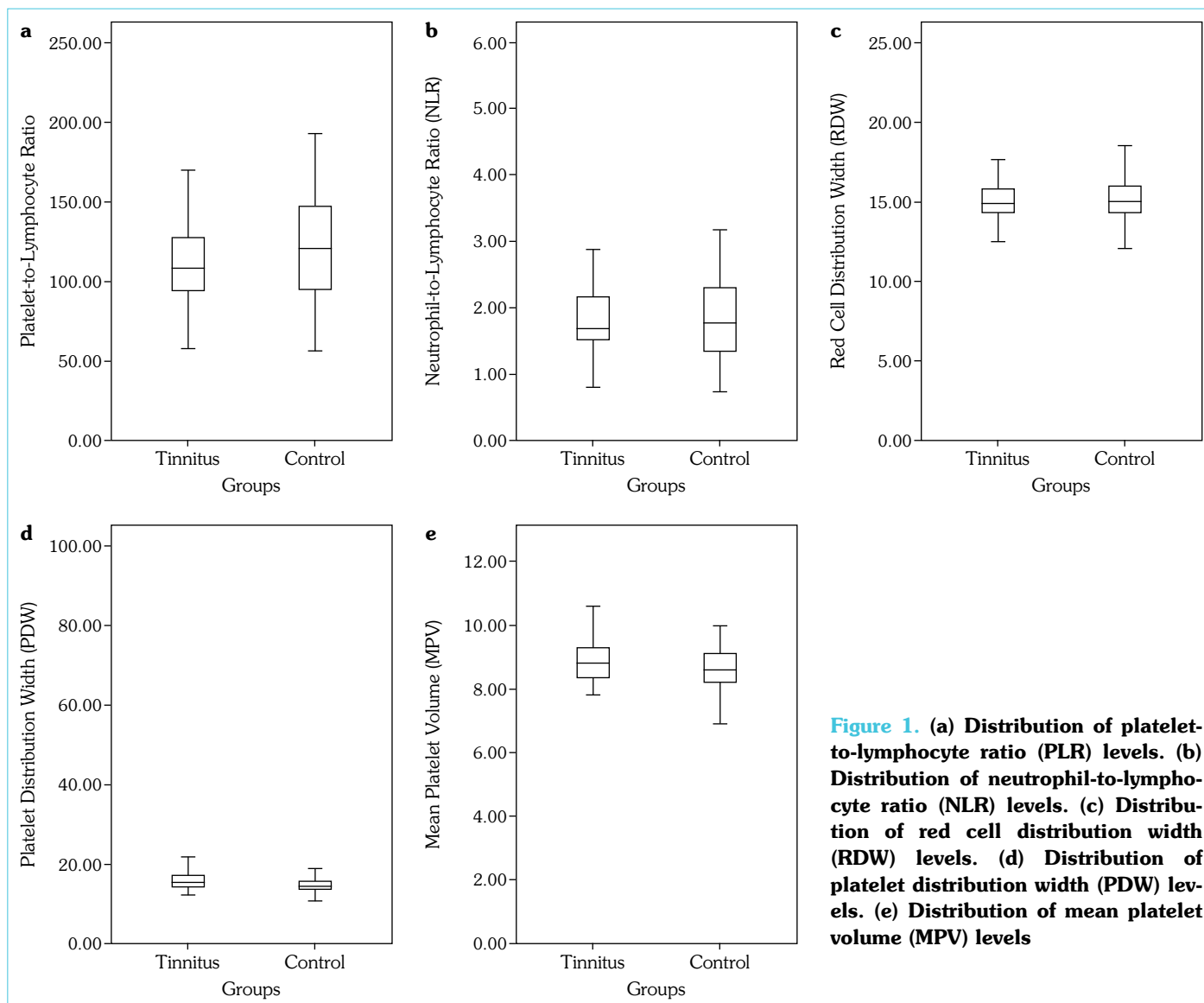


Figure 1. (a) Distribution of platelet-to-lymphocyte ratio (PLR) levels. (b) Distribution of neutrophil-to-lymphocyte ratio (NLR) levels. (c) Distribution of red cell distribution width (RDW) levels. (d) Distribution of platelet distribution width (PDW) levels. (e) Distribution of mean platelet volume (MPV) levels

the MPV levels were significantly higher in the tinnitus group compared to the control group ($p=0.002$) (Fig. 1e, Table 3).

DISCUSSION

Despite its high prevalence, tinnitus has an unknown etiology. However, tinnitus has been reported after inflammation, ischemia, and damage to the auditory system, surgery, and acoustic trauma (1). Additionally, tinnitus has been associated with the changes at the peripheral and central levels of the auditory system. The severity of tinnitus has been reported to be exacerbated by stress. Serotonin plays a pivotal role in the sensorial system, and auditory streaming and serotonin expression have been shown to be increased in several brain areas during stress; therefore, serotonin dysfunction may also have a role in the development of tinnitus (9). Literature indicates that there is a strong relationship between stress and inflammation, and stress is associated with increased levels of WBC and some inflammatory cytokines (10). Meaningfully, given that the elevated neutrophil and platelet levels indicate the presence of inflammation and decreased lymphocyte levels are suggestive of

general stress and lack of well-being, it is tempting to consider that tinnitus could be related to inflammatory markers as well (11).

