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Research

Evaluation of White Blood-cell-based Inflammatory Markers in Gestational Diabetes Mellitus

Gestasyonel Diabetes Mellitusta Beyaz Kan Hücresi Temelli Enflamatuvar Belirteçlerin Değerlendirilmesi

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ABSTRACT

Objective: It was aimed to evaluate the white blood-cell-based inflammatory markers in the normal pregnancy reference value range in terms of the presence of low-grade systemic inflammation in gestational diabetes mellitus (GDM).

Methods: A total of 690 subjects were included in the study. GDM was defined according to the criteria of the international association of diabetes and pregnancy study groups. Four hundred seventy six pregnant women with normal glucose tolerance (NGT) and 214 pregnant women with GDM were included in the control and the case groups, respectively.

Results: Age was statistically significantly higher in the GDM group than the NGT group (p=0.030). Hemoglobin levels, mean corpuscular volume levels and the mean hematocrit level were statistically significantly higher with no clinical significance in the NGT group, compared to the GDM group; (p=0.024), (p<0.001) and (p=0.008) respectively. Fasting plasma levels of glucose and post 75 g load glucose (oral glucose tolerance test); 1 h and 2 h plasma glucose were significantly higher in the GDM group than in the NGT group (p<0.001). No statistically significant differences in white blood cell count, neutrophil count, lymphocyte count, platelet count, mean platelet volume value, neutrophil-to-lymphocyte ratio value, the platelet-to-lymphocyte ratio value and the systemic immune- inflammation index value were found between the two groups.

Conclusion: There was no statistically significant difference between white blood cell-based inflammatory markers in normal pregnancy reference values between pregnant women with GDM and pregnant women with NGT in this study. White blood cell-based inflammatory markers can be useful in understanding the pathophysiology of GDM and future studies may provide further evidence on the role of white blood cell-based inflammatory markers as an indicator of subclinical inflammation in GDM.

Keywords: Gestational diabetes, inflammation, oral glucose tolerance test, platelet, white blood cells

ÖZ

Amaç: Gestasyonel diabetes mellitusta (GDM) düşük dereceli sistemik enflamasyon varlığı açısından gebelerde, normal gebelik referans değer aralığında, beyaz kan hücresi temelli enflamatuvar belirteçlerin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya toplam 690 gebe dahil edildi. GDM, uluslararası diyabet ve gebelik çalışma grupları derneği kriterlerine göre tanımlandı. Normal glukoz toleransı (NGT) olan 476 gebe kontrol grubuna ve GDM olan 214 gebe olgu grubuna dahil edildi.

Bulgular: GDM grubunda yaş, NGT grubuna göre istatistiksel olarak anlamlı daha yüksekti (p=0,030). Hemoglobin, ortalama eritrosit hacmi ve ortalama hematokrit seviyesi, GDM grubuna kıyasla NGT grubunda klinik olarak anlamlı olmaksızın istatistiksel olarak anlamlı derecede yüksekti; sırasıyla (p=0,024), (p<0,001) ve (p=0,008). Açlık plazma glikoz seviyeleri ve 75 g yükleme sonrası glikoz (oral glukoz tolerans testi); 1 saat ve 2 saat plazma glikozu GDM grubunda NGT grubuna göre anlamlı derecede yüksekti (p<0,001). İki grup arasında beyaz kan hücresi sayısı, nötrofil sayısı, lenfosit sayısı, trombosit sayısı, ortalama trombosit hacmi değeri, nötrofil-lenfosit oranı değeri, trombosit-lenfosit oranı değeri ve sistemik immün enflamasyon indeksi değerinde istatistiksel olarak anlamlı fark bulunmadı.

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Sonuç: Bu çalışmada, GDM'li gebeler ile NGT olan gebeler arasında normal gebelik referans değerlerinde beyaz kan hücresi temelli enflamatuvar belirteçler arasında istatistiksel olarak anlamlı bir fark yoktu. Beyaz kan hücresi temelli enflamatuvar belirteçler, GDM'nin patofizyolojisinin anlaşılmasında yararlı olabilir ve gelecekteki çalışmalar, GDM'de subklinik enflamasyonun bir göstergesi olarak beyaz kan hücre temelli enflamatuvar belirteçlerin rolü hakkında daha fazla kanıt sağlayabilir.

Anahtar Kelimeler: Gebelik diyabeti, enflamasyon, oral glukoz tolerans testi, trombosit, beyaz kan hücreleri

INTRODUCTION

Gestational diabetes mellitus (GDM) is a substantial and growing health concern in many parts of the world and is defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or the first recognition during pregnancy (1). The condition is present when blood glucose values are above normal but still below those diagnostic of diabetes (2). Gestational diabetes is associated with both short- and long-term complications in both the mother and the child. Additionally, women with GDM are at increased risk of the development of type 2 diabetes mellitus (T2DM), after pregnancy (3).

The white blood cell (WBC) count increases during pregnancy, and both the lower and upper limit of the reference range during pregnancy are quite high, with a typical reference range of 6 10^9-16×10^9/L (4). To assist the survival of the fetus pregnancy is associated with normal physiological changes. During normal pregnancy, the innate immune system is activated but the adaptive immune system is suppressed. Peripheral circulation of pregnancy is characterized by an increased percentage of granulocytes (5) and particularly in the third trimester platelet (PLT) count decreases during pregnancy (6). Recently, inflammation play a role in GDM pathogenesis (7). Compared with normal pregnancy, GDM is characterized by increased insulin resistance and although the association between inflammation and GDM is a new discovery, the connