Title page

Association between platelet distribution width with serum uric acid in Chinese

Short running title: PDW and UA

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Competing conflict of interest statement

We declare no conflict of interest in the paper.

Abstract

Platelet distribution width (PDW) is a simple and inexpensive parameter, which could predict activation of coagulation efficiently. And it has been confirmed to have a significant role in many diseases. We aimed to explore the association between PDW and hyperuricemia in a large Chinese cohort. This cross-sectional study recruited 61091 ostensible healthy participants (29259 male, 31832 female) after implementing exclusion criteria. Clinical data of the enrolled population included anthropometric measurements and serum parameters. Database was sorted by gender, and the association between PDW and hyperuricemia was analyzed after dividing PDW into quartiles. Crude and adjusted odds ratios (OR) of PDW for hyperuricemia with 95% confidence intervals were analyzed by binary logistic regression models. We found no significant difference in PDW values between the genders. Males showed significantly higher incidence of hyperuricemia than femals. From binary logistic regression models, significant hyperuricemia risks only were demonstrated in PDW quartiles 2 and 3 in males ($p<0.05$). This study displayed close association between PDW and hyperuricemia as a risk factor. It is meaningful to use PDW as a clinical risk predictor for hyperuricemia in males.

Key words: Platelet distribution width (PDW); hyperuricemia; uric acid (UA); platelets (PLT); gender

1. Introduction

Hyperuricemia is a state of abnormally high level of uric acid (UA) in the blood. A number of epidemiologic studies have indicated that hyperuricemia is closely associated with a wide range of diseases, such as type 2 diabetes mellitus(1), hypertension(2, 3), obesity(4), incident kidney disease(5), metabolic syndrome(6, 7), stroke(8), heart failure(9), thyroid disorders(10), peripheral artery disease(11) and et al. Platelet distribution width (PDW), which is considered as one of integral components in the general assessment of platelet (PLT) function, is a morphometric index as well as quantitative measure of size distribution and variability of PLT(12). In recent years, PDW has also been identified to be related with many diseases just like hyperuricemia, such as myocardial infarction(13), carotid artery stenosis(14, 15), type 2 diabetes mellitus(16), obesity(17), acute appendicitis(18), bone mineralization(19), contrast-induced nephropathy(20) and et al. Based on these phenomena, we may wonder whether PDW and hyperuricemia could be related. Therefore, in the present study, we sought to determine the association between PDW and hyperuricemia in a gender-specific manner in a representative sample of Tianjin municipality population.

2. Methods

2.1. Design

We used data from a cross-sectional, community-based health-check investigation in Tianjin Medical University General Hospital. The rational and methodology have been reported previously(7, 21-24, 10, 25-30). In brief, a questionnaire was self reported by the ostensible healthy participants, who came to our institution for the annual medical checkup. And a blood sample was obtained subsequently for each person. In order to avoid the confounding factors, exclusion criteria were exercised for the following situations: participants with histories of hematological, hepatic, renal, gastro-intestinal, inflammatory, infectional, thyroidal, oncological or immunological diseases; subjects taking any medicine that might influence hematology, UA level, thyroid, inflammation, infection or immune;

pregnancy. For the purpose of this particular study, a total of 61091 eligible subjects (29259 male, 31832 female) with adequate data for analysis were compiled and included during the period from September 2010 to September 2015. The institutional review board and ethic committee of Tianjin Medical University General Hospital approved this study. And all of participants provided their written consents.d pressure (SBP), diastolic blood pressure (DBP), ALT, TBIL, BUN, Cr, UA, TC, TG, HDL, WBC, RBC, PLT, PDW and MPV were significantly different between two genders. However,there was no significant difference in LDL values between the two genders.

3.2. UA values based on different genders and PDW groups

We used different quartiles for different data sets for Kruskal-Wallis test (**Table 2, Figure 1**). In total data, statistics for PDW subgroups was χ^2=13.779 (P<0.01). Further Mann-Whitney U test revealed that the differences in UA between each two groups of PDW ≤11.20, 11.20< PDW ≤12.30, 12.30< PDW ≤13.70 and PDW >13.70; and the differences between PDW ≤11.20 and PDW >13.70(P<0.01), the differences between 11.20< PDW ≤12.30 and PDW >13.70(P<0.01), and the differences between 12.30< PDW ≤13.70 and PDW >13.70 were significant (P<0.05).

