Experimental
&
Clinical Article

Can the First Trimester Mean Platelet Volume and Mean Platelet Volume/Lymphocyte Ratio Predict Gestational Diabetes Mellitus?

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ABSTRACT

OBJECTIVE: This study aimed to evaluate whether there were differences in the first-trimester inflammatory markers: NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), MPV (mean platelet volume), and MPVLR (MPV-to-lymphocyte ratio), between cases with and without gestational diabetes mellitus (GDM).

STUDY DESIGN: The study was designed by examining the first-trimester hemogram parameters of cases who underwent GDM screening. The primary outcome was to determine the differences and effectiveness of NLR, PLR, MPV, and MPVLR values in the first trimester between study groups before the diagnosis of GDM.

RESULTS: A total of 878 cases were analyzed in the study. Patients were divided into two groups based on the 75-gram oral glucose tolerance test (OGTT). The study groups consisted of cases with GDM (n=127) and without GDM (n=751). While leukocyte count was found to be marginally higher in the GDM group (8.6±2.2 x103/mm3 vs. 9.0±2.4 x103/mm3, p=0.047), NLR and PLR values did not differ between the groups. Although a minimal increase in MPV values was observed in the GDM group, it did not reach statistical significance (10.0±1.1 fL vs. 9.9±1.0 fL, p=0.785). Similarly, MPVLR values were comparable between the groups. However, the ROC analysis revealed MPVLR as the most effective marker for GDM detection (AUC: 0.537).

CONCLUSION: Simple and cost-effective inflammatory markers examined in the first trimester may provide insights into predicting GDM. NLR, PLR, and MPV values stand out in this regard. Additionally, the newly examined MPVLR in GDM cases suggests its potential as a more effective predictor than these markers in our study.

Keywords: Gestational diabetes; Mean platelet volume; Mean platelet volume-to-lymphocyte ratio; Neutrophile-to-lymphocyte ratio.

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Introduction

Gestational diabetes mellitus (GDM) is a widely prevalent complication during pregnancy. The incidence of the condition varies significantly, ranging from 4% to 30% depending on the diagnostic test used and the demographic characteristics of the population (1,2). Generally, GDM is associated with a low-grade inflammatory response (3). The emergence of this systemic inflammatory response is thought to stem from pancreatic dysfunction leading to insulin resistance, which can contribute to a low-grade inflammatory response after the first trimester (4,5). Perinatal risks associated with GDM include an increased likelihood of conditions such as macrosomia, shoulder dystocia, asphyxia, polyhydramnios, and other complications (6-8). Therefore, early screening and diagnosis of the disease become crucial (9-11). Studies have indicated that the pathophysiological processes related to diabetes commence weeks before diagnosis and can be detected in the blood even before the diagnosis of conditions like GDM (12). We know that neutrophils, leukocytes, and some other hematological parameters may play a role in the immune re-

sponse (13). They can show changes, especially in clinical conditions where inflammatory processes are more prominent, such as infections and autoimmune diseases. These hematological parameters and their ratios have been shown to be important predictors in conditions involving an inflammatory response, such as coronary artery disease and certain rheumatic disorders (14,15). Various studies have suggested that parameters such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), white blood cell count (WBC), and mean platelet volume (MPV) may play a role in predicting and screening GDM cases (16,17). Recent studies have been conducted indicating that MPV values in the first trimester examination might predict the presence of GDM (18,19). Some studies in the literature have shown that the MPV-to-lymphocyte ratio (MPVLR) is associated with inflammatory response in cases of type 2 diabetes mellitus and in individuals who have had myocardial infarction (20,21). However, there is no significant study addressing the predictive role of MPVLR values in GDM cases. Therefore, we aimed to conduct a study evaluating the utility of hematologic values, particularly MPV and MPVLR parameters, along with markers of inflammatory response, in predicting GDM cases based on blood samples taken in the first trimester.

Material and Method

This retrospective observational study was undertaken at a university-based teaching hospital between 2018 and 2020. The Local Ethics Committee of the University approved the study (2020/37), and the study was conducted in accordance with the Declaration of Helsinki. All subjects gave their informed consent for using the data for the study. The inclusion criteria were women between 18 and 42 years old who had single pregnancies, underwent first-trimester and gestational diabetes screening tests, and whose pregnancies resulted in delivery. We excluded pregnancies with pregestational diabetes mellitus, some gestational conditions such as gestational hypertension, hematological problems, thyroid disorders, chronic inflammatory problems, and conditions that may affect the inflammatory state.

