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RELATIONSHIP BETWEEN PLATELET PARAMETERS AND SUDDEN SENSORINEURAL HEARING LOSS: A SYSTEMATIC REVIEW AND META-ANALYSIS
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# RELATIONSHIP BETWEEN PLATELET PARAMETERS AND SUDDEN SENSORINEURAL HEARING LOSS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## ABSTRACT

***Background:*** **Sudden deafness or sudden sensorineural hearing loss (SSNHL) is defined as sensorineural hearing loss of greater than 30 dB over 3 contiguous pure-tone frequencies occurring within 3 days' period**
***Objective:*** **To investigate the relationship of some platelet parameters including platelet count (PC), mean platelet volume (MPV) and platelet distribution width (PDW) with the occurrence of SSNHL.**
***Data source:*** **A PubMed, Science Direct, Scopus, OVID, EMBASE and Google Scholar search (date last searched April 2016) search was done. No restrictions of time, language and location were placed.**
***Study selection:*** **All case-control studies which have been studied the relationship of PC, MPV and PDW with the occurrence of SSNHL were included in the meta-analysis.**
***Data extraction:*** **The required data from selected studies including the title, authors, publication date, location of study, sample size of patients and control groups, number of withdrawals, the mean and standard deviation of PC, MPV and PDW for patients and control groups and the result of different tests were extracted and entered to EXCELL.**
***Data synthesis:*** **A total of 9 case-control studies were r found in our search from them 8 studies have reported mean PC, 7 studies have reported mean MPV and 4 studies have reported mean PDW. Our analysis showed that mean PC of patients is 0.03 (-0.14-0.20) unit higher than that of controls with 95% CI which is not statistically significant. Also, mean MPV of patients is 0.31 (-0.03-0.65) unit higher than that of controls with 95% CI which is statistically not significant too. Finally, mean PDW of patients is 0.70 (0.03-1.37) unit higher than that of controls with 95% CI which is statistically significant.**
***Conclusions:*** **Our study confirmed only the probable relationship of PDW and SSNHL but due to the limited studies on this subject more studies is needed.**

## INTRODUCTION

Hearing loss is a common and growing global condition that poses numerous negative consequences (1-3). Sudden sensorineural hearing loss (SSNHL), a common otologic emergency, is a sudden hearing loss with sensorineural origin (4). Sudden deafness or sudden sensorineural hearing loss is defined as sensorineural hearing loss of greater than 30 dB over 3 contiguous pure-tone frequencies occurring within 3 days' period (5-10). However, based on the clinical guidelines 30 dB hearing loss should not be considered as absolute and some hearing losses lower than this threshold can be considered as SSNHL

(11-13). Fortunately, the vast majority of cases of sudden sensorineural hearing loss are unilateral and less than 1 to 5% of cases occur bilaterally. Usually this disorder presents as unilateral loss of hearing; bilateral involvement is rare and simultaneous bilateral involvement is very rare. (1,8). The etiology of SSNHL remains unknown. Although, various studies have proposed many possible etiologies but more than 85% of cases are idiopathic or without any established causes (3,5,8,14,15). Also, the severity of hearing loss in this condition can vary from mild to severe or profound hearing loss which can occur in different frequencies (8). Accordingly, in clinical texts usually sudden hearing loss is subcategorized to Ascending (hearing loss at low frequencies), Descending (hearing loss in high frequencies), U-shaped (hearing loss in moderate frequencies) and Flat-type or Pancochlear hearing loss (hearing loss at all frequencies) (16). Sudden sensorineural hearing loss has a high rate of spontaneous recovery. Various studies indicate that recovery occurs in 30 to 81 percent of the cases within 14 days without treatment (8,9,17-19) but if recovery does not occur in this period spontaneous recovery will be unlikely (18). The prevalence of SSNHL varies in different countries. Reports indicate that the prevalence rate is between 5 to 30 cases per 100000 population but recent studies show that the worldwide prevalence of this condition is increasing (20,21). However, the exact estimation of SSNHL prevalence is not possible because of its high rate of spontaneous recovery without treatment. Therefore, the actual prevalence of SSNHL is probably much higher than the reported ones (22-24). Sudden sensorineural hearing loss occurs at all ages, in booth men and women and in different seasons, although some studies have shown that its prevalence in some ages and in some seasons is higher (25,26). In all cases, sudden sensorineural hearing loss needs immediate attention and can be considered as an emergency condition (1,27) because although in many cases its severity is mild but the condition can be leaded to long-term or permanent hearing loss or deafness or to long-term disturbing complications such as tinnitus (28,29). Also, because SSNHL occurs suddenly, so it can cause significant anxiety for suffered patients. Therefore, mentally it is a frightening incident that can severely reduce the of affected people's life quality (18). So far, the treatment of SSNHL has not been satisfactory due to the diversity of its etiology (30). Therefore, the study of its different aspects is one of the important research topics. In recent years, some studies have been done to establish the relationship of SSNHL with blood factors such as platelet parameters because of the similarity of SSNHL clinical manifestations to those of vascular disorders. This study was aimed to analyze the results of existing studies on the relationship of platelet parameters and the occurrence of SSNHL.