In males, the statistics for PDW subgroups was χ^2=35.250 (P<0.01). Further Mann-Whitney U test revealed that the differences in UA between each two groups of PDW ≤11.10, 11.10< PDW ≤12.20, 12.20< PDW ≤13.60 and PDW >13.60; and the differences between PDW ≤11.10 and 11.20< PDW ≤12.30 (P<0.01), and the differences between PDW ≤11.10 and 12.20< PDW ≤13.60 (P<0.01), and the differences between PDW ≤11.10 and PDW >13.60 were significant (P<0.01).

Furthermore, in females, the statistics for PDW subgroups was χ^2=12.691 (P<0.01). Further Mann-Whitney U test revealed that the differences in UA between each two groups of PDW ≤11.30, 11.30< PDW ≤12.30, 12.30< PDW ≤13.80 and PDW >13.80; and the differences between PDW ≤11.30 and 12.30< PDW ≤13.80 (P<0.05), and the differences between 11.30< PDW ≤12.30 and PDW >13.80 (P<0.01), and the differences between 12.30< PDW ≤13.80 and PDW >13.80 were significant (P<0.01).

3.3. Correlations between PDW and other key variables

The results of the Pearson bivariate correlations between PDW and other variables based on different genders showed that PDW demonstrated significant negative relationships with some variables, including age, PLT and UA in males, as well as age, RBC, PLT and UA in females (**Table 3**). In addition, PDW showed significant positive relationships with some variables, including ALT, TBIL, TG, WBC and MPV in males, as well as BMI, ALT, TBIL and MPV in females.

3.4. Incidence of hyperuricemia according to PDW quartiles

PDW quartiles were calculated and respective incidence of hyperuricemia was compared between genders. Males showed significantly higher overall incidence of hyperuricemia than females. Detailed incidences inPDW quartiles showed an increasing trend among males, but this trend was not obvious in females (**Table 4**).

3.5 Diagnostic value of PDW for hyperuricemia

From receiver operating characteristic (ROC) analysis, PDW demonstrated limited diagnostic and predictive values for hyperuricemia in males, while, there is no statistical value of PDW in females. Areas under the curves were found to be 0.514 ($p<0.01$) in males and 0.508 ($p>0.05$) in females respectively. Cut-off value for males was calculated to be 12.25%, diagnostic accuracy to be 51.813%, sensitivity to be 50.037%, specificity to be 52.218%, PPV to be 19.258% and NPV to be 82.106%.

3.6. Risks of hyperuricemia in different genders

Binary logistic regression models were implemented to calculate the risks of hyperuricemia in different variables including age, BMI, ALT, TBIL, BUN, Cr, TC, TG, HDL, LDL, WBC, RBC, PLT and PDW (**Table 5**).Most parameters displayed detrimental effects for an association with hyperuricemia in both genders, except for TBIL in both genders and PDW in females.

Moreover, binary logistic regression models were implemented to calculate the risks of hyperuricemia in different genders with the lowest PDW quartile as reference (**Table 6**). Significant risks were demonstrated for hyperuricemia in high PDW quartiles in males. Adjusted risk factors included age, BMI, ALT, BUN, Cr, TC, TG, HDL, LDL, WBC,

RBC and PLT as covariates. After adjustment, significant risks maintained for hyperuricemia only in the second and third PDW quartile in males, while the result had no significance in females.

4. Discussion

There is one piece of previous evidence focusing on the independent association between PDW and UA. Tayefi et al.(31){Tayefi, 2018 #2060} showed a significant positive association between PLT and UA in hypertension patients, and PLT and PDW could be independent determinants of a high serum UA in newly diagnosed hypertensive patients. But this study had limitations of restricted case number, not focusing on gender differences, and all cases being hypertensive. The present study is a research focusing on the independent association between PDW and hyperuricemia in a huge sample size of health examination participants. And our study indicated that a high level of PDW could be associated with an increased risk for hyperuricemia only in males.