The hospital database was reviewed, and the data were collected for evaluation. The maternal age, parity, and body mass index were baseline data of the patients. All the blood tests were obtained between 11 and 13 gestational weeks. The first trimester routine screening tests of PAPP-A and other routine biochemical and hematological assessments, such as fasting glucose, leukocyte counts, platelet counts, and MPV, were also recorded. NLR and PLR were calculated by using neutrophil, lymphocyte, and platelet values. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR was calculated by dividing the platelet count by the absolute lymphocyte count. MPVLR was also calculated by dividing the MPV value by the lymphocyte count.

Gestational age at the first trimester test, gestational age at birth, and birth weight were recorded. Patients were classified into two groups, gestational diabetes and non-gestational diabetes, based on the results of a glucose tolerance screening test. Statistical analysis

We used IBM SPSS Statistics version 21.0 to analyze the data. The normality of quantitative variables was assessed using the Shapiro-Wilk test. Normally distributed variables were analyzed with the parametric tests such as Student's t-test and ANOVA, whereas skewed variables were analyzed with non-parametric tests, such as Mann-Whitney U and Kruskal-Wallis tests. The categorical variables were presented as percentages. The cut-off values for the parameters were determined using ROC curves, and the areas under the curve (AUC) were calculated. The Youden index was used to identify the optimal criterion and the sensitivity and specificity values for all parameters separately. In terms of the identified values, the parameters were compared with each other using ROC curves. A p-value below 0.05 was considered statistically significant.

Results

We evaluated a total of 1099 patients, of whom 221 were excluded according to the previously stated exclusion criteria. Finally, 878 patients were included in the analyses. The mean gestational weeks for the first trimester laboratory tests evaluation was 12.24±0.84 weeks for the overall population. The study population was divided into two groups, the GDM and non-GDM groups, based on the oral glucose screening test performed at 24-28 gestational weeks. The GDM group included 127 patients, whereas the non-GDM group included 751 patients. We found significant differences between the study groups in terms of age and parity (Table I). All comparisons of first-trimester results are presented in Table I. No significant differences were observed between the study groups, except for first-trimester glucose and leukocyte count. The inflammatory parameters, such as NLR, PLR, and MPV, did not differ between the GDM and control groups (Table I). Although MPV levels were higher in the GDM group, this difference did not reach significance. MPVLR was studied in the prediction of GDM for the first time in the literature. However, MPVLR was not high in the GDM group, and there were no significant differences between the GDM and non-GDM groups.

We have also performed regression analysis to determine the potential confounding inflammatory markers on predicting GDM by first-trimester blood parameters. On univariate regression analysis, there were no significant differences for the first-trimester inflammatory markers (NLR, PLR, MPV, and MPVLR) (Table II). We only found significant differences for the first-trimester fasting glucose level in the regression analysis.

Table I: *Demographic parameters and first trimester haematological values*

	Non-GDM (n=751)	GDM (n=127)	p
Age (years)	28.3 ± 5.6 (28)	30.0 ± 5.2 (30)	<0.001
P	2.0 ± 1.0 (2)	2.3 ± 1.0 (2)	0.015
BMI (kg/m^2)	24.4 ± 5.7 (24)	25.8 ± 5.6 (25)	0.055
Gestational Age (on the test day) (days)	85.6 ± 6.1 (86)	86.4 ± 5.0 (86)	0.287
Glucose (mg/dL)	86.9 ± 10.7 (86)	91.8 ± 14.8 (90)	<0.001
PAPP-A	3.1 ± 2.2 (2.6)	2.8 ± 2.1 (2.3)	0.173
WBC (10^3/mm^3)	8.6 ± 2.2 (8.4)	9.0 ± 2.4 (8.7)	0.047
PLT (10^3/mm^3)	253.4 ± 57.9 (247)	260.2 ± 61.8 (253)	0.268
NLR	3.1 ± 1.4 (2.9)	3.1 ± 1.3 (2.8)	0.828
PLR	132.4 ± 40.7 (127)	127.9 ± 35.9 (121)	0.233
MPV (fL)	9.9 ± 1.0 (9.9)	10.0 ± 1.1 (9.8)	0.785
MPVLR	5.3 ± 1.8 (5)	5.1 ± 1.7 (4.9)	0.188
Gestational Age (on the delivery) (days)	270.3 ± 12.0 (270)	268.9 ± 15.2 (269)	0.167
Newborn Weight (kg)	3212.5 ± 519.4 (3210)	3310.9 ± 513.3 (3307)	0.078

Values were defined as mean standard deviation (median), P: Parity, BMI: Body mass index, WBC: White blood cell, PLT: Platelet, NLR: neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MPV: Mean platelet volume, MPVLR: MPV-to-lymphocyte ratio