The PLR and NLR are systemic inflammatory markers that can be easily calculated from CBC. NLR is highly valuable in the prediction of long-term mortality and poor prognosis in malignancies (12). Moreover, NLR has been reported to increase in inflammatory diseases, including head and neck squamous cell carcinoma, vestibular neuritis, SSHL, peripheral facial palsy, and ulcerative colitis (3–5, 13, 14). This elevation has been attributed to increased inflammation associated with stress. A study by Ozbay et al. (15), unlike our study, reported that the NLR levels were significantly increased in the tinnitus group and proposed that NLR could be a valuable clinical indicator of tinnitus. However, the significantly increased NLR levels in that study could be attributed to that the study did not contain patients with mild and moderate tinnitus. In our study, we included patients at all stages of tinnitus based on the classification achieved by THI.

The PLR is a novel marker of chronic inflammation. Şahin et al. (3) and Chung et al. (16) showed that the PLR was significantly in-

creased in vestibular neuritis. Contrariwise, Bayram et al. (17) and Atan et al. (18) found no significant difference concerning PLR levels in patients with tinnitus and chronic otitis media, respectively. Additionally, there are some studies suggesting that PLR is a better indicator compared to the NLR in patients with end-stage renal disease and soft-tissue carcinomas (19, 20). To our knowledge, there is not a research article in the literature reporting on a significant change in the PLR levels in tinnitus.

MPV is another inflammation marker that can be easily calculated from CBC and has been shown to indicate increased platelet activation, which intensifies the inflammation (6). Moreover, increased MPV levels have been reported in cardiovascular diseases and in deep vein thrombosis (21, 22). In otorhinolaryngological practice, on the other hand, MPV has been shown to increase significantly and to be a useful marker in patients with septal deviation, hypoxic conditions, and subjective tinnitus (6, 23, 24). On the contrary, Ozbay et al. found no significant change concerning MPV values in the tinnitus group (15). A study by Şahin et al. (3) declared that the NLR, MPV and PLR were significantly elevated in vestibular neuritis. According to the results, increased NLR and PLR levels supported the role of inflammation and increased MPV levels indicated the possible role of vascular thrombosis in the etiology of vestibular neuritis.

Literature reviews indicate a limited number of studies reporting on RDW and PDW levels in tinnitus patients. RDW is a potential marker of acute hypoxemia, which can be increased in anemia, hematologic diseases, and myelodysplastic syndromes and may also cause peripheral vascular thrombotic occlusion (25). Nakashima et al. (26) indicated the role of RDW in determining the prognostic factor of hospitalized elderly patients with heart failure or infection. Based on this, the present study investigated the relationship between RDW and tinnitus; however, no significant relationship was found. Similarly, Sahin et al. (27) also found no significant difference in patients with SSHL concerning RDW levels.

PDW reflects the heterogeneity in platelet morphology and variability in platelet size. Increased PDW is considered to indicate thrombosis. Ischemic and hypoxic tissues stimulate the production of immature reticulated platelets from the bone marrow and thereby promote platelet production and increase the PDW levels (28). Duzenli et al. (29) evaluated patients that had been suffering from bilateral tinnitus for the last six months and reported that although the PDW and NLR levels were significantly increased in tinnitus group compared to the control group, no significant difference was found between tinnitus and control groups concerning RDW levels. The authors also noted that the NLR levels were significantly lower in the tinnitus patients compared to the control group.

In this study, no significant difference was found between tinnitus and control groups about NLR, PLR, RDW, and PDW levels. This finding could be attributed to several factors, including the meticulous selection of patients and control subjects based on the exclusion criteria of the study, detection of normal PTA thresholds at all frequencies, small sample size, heterogeneity of the tinnitus group, and the inclusion of tinnitus patients at all stages. Additionally, the absence of a significant difference concerning the NLR and PLR levels could be explained by that these parameters are commonly

reported as poor prognostic factors. On the other hand, MPV levels were significantly higher in the tinnitus group compared to the control group, which could be an indicator of increased platelet activation in tinnitus. A similar finding was reported by Kemal et al. (30), who found increased MPV levels in tinnitus patients and proposed that this increase could be associated with thrombosis induced by the perfusion of the internal auditory artery. Further studies with larger patient series and longer follow-up periods are needed to substantiate our results.

CONCLUSION

The results indicated that, of the parameters analyzed in this study (PDW, RDW, NLR, PLR, and MPV), only MPV was found to have an important role in the routine clinical diagnosis and prognosis of tinnitus. Elevated MPV indicates a possible role of thrombosis and vascular diseases in the etiology of subjective tinnitus, so increased MPV can be used as a thrombosis indicator in patients with subjective tinnitus. Accordingly, vascular diseases and thrombosis should be kept in mind in patients with subjective tinnitus.

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