## METHODS SEARCH STRATEGY

An electronic databases' search including PubMed, EMBASE, Science Direct, OVID, Scopus and Google Scholar, (date last searched April 2016) with the use of text search terms haring loss, sudden hearing loss, sudden sensorineural hearing loss, platelet, platelet parameters, platelet count, mean platelet volume, platelet distribution width with "AND" and "OR" operations was done. The reference lists of retrieved studies were searched by hand to find publications which may not be retrieved through the databases' search. No geographical location, time or language restrictions were applied. Search was done by 2 researchers independently and the third researcher checked the agreement of retrieved studies.

## STUDY SELECTION

All case control studies which have been done to investigate the relationship of platelet parameters including PC, MPV and PDW with the occurrence of SSNHL were included in the study. For this, full texts of all articles were retrieved through an advanced search. The repeated or unrelated studies were removed and the investigation of the findings of the reminders was done to prevent bias caused by reprint (publication bias of transverse and longitudinal). The remaining results were investigated based on the study inclusion criteria.

### INCLUSION CRITERIA

All case control studies which have been done on age and sex-matched cases and controls and have reported the mean and standard deviation of PC, MPV and PDW or some of them for patients and controls were included in our meta-analysis.

## DATA EXTRACTION

The required data from selected studies including the title, authors, publication date, location of study, sample size of patients and control groups, number of withdrawals, the mean and standard deviation of PC, MPV and PDW for patients and control groups and the result of different tests were extracted and entered to EXCELL.

## DATA ANALYSIS

We used STATA ver.11 software for data analysis. The heterogeneity index between studies was determined using Cochran (Q) and I-squared tests. Random effect model was used to estimating the standardized difference of PC, MPV and PDW of patients and controls. Inverse variance method and Cohen statistics were used for estimation. The point estimation of

standardized difference of mean gestational age at delivery was calculated using forest plot and 95% confidence interval. In this plot, the size of square represents the weight of each study and its booth side's lines represent 95% confidence interval. P value < 0.01 was considered statistically significant.

## RESULTS

A total number of 13600 studies were found in the initial search from which 12548 ones were removed by limiting the search. From reminding 1052 studies, 718 studies were removed because of overlapping of searched databases. The reviewing of titles and abstracts of 334 studies indicated that 217 studies are unrelated. The remaining 117 studies were selected to investigating the full text after that 108 studies were removed from study due to their inappropriateness. The remaining 9 studies were entered to be assessed based on the inclusion criteria from them 9 studies were found to be appropriate for our study (Fig.1). From these 10 studies, 8 studies have reported PC (804 patients and 988 controls), 7 studies have reported MPV (394 patients and 372 controls) and 4 studies have reported PDW (227 patients and 218 controls) of patients and controls. It is notable that 1 study from those which have reported PC and 1 from those have reported PDW were not entered into meta-analysis because they have not reported the standard deviation of studied parameter. The characteristics of primary studies which have reported mean PC, MPV and PDW of patients and controls are presented in Table.1, Table.2. and Table.3.