Table II: *Univariate Logistic Regression Analysis of the Parameters Related to Gestational Diabetes Mellitus*

	OR	95% CI	p
BMI (kg/m^2)	1.019	0.974 – 1.066	0.406
First Trimester Glucose (mg/dL)	1.042	1.014 – 1.071	0.003
First Trimester NLR	1.211	0.931 – 1.574	0.153
First Trimester PLR	0.996	0.983 – 1.008	0.494
First Trimester MPV (fL)	1.036	0.688 – 1.560	0.867
First Trimester MPVLR	0.902	0.653 – 1.247	0.534

BMI: Body mass index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MPV: Mean platelet volume, MPVLR: MPV-to-lymphocyte ratio

Separate threshold values were determined for NLR, PLR, MPV, and MPVLR. However, none of these thresholds demonstrated statistical significance. Nevertheless, the areas under the curve (AUC) for each parameter were calculated, and the parameters were compared (Figure 1). The threshold values that we have determined for MPV and MPVLR measurements are 9.9 and 3.74, respectively, according to the Youden index criteria. Although statistical significance was not achieved, MPVLR showed the highest potential for predicting GDM, followed by PLR.

Additionally, when examining the sensitivity and specificity values of the parameters, it was found that although MPVLR had the lowest sensitivity (23.8%) among the parameters, it exhibited the highest specificity (84.8%). The parameter with the highest sensitivity value was identified as PLR (89.7%). These findings suggest that MPVLR may be particularly effective in identifying individuals without GDM.

Discussion

In the current study, we determined that the hematological parameters and biochemical values examined during the first-trimester screening tests did not have a significant effect on predicting GDM. Our main aim was to assess platelet-related parameters like MPVLR and MPV, along with inflammatory markers NLR and PLR, and we found no significant differences between patients with and without GDM. However, when comparing the effectiveness of these parameters in predicting GDM, the findings suggest that MPVLR stands out more prominently compared to other parameters. Additionally, we observed significant differences in both fasting blood sugar and white blood cell count values among GDM cases.

The pathological mechanism in the development of gestational diabetes is associated with hyperglycemia and insulin resistance. Obesity is generally recognized as a known risk factor for both DM and GDM. It notably affects approximately half of the pregnant population (22). Adipose tissue can lead to a range of inflammatory metabolic effects through the action of adiponectin, leptin, and various cytokines such as TNF-α, IL-6, and IL-1 (23,24). In particular, adipose tissue serves as a significant source of cytokine secretion in pregnant individuals. Inflammation plays a role in the development of both DM and GDM, accompanying a chronic low-grade inflammatory process (19,25,26). The placenta contributes to inflammation and insulin resistance through the release of proinflammatory cytokines. During pregnancy, weight gain leads to alterations in cytokine secretion, shifting the balance between proinflamma-