The underlying reason of the relationship between PDW and hyperuricemia deserves discussion. We postulate that the serum UA may affect the value of PDW by affecting PLTs in different ways. Firstly, serum UA has a low physical solubility in the blood. A high concentration of serum UA is easy to form urate crystals and to deposit in the blood vessel walls which could damage vascular endothelial cells and activate PLTs. Then the aggregation function of PLTs will increase, which will show up as the increased cell surface granule membrane protein expression and then being released into the blood(32). Secondly, a high UA concentration could impair endothelium-dependent vasodilatation significantly by activating the renin-angiotensin system. Activated renin-angiotensin system could not only increase renin activity and the adhesion and aggregation of PLTs,but also reduce nitric oxide production via inhibiting nitric oxide synthase synthesis, which could also enhance PLT activation(33). Thirdly, a high level of UA also promotes LDL cholesterol oxidating and lipid peroxidating. Oxidized LDL activates PLTs via combining with lipoprotein specific binding sites on PLTs'

surface(34). Fo, oxidative stress response caused by hyperuricemia can activate WBCs and promote adhesion of leukocytes and endothelial cells, and has a positive correlation with the level of inflammatory cytokines *in vivo*, suggesting that blood UA involved in vascular inflammation. Besides, UA causes vascular injury through inflammatory reactions, complements activation through classical and alternative pathways, mast cells stimulation, and PLTs and enhance thrombosis activation. has All the above changes have been reported to be the mechanisms of developing cardiovascular and cerebrovascular diseases(35, 36). Fifthly, it has been suggested that serum UA has a significant positive correlation with C-reactive protein (CRP), a soluble inflammatory marker(37). It has also been confirmed that a significant positive correlation between CRP and thrombopoietin exists(38), thus it can be deduced that CRP and thrombopoietin could play a crucial role in promoting the generation of PLT and affecting PLT activity. Besides, PLT is independently related to the level of CRP, which is regarded as the underlining reason linking PLT and inflammation(39). Finally, as we all know that PDW is a direct flow cytometric measurement of PLT cell volume. And it has been confirmed that PDW increases during PLT activation and it could predict activation of coagulation efficiently(40). From the above, we could hold the opinion that hyperuricemia is closely related with PDW increasement, which means that we could reflect the level of serum UA through different values of PDW.

PDW showed significant effect for hyperuricemia in males, while no significance in females in the current study. About this phenomenon, we think it should be related with sex hormones. Evidence that gender differences play a role in PLT reactivity has been confirmed in previous studies(41). And it has also been observed that women have a higher magnitude of PLT reactivity than men(42). The process by which megakaryocytes proceed to proplatelet formation and production of PLTs is reportedly under the influence of

autocrine estrogen(43). Additionally, estrogen-receptor antagonists inhibit PLT production in vivo, supporting a role of estrogen in PLT production(44). On the other hand, UA is generally higher in male than female after sexual maturity, while this difference decreases after menopause. This means that female hormone of estrogenhas a significant protective effect against hyperuricemia. The current study indicated although the levels of PDW were not significantly different between genders (**Table 1**), the male-dominance phenomenon of hyperuricemia still existed in terms of PDW-based gender difference (**Table 6**). It could be deduced that sex hormones could be the inherent driving force, making such a difference.

There are several limitations in this study. First, causality relationship cannot be determined in such a cross-sectional designed study. Prospective or interventional investigations should be conducted in the future. Second, lifestyle factors, such as dietary habits, exercise frequency might influence serum UA and PDW values but was not recorded in details as confounding factors. Third, we checked blood parameters only once, andwe did not measure sex hormones and inflammatory factors, these are due to budget shortage. Fourth, although we applied strict exclusion criteria to rule our PDW influencing diseases, a number of the participants withvarious diseases might not be aware of their medical conditions, which could be a confounding factor in our research.

In conclusion, the current study proves that PDW and hyperuricemia are closely related. A high level of PDW is associated with a high risk of hyperuricemia in males. It seems reasonable to suggest that the assessment of PDW, a simple and inexpensive parameter, could be used as a clinical risk predictor for hyperuricemia in males.

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