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SYSTEMIC IMMUNE-INFLAMMATION INDEX AND OTHER INFLAMMATION BIOMARKERS IN THE DIAGNOSİS OF GESTATIONAL DIABETES MELLITUS

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Abstract

Aims: Gestational diabetes mellitus (GDM) emerges during pregnancy due to physiological shifts, resulting in an adverse intrauterine environment characterized by insulin resistance and hyperglycemia, with inflammation believed to play a significant role. While inflammatory processes are typically protective, they may become dysregulated. Recognized biomarkers of inflammation include neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and lymphocyte-to-monocyte ratio (LMR).

Methods: This retrospective cohort study took place between January 2022 and December 2023 at a tertiary training and research hospital. A comparison of inflammation markers was conducted between patients with (Group B) and without (Group A) GDM.

Results: A total of 567 patients were included in the study. A significant difference was observed in the mean SII values between the groups, with group A exhibiting 1144±400 and group B having a mean SII of 1280±496 (p=0.002). Another significant difference observed between groups for NLR (p=0.001).

Conlusion: The significant differences observed in SII values between patient groups, coupled with the discriminative abilities of SII and NLR in diagnosing GDM, underscore the potential clinical relevance of these markers.

Keywords: *Systemic immune inflammation index, gestational diabetes, inflammation markers, neutrophil lymphocyte ratio.*

Introduction

Gestational diabetes mellitus (GDM) is a condition that manifests during pregnancy as a result of physiological changes associated with gestation. An unfavorable intrauterine environment due to insulin resistance and hyperglycemia is linked to negative outcomes during pregnancy and for newborns. These include preeclampsia, fetal macrosomia, neonatal metabolic and respiratory issues, a higher rate of cesarean sections, and related health complications.[1] The global incidence of GDM is on the rise, with prevalence rates ranging from 1% to 14% in various studies.[2] The American College of Obstetrics and Gynecology (ACOG), recommends oral glucose tolerance testing (OGTT) as a primary method for assessing glucose intolerance in pregnant patients.[3] Given the challenges associated with patient compliance for OGTT and the physical repercussions, such as nausea and vomiting, there is a pressing need to explore alternative methods for screening for potential GDM.

Inflammation is a biological response triggered by cellular damage, characterized by heightened blood flow, capillary dilation, leukocyte infiltration, and the release of specific chemical mediators. While inflammation is usually protective, it can, in certain instances, lead to detrimental effects. Chronic low-level inflammation represents a pathological state observed in specific conditions, like metabolic syndrome, diabetes mellitus (DM), and cardiovascular diseases. The significance of low level but chronic inflammation lies in its role in the initiation and advancement of these diseases.[4] Assessing the extent of inflammation in both maternal and fetal contexts can be achieved through various invasive and noninvasive methods. In addition, there has been increased interest in recent years for cost-effective, practical, and noninvasive approaches to estimating inflammation, particularly in the field of obstetrics. This estimation has often been based on maternal complete blood count parameters.[5,6]

Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV) are recognized as biological indicators of inflammation.[7] Prior research has demonstrated associations between increased platelet count and volume with conditions such as diabetes, impaired fasting glucose, and insulin resistance.[8] Studies have indicated significant correlations between NLR and PLR levels with metabolic syndrome. NLR and PLR serve as straightforward, easily calculable, and cost-effective indices of systemic inflammatory burden, with correlations to prognosis in various diseases, including tumors, inflammatory bowel disease, and ischemic cardiomyopathy.[9,10] The systemic immune inflammation index (SII), a newly established metric, has been used for predicting various medical conditions, such as coronary heart disease, diabetes mellitus, arthritis, and ulcerative colitis. Recently, it has garnered attention for its potential utility in pregnancy-related disorders, including GDM.[11]

In this study, the objective was to explore a potential connection between inflammation biomarkers derived from a complete blood count and their feasibility in establishing a novel diagnostic approach for GDM or, if this is not sufficiently discriminatory, then a screening algorithm for GDM using these biomarkers prior to selection for OGTT.