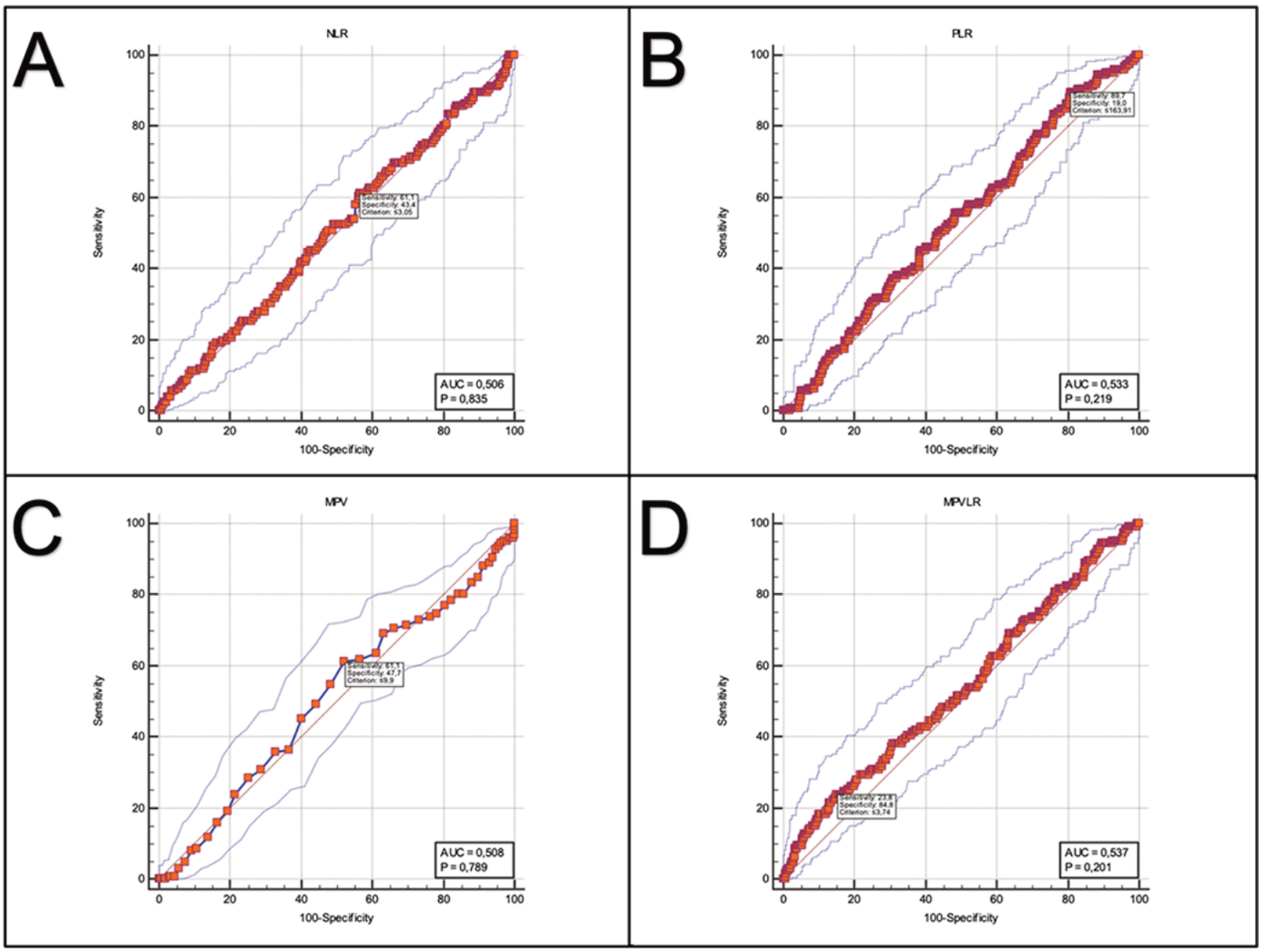

Figure 1: *ROC curves of the NLR, PLR, MPV, and MPVLR (A - NLR, Neutrophil-lymphocyte ratio; B - PLR, platelet-lymphocyte ratio; C - MPV, mean platelet volume; D - MPVLR, MPV-lymphocyte ratio)*

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; MPV: Mean platelet volume; MPVLR: MPV-to-lymphocyte ratio

tory and anti-inflammatory cytokines toward a proinflammatory state, thereby increasing the risk of GDM. Although oxidative stress can occur in normal pregnancies, its impact is more pronounced in pathological conditions such as GDM (27,28). GDM has been associated with markers of oxidative stress, and defects in antioxidant mechanisms have also been observed (29). Insulin resistance holds a crucial role in the inflammatory mechanism associated with GDM (30). At this point, several simple biomarkers that can be detected in the blood may help predict the course of the condition. Increases in leukocyte counts, particularly in neutrophils, and changes in platelet values such as MPV are frequently observed in both acute and chronic inflammatory processes (26,31).

Elevated leukocyte counts detected at the beginning of pregnancy have been associated with a higher risk of GDM (32). In our study, we also found statistically significantly higher values in the leukocyte counts of cases diagnosed with GDM during the first trimester. Parameters considered more valuable in terms of inflammation, like NLR and PLR, are also used in the identification of GDM cases (16). Some studies suggest that NLR and PLR values might reflect chronic inflammation in GDM and are significantly elevated in GDM (16,33,34). However, conflicting results exist; for instance, Sargın et al. found no significant correlation between GDM and non-GDM patients in terms of NLR and PLR values (35). Similarly, while we found significant differences in leukocyte values, such significance was not observed between the study groups for NLR calculations in our study.

MPV emerges as an important indicator in demonstrating platelet function and activation and is considered a marker that could correlate with blood glucose. It has been observed that larger platelets possess a more active metabolic and enzymatic profile, as well as a larger prothrombotic potential (36). Platelet counts can increase in response to various systemic inflammatory conditions and events, with elevated platelet levels indicating underlying inflammation. In this context, MPV and assessments involving it possess the potential to serve as significant markers in predicting and monitoring some inflam-

mation-related diseases. Some previous studies have shown an increase in MPV values in DM and coronary artery diseases, indicating its role as an inflammatory marker (37,38). Additionally, in conditions associated with diabetes and metabolic syndrome, higher MPV levels have been found to correlate with poor glycemic control (39). Earlier studies have indicated a relationship between high MPV values and gestational DM and preeclampsia (40,41). GDM screening is routinely performed in the 2nd trimester, and some studies have evaluated the correlation of parameters obtained from tests conducted during this period with diagnosed GDM cases. Some significant elevation in MPV values measured in the 2nd trimester has been observed in GDM cases (16,34). In a case-control study comparing hematologic parameters between GDM cases and a control group, no statistical difference was detected, with lower values noted in the GDM group (42). Erdogan et al. identified lower MPV values in the GDM group in a retrospective study (43). In a cross-sectional study, Gorar et al. reported statistically significantly lower MPV values in GDM cases (44). In a meta-analysis, 19 studies were included, and the relationship between MPV and GDM was evaluated (26). According to the results of the meta-analysis, the MPV value was found to be significantly higher in cases of GDM. In our study, no significant difference was found between the groups in terms of MPV values. The differences in results among the studies may suggest that the study design and ethnic variations could have an impact on the results.

In most studies, the inflammation markers are measured during GDM screening. However, in our study, we aimed to determine the value of these simple parameters in diagnosing gestational diabetes early without conducting GDM screening based on the values that we measured in the first trimester. Although the results we obtained did not show significant significance in terms of NLR, PLR, and MPV, the evaluation of the tests in the first trimester and the results obtained led us to consider that inflammatory processes may have started in the early stages of pregnancy. Similarly, in two relatively recent retrospective studies, the values measured during the first-trimester screening were evaluated for differences in patients diagnosed with GDM. In a study by Huang et al., it was reported that the MPV values determined in the first trimester were statistically significantly higher in GDM cases (19). They also determined a threshold value of 10.1 for MPV, and it was reported that the MPV values varied in correlation with GDM in the multivariate analysis. Colak et al. have performed a retrospective study, and the MPV value was found to be significantly higher in GDM cases and in older cases (18). In this study, a threshold value of 7.38 was determined for MPV in predicting GDM. In our study, the threshold value for MPV was determined to be 9.9, similar to the study by Huang et al (19). However, we could not find a statistically significant difference in the threshold value that we determined in our study. It is known that the potential detection of GDM in the first trimester is crucial for taking early preventive measures. Although the effects of GDM can occur at any stage of pregnancy, most patients are diagnosed in the 2nd trimester. In this context, being able to make an early diagnosis and intervene early becomes crucial.

MPVLR, a relatively new inflammatory marker, has been used to diagnose certain diseases and assess their severity. Hudzik et al. observed that the group with higher MPVLR values in cases of diabetes and acute myocardial infarction had higher mortality rates (20). In their study, they established a threshold value for MPVLR at 4.46. In another retrospective study, Bilgin et al. found higher MPVLR values in the frail group of Type 2 DM cases, whereas the NLR value did not differ significantly (21). To the best of our knowledge, there hasn't been a study evaluating the association between MPVLR values in the first trimester and the prediction of GDM. Therefore, our study seems to be the first study to conduct this evaluation. Despite the statistically insignificant differences observed in MPVLR values between groups with and without GDM, being the pioneering study in this field gives it significance. Further studies assessing MPVLR values could provide more insights into the importance of this examination. Additionally, our study is the first to compare the efficacy of the parameters we assessed in predicting GDM using MPVLR. Although statistically not significant, our results indicated that MPVLR provided the most effective prediction.

Limitations and Strengths: Our study has certain strengths and limitations. Among the limitations, it is important to note that the study was retrospective and conducted at a single center. Additionally, the control group cases for GDM were not matched based on similar age and demographic characteristics. While this could be challenging due to the retrospective nature of the study, it stands as a limitation. On the other hand, one of the strengths of the study can be considered its position as one of the few studies to predict GDM in early gestational weeks. Furthermore, the analysis of a relatively substantial number of cases is an important aspect. As well, being one of the first studies in the literature to use MPVLR values for this purpose and compare them with other parameters is also highly significant.

Conclusion

In conclusion, the early detection of gestational diabetes cases and the prevention of potential risks are crucial. In this context, utilizing tests that can be applied in the first trimester to detect this condition would be a highly beneficial approach. Inflammatory processes associated with GDM, including NLR, PLR, MPV, and the recently introduced MPVLR markers, can be used in identifying potential cases. According to the results we found in our study, MPVLR stands out with the highest likelihood of effective detection among these markers. However, further studies are needed regarding the effectiveness of MPVLR and other markers in first-trimester examinations.

Declarations
Funding: None declared.
Ethical approval: Research with human subjects complies with all relevant national regulations and institutional policies and the principles of the Declaration of Helsinki (revised in 2013) and was ap-proved by the Karabuk University Ethics Committee with the decree numbered 2020/373.
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