Investigation of the results of retrieved studies showed that in 4 studies from 8 ones mean PC of patients is higher than that of controls but this difference is statistically significant in 1 study. The meta-analysis of results of 7 studies which have reported standard deviation of PC for patients and controls showed that PC of patients is 0.03 (-0.14-0.20) unit higher than that of controls with 95% CI which is not statistically significant. The heterogeneity between these studies was relatively high (I-squared=56.6%, Q=13.8, P=0.032). These results are presented in Fig.2. Also, in 5 studies from 7 ones which have reported MPV, the mean MPV of patients is higher than that of controls but this difference, is statistically significant in 2 studies. Analyzing the results of these studies showed that the mean MPV of patients is 0.31 (-0.03-0.65) unit higher than that of controls with 95% CI which is not statistically significant. The heterogeneity between these studies was relatively high (I-squared=81.1%, Q=31.08, P<0.001). These results are presented in Fig.3. Finally, investigation of the results of retrieved studies showed that in all 4 studies which have reported mean PDW, this parameter is higher for patients than controls but the difference of patients and controls is statically significant in 2 studies. The meta-analysis of results of 3 studies which have reported standard deviation of PDW for patients and controls showed that PDW of patients is 0.70 (0.03-1.37) unit higher than that of controls with 95% CI which is statistically significant. The heterogeneity between these studies was relatively high (I-squared=87.8%, Q=16.33, P<0.001). These results are presented in Figure 4.

**Figure 1**

*Flow diagram of the study selection process for this meta-analysis*

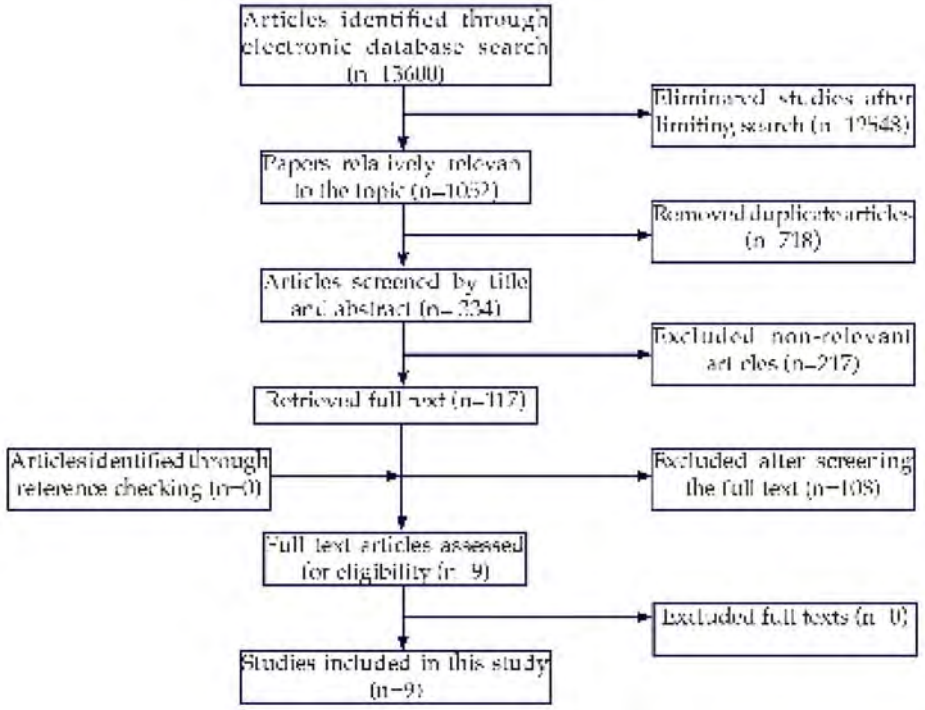


**Table 1**

*Characteristics of primary studies which have reported PC of patients and controls*

| No. | First author | Publication year | Country | Sample size | | PC, patients | | PC, controls | | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | Mean | SD | Mean | SD | |
| 1 | Ezerarslan (31) | 2016 | Turkey | 62 | 49 | 234 | 53.5 | 236 | 39 | 0.84 |
| 2 | İkincioğulları (32) | 2014 | Turkey | 102 | 119 | 263.274 | 64.108 | 259.321 | 64.797 | 0.844 |
| 3 | Karlie (22) | 2013 | Turkey | 46 | 46 | 243 | - | 275 | - | 0.27 |
| 4 | Kum (33) | 2015 | Turkey | 59 | 59 | 249.44 | 48.16 | 244.86 | 47.25 | 0.603 |
| 5 | Mirvakili (12) | 2016 | Iran | 108 | 108 | 228.51 | 62.45 | 222.86 | 36.80 | 0.418 |
| 6 | Ozturk (34) | 2014 | Turkey | 39 | 40 | 257 | 57 | 268 | 63 | 0.42 |
| 7 | Seo (35) | 2014 | Korea | 348 | 537 | 252.4 | 60.07 | 238.64 | 49.98 | 0.001 |
| 8 | Xuesong (36) | 2014 | China | 40 | 30 | 212 | 47.9 | 237.8 | 46.2 | - |

**Table 2**

*Characteristics of primary studies which have reported MPV of patients and controls*

| No. | First author | Publication year | Country | Sample size | | MPV, patients | | MPV, controls | | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | Mean | SD | Mean | SD | |
| 1 | Ezerarslan (31) | 2016 | Turkey | 62 | 49 | 8.1 | 1.2 | 8.4 | 1.2 | 0.172 |
| 2 | Karlie (22) | 2013 | Turkey | 46 | 46 | 8.25 | 0.86 | 7.98 | 0.87 | 0.113 |
| 3 | Kum (33) | 2015 | Turkey | 59 | 59 | 9.83 | 1.5 | 9.98 | 0.07 | 0.47 |
| 4 | Mirvakili (12) | 2016 | Iran | 108 | 108 | 10.02 | 0.76 | 9.85 | 0.67 | 0.088 |
| 5 | Ozturk (34) | 2014 | Turkey | 39 | 40 | 8.19 | 1.07 | 8.01 | 1.05 | 0.47 |
| 6 | Ulu (5) | 2013 | Turkey | 40 | 40 | 10.5 | 0.9 | 9.6 | 0.5 | 0.001 |
| 7 | Xuesong (36) | 2014 | China | 40 | 30 | 10.9 | 0.8 | 10.3 | 0.8 | - |

**Table 3**

*Characteristics of primary studies which have reported PDW of patients and controls*

| No. | First author | Publication year | Country | Sample size | | PDW, patients | | PDW, controls | | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | Mean | SD | Mean | SD | |
| 1 | Mirvakili (12) | 2016 | Iran | 108 | 108 | 12.45 | 1.5 | 12.11 | 1.24 | 0.076 |
| 2 | Ozturk (34) | 2014 | Turkey | 39 | 40 | 17.7 | - | 17.6 | - | 0.68 |
| 3 | Ulu (5) | 2013 | Turkey | 40 | 40 | 13.4 | 2.1 | 11.1 | 1 | 0.001 |
| 4 | Xuesong (36) | 2014 | China | 40 | 30 | 12.9 | 2 | 12 | 1.3 | - |