Methods

This retrospective cohort study was conducted between January 2022 and December 2023 at a tertiary training and research hospital. The study included electronic records of patients at 24-28 weeks of pregnancy who underwent 75 g glucose, 2-hour OGTT (Fasting glucose level ≥92 mg/dL; 1-h glucose level ≥180 mg/dL; 2-h glucose level ≥153 mg/dL) and subsequently delivered at the aforementioned institution. Patients were diagnosed with GDM if one or more of their values exceeded the specified levels. Blood glucose levels in patients with GDM are initially managed through dietary measures. If dietary modifications alone fail to adequately control glucose levels, then insulin therapy is initiated. Patient demographic characteristics, OGTT results, complete blood count (obtained at the same time when patients underwent OGTT), and derived inflammation markers including SII, NLR, PLR, and Lymphocyte to Monocyte Ratio (LMR) were documented, along with data related to delivery, such as birthweight, and gestational week at delivery.

A total of 2158 patients who underwent OGTT during the 24th to 28th weeks of gestation were screened. Exclusion criteria were individuals who did not undergo a complete blood count on the same day as OGTT, those who had multiple gestational pregnancies, individuals with pregestational diabetes, and those who did not deliver at our institution. After exclusions, the study encompassed patients for whom all records, including birth-related documentation, were successfully obtained.

SII was determined by multiplying the neutrophil count (in $10^3/\mu L$) by the ratio of platelet count (in $10^3/\mu L$) to lymphocyte count (in $10^3/\mu L$). NLR was computed as the ratio of neutrophil count (in $10^3/\mu L$) to lymphocyte count (in $10^3/\mu L$), and PLR was obtained by dividing the platelet count (in $10^3/\mu L$) by the lymphocyte count (in $10^3/\mu L$). LMR was calculated with dividing absolute lymphocyte count (in $10^3/\mu L$) by the absolute monocyte count (in $10^3/\mu L$). The primary outcome of the study focused on comparing the mean SII values between patients with and without GDM. The secondary outcomes of the study involve comparing demographic values and other inflammatory markers between the aforementioned two groups.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) v23.0 (IBM Inc., Armonk, NY, USA). Post hoc power analysis was performed using G-Power.[12] Independent sample t-test, Pearson correlation test, Chi-Square test and Receiver Operating Characteristic (ROC) for defining sensitivity and specificity tests were applied as appropriate. A p-value <0.05 was considered statistically significant. In this retrospective study, a post hoc power analysis was conducted for the primary outcome, which focused on the comparison of mean SII values between patients with and without GDM. The study cohort's effectiveness and power were found to be 0.81, indicating a satisfactory level of statistical power. The effect size (Cohen's d) associated with this comparison was 0.30.

Table 1. Comparison of demographic characteristics between patients with and without gestational diabetes.

		Group A Without GDM n:454	Group B With GDM n:113	Significance (*p*)
Age		28.4 ± 5.4	31.2 ± 5.2	**< 0.001**
Gravida		2.32 ± 1.23	2.55 ± 1.28	0.086
Duration of gestation (days)		272.1 ± 9.2	269.2 ± 11.8	**0.005**
Birthweight (grams)		3286 ± 439	3331 ± 540	0.359
Newborn Length at birth (cm)		49.8 ± 1.0	49.7 ± 1.5	0.262
OGTT Fasting (mg/dl)		80.1 ± 5.6	95.4± 14.4	**< 0.001**
OGTT 1-st Hour (mg/dl)		124.9 ± 28.2	176.1 ± 35.9	**< 0.001**
OGTT 2-nd hour (mg/dl)		99.9 ± 21.7	137.1 ± 37.8	**< 0.001**
Delivery Method	**Vaginal Delivery**	194 (42.7%)	33 (29.2%)	**0.005**
	Cesarean Section	260 (57.3%)	80 (70.8%)	

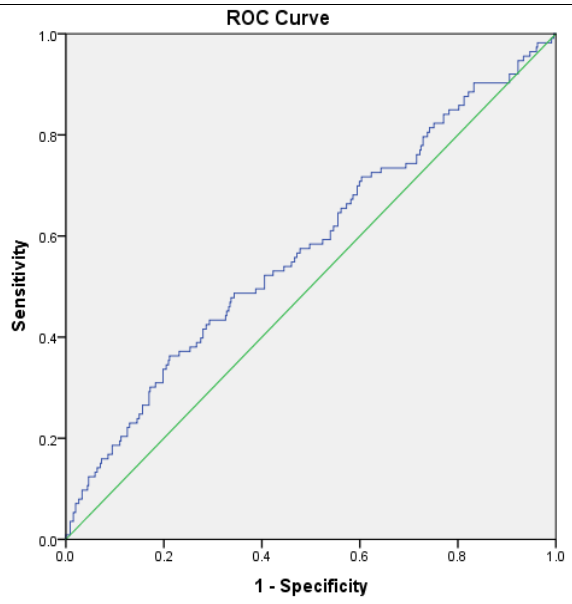
Results

No A total of 567 patients were categorized into two groups based on the presence or absence of gestational diabetes. Group A (n=454) was the control group without GDM, while Group B (n=113) were formed by patients with GDM. The occurrence of GDM among the studied groups was observed to be 19.9%. The mean age for Group A was 28.4 ± 5.4 and for Group B, it was 31.2 ± 5.2 (p<0.001). Table 1 presents a comparison of other demographic properties and birth-related data between the two groups.

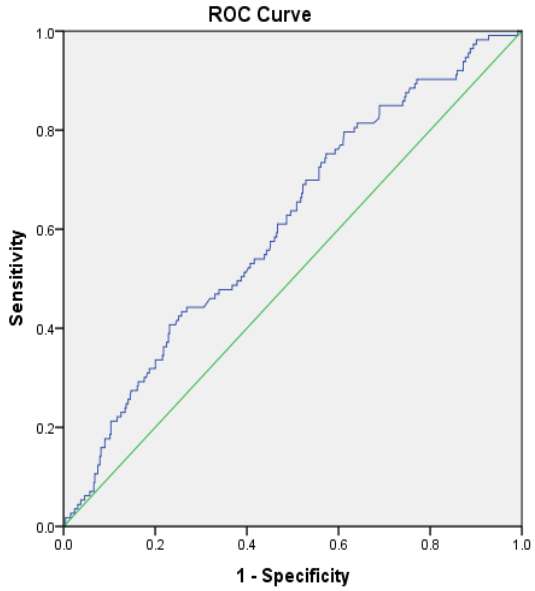
A significant difference was observed in the mean SII values between the groups, with group A exhibiting 1144±400 and group B having a mean value of 1280±496 (p=0.002). Employing ANCOVA to account for the potential impact of maternal age, which emerged as significantly different across the groups, yielded a corrected significance level of p=0.009. Other systemic inflammation markers and their associations with GDM are shown in Table 2.

The ROC curve analysis disclosed an area under the curve (AUC) of 0.577 for SII and 0.607 for NLR. Figure 1 presents various cut-off values and curves, along with their representation for sensitivity and specificity. SII and NLR exhibited significant positive correlations with OGTT fasting values and 2-hour glucose values (correlation coefficients (r) of 0.170 and 0.102 for fasting, and 0.139 and 0.138 for the 2nd hour, respectively).

SII



NLR



AUC:0.577			AUC:0.607		
Value	Sensitivity	1-Specificity	Value	Sensitivity	1-Specificity
769	.903	.833	2.73	.903	.771
829	.850	.782	2.97	.850	.689
948	.735	.645	3.06	.814	.641
1032	.655	.562	3.41	.690	.522

Figure 1. The results of ROC curve analysis for SII and NLR, showcasing the varying cut-off values and their respective abilities in identifying patients with GDM.

Table 2. Values for Systemic Immune Inflammatory Index (SII), Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR) and Lymphocyte Monocyte Ratio (LMR) between women with (Group B) and without (Group A) diagnosed gestational diabetes mellitus.

	Group A n=454	Group B n=113	Significance (*p*) (Corrected for age)
SII	1144 ± 400	1280 ± 496	**0.002 (0.009)**
NLR	3.63 ± 1.21	4.05 ± 1.25	**0.001 (0.003)**
PLR	122.9 ± 41.6	127.6 ± 50.1	0.307 (0.256)
LMR	3.92 ± 1.31	3.65 ± 1.08	**0.040** (0.067)

Independent sample t-test was utilized for analysis. Significant values have been denoted in bold. Corrected significances were computed by accounting for the influence of age on the comparisons.

Discussion

Our analysis revealed significant differences in mean SII and NLR values between patients with and without GDM. Specifically, patients with GDM displayed a significantly higher mean SII value compared to those without GDM. Despite the observed differences in age between the groups, which may be influenced by the natural progression of diabetes later in life, the significance of this difference persisted even after adjusting for the potential impact of maternal age using ANCOVA. This finding holds particular significance, especially in light of a previous population-based study that demonstrated a peak in NLR and PLR values achieved during the second trimester which were found to be also positively correlated with increasing maternal age.[13] The observed incidence of GDM in our cohort appears to be higher than anticipated. We suspect that this finding may be attributed to stringent exclusion criteria, resulting in the exclusion of many patients due to insufficient information at any stage during pregnancy follow-ups or delivery.