**figure 2**

*The difference of PC of patients and control groups (CI=95%)*

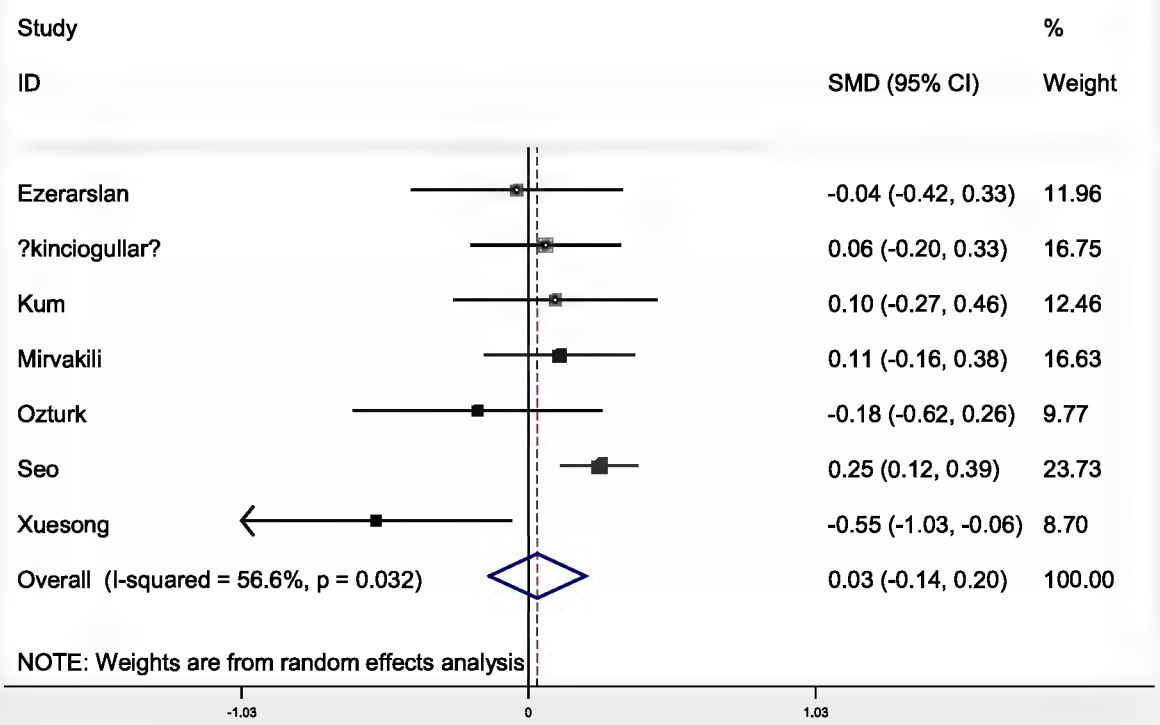



**Figure 3**

*The difference of MPV of patients and control groups (CI=95%)*

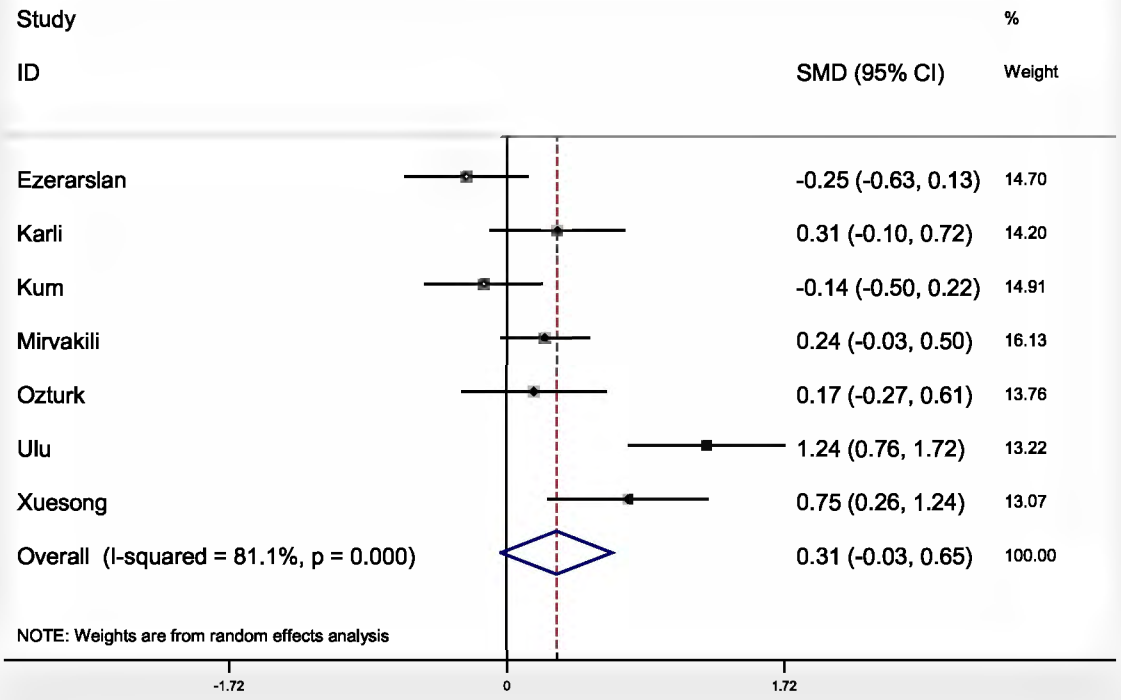
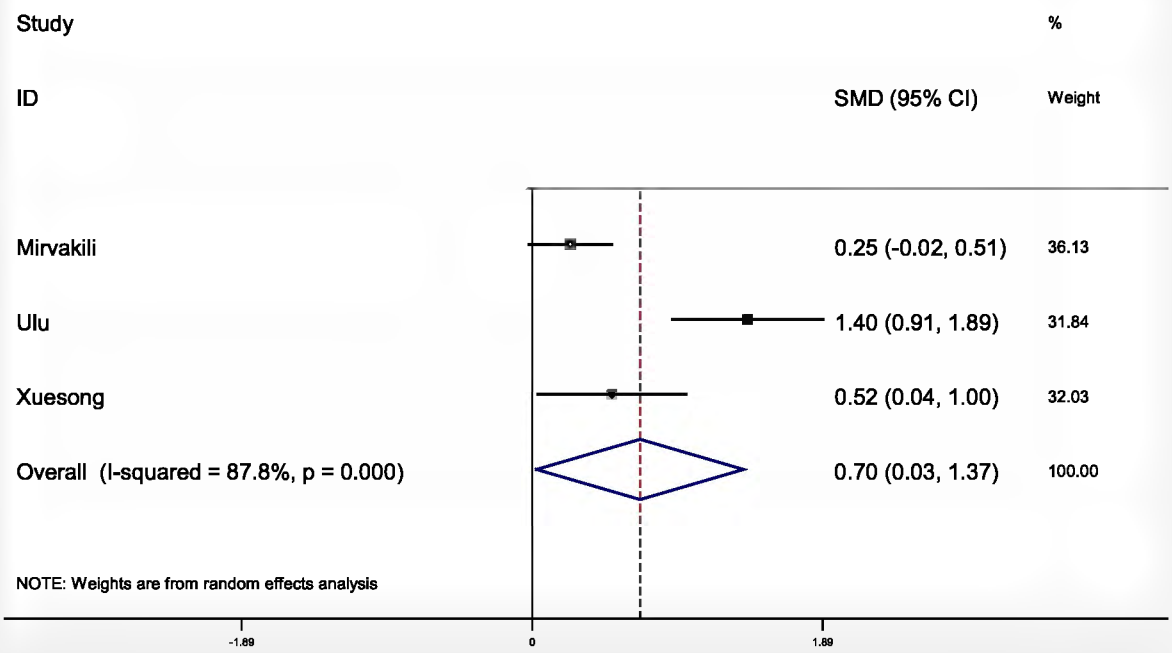


**Figure 4**
*The difference of PDW of patients and control groups (CI=95%)*




## DISCUSSION

Hearing loss is a common global problem with increasing prevalence especially in developing countries that poses numerous negative consequences. Studies show that about 50% of world population experiences some kinds of hearing impairment with age increasing. Also, the trends show that in recent decades the growth rate of hearing loss prevalence has been high, so that only between years 1965 and 1994 it has been doubled (1-3). Sudden hearing loss is a kind of hearing loss which occurs in 72 hours period in one or both ears. Sudden sensorineural hearing loss (SSNHL) is also a subset of sudden hearing loss which has sensory-neural origin (4). Although the causes of SSNHL are not known in most cases but researchers have mentioned a variety of etiologies for this condition including infectious, cardiovascular and immunological causes, damage to the tympanic membrane, genetic causes and mutations, systemic stress, autoimmune disorders, using ototoxic drugs such as aminoglycosides or salicylates, medical history, damage to the ear due to aging, prenatal and perinatal problems like as some rare childhood diseases, tumors of inner ear, exposure to high loud, arthritis temporal, coagulation disorders, local histamine production, neoplasms, prothrombotic risk factors, unusual adverse effects of some surgical procedures such as cardiopulmonary bypass surgery (1,5,6,8,9,16,20,22,25,37,38). However, each of these etiologies has been confirmed in some studies while failed to be confirmed in other ones (15). Thus, the etiology and risk factors of SSNHL still remain unknown and controversial. However, despite this anonymity, SSNHL has many known negative effects. This disorder, often is accompanied with symptoms such as tinnitus (in up to 80% of cases), dizziness (in up to 30% of cases and in 10% of cases of dizziness accompanied by nausea and vomiting), feeling of fullness of the ear (in 80% of cases), vestibular disorder, a feeling of pressure in the ears, headaches and symptoms of the viral infection of the upper respiratory tract. Also, in some cases, patients may become very anxious or experience stress and depression (4,8,17,18). Recent epidemiologic surveys also show that the prevalence of this condition is increasing (21). Thus, in recent years some researchers have attempted to identify factors associated with SSNHL. Identification of these factors can contribute highly to its diagnosis and treatment. In this time, one hypothesis which is under consideration is a possible relationship of the occurrence and severity of SSNHL with platelet parameters. Therefore, in recent years a number of studies have been done to test this hypothesis. In these studies the relationship of some platelet parameters such as platelet count, mean platelet volume and platelet distribution width with the occurrence and severity of SSNHL have been

studied with the conflicting results. Platelet count (PC) is an index of platelet function. In the scientific literature, the normal number of platelets has been noted as $150 \times 10^9$ to $400 \times 10^9$ per liter. In regarding to their count, platelets can show 2 types of abnormalities called low platelet level (thrombocytopenia) or high platelet level (thrombocytosis) (39). Mean platelet volume (MPV) is a potential indicator of the rate of production, size, function and activity of platelet. Larger platelets are more active in terms of metabolic as well as enzymatic activity. Also, they are more prone to aggregate than the smaller ones. Although the primary role of platelets is in hemostasis and thrombosis at the site of damage and bleeding but it is known that they have also a dominant role in inflammatory processes and autoimmune responses (40). Various studies have established a correlation between MPV and some clinical events such as ischemic events, heart attack, infarction, vascular thromboembolism, acute or chronic syndromes, autoimmune diseases and inflammatory conditions. (5,22) Platelet distribution width (PDW) is another important platelet parameter (41) which recently has been widely studied as an indicator of platelet activity (42). While mean platelet volume is the mean platelet size, platelet distribution width reflects the variation of platelets size in a blood sample (43). The aim of our study was to analyze the results of studies which have been done on the relationship of these 3 platelet parameters (PC, MPV and PDW) with the occurrence of SSNHL. For this, an extensive search was done, 10 studies which had the eligibility to be included in the meta-analysis were retrieved and their results were analyzed. In summary, showed that 2 of 3 studied parameters including PC and MPV have not relationship with the occurrence of SSNHL but the relationship between PDW and the occurrence of SSNHL was confirmed. In primary studies which have been included in our meta-analysis also, the relationship of the occurrence of SSNHL with PC in 1 study, with MPV in 2 studies and with PDW in 2 studies had been confirmed. Therefore, it seems that making definitive conclusion requires further studies.

In conclusion, our meta-analysis showed that PDW has a significant relationship with the occurrence of SSNHL while PC and MPV have not the same relationship. However, due to the scarcity of literature on this subject more studies are needed.

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