Prior research conducted on type 2 diabetes mellitus (T2DM) has demonstrated a positive correlation between SII levels and the incidence of T2DM. In addition, certain complications such as diabetic osteomyelitis and macular degenerations associated with diabetes have been diagnosed using SII measurements.[14] Recently SII was found to increase in the third trimester of pregnancy and be associated with the presence of GDM.[11] Our findings are consistent with those previous studies showing SII to be significantly higher in patients with GDM compared to control group.

Ye et al. illustrated an elevation in NLR values during both early and mid-pregnancy among patients with GDM, which is consistent with findings from a study conducted by Sahin et al. Both studies reported increased NLR values during the first trimester in patients who later developed GDM.[15,16] While the precise mechanisms underlying the association of inflammatory blood cell parameters with GDM remain to be fully elucidated, our findings of increased NLR among patients with GDM are biologically plausible. Recent research has highlighted the potential involvement of RNAs and genes expressed in white blood cells (WBC) in the development of GDM. Specifically, WBCs may contribute to insulin resistance by downregulating microRNAs, such as miR-155-5p or miR-21, which are known to enhance insulin sensitivity and play a role in normal blood glucose homeostasis.[17,18] Moreover, studies have reported increased neutrophil activity and reactive oxygen species in women with GDM, leading to downstream inflammatory responses and insulin resistance through the production of neutrophil extracellular traps.[19]

In contrast to a study conducted by Xuan et al. in a Chinese population, our study did not find any association between PLR with the development of GDM. Similarly, consistent with our findings, Hassan et al. observed no significant relationship between PLR and GDM in Sudanese women. These conflicting results may be attributed to racial differences or variations in the methods used to identify GDM, such as the use of different OGTT protocols, including 75g or 100g OGTT among different protocols.

LMR is indeed an inflammation marker that has been extensively studied in the context of solid tumors to establish progression levels and calculate risk in various research studies.[20,21] However, its potential role in the diagnosis of GDM has not been thoroughly investigated. Although we initially observed statistically significant differences in LMR values between patients with and without GDM, controlling for age within the groups resulted in a reduction in the significance of this marker. Further research is needed to evaluate the utility of LMR as a biomarker associated with GDM and to determine its potential significance in clinical practice. Notably, the ROC curve analysis revealed modest but statistically significant discriminative abilities for both SII and NLR, with respective AUC values of 0.577 and 0.607. We also aimed to present various cut-off values for SII and NLR, alongside their corresponding sensitivity and specificity. These values serve as valuable reference points for clinicians when interpreting test results and making diagnostic decisions.

The significantly higher cesarean section rate observed among patients with GDM in our study (70.8% vs. 57.3%, p=0.005) aligns with previous evidence linking GDM to adverse obstetric outcomes, such as fetal macrosomia and labor dystocia. This tendency may be further reinforced in healthcare environments where high rates of medico-legal litigation pressure clinicians toward defensive medical practices, favoring cesarean delivery as a perceived safer alternative.

Conclusion

Our study contributes to the growing body of evidence regarding the relationship between biomarkers of systemic inflammation and GDM. Despite the inherent limitations of a retrospective design, including selection bias and the inability to control for potential confounding factors, such as other systemic diseases, that may not have been recorded, we endeavored to mitigate these shortcomings by increasing the sample size compared to existing literature, thereby enhancing the study's statistical power. The significant differences observed in SII values between patient groups, coupled with the discriminative abilities of SII and NLR in association with GDM, underscore the potential clinical relevance of these markers. However, further research is warranted to elucidate their precise roles in GDM pathophysiology and to validate their diagnostic accuracy in larger and more diverse patient populations

Conflict of Interest

The authors declare that there are no conflicts of interest to disclose.

Compliance of Ethical Statement

This study received approval from the Buca Seyfi Demirsoy Training and Research Hospital Institutional Review Board with ID number 2023/204 on 27/12/2023. All procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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Author Contributions

T.B.B.: Study idea/Hypothesis; T.B.B, C.A., S.E.: Design; C.A., M.N.Ç., H.A.A.: Data Collection; T.B.B., S.E.: Analysis; U.A., M.N.Ç.: Literature review; T.B.B.: Writing; U.A., S.E.: Critical review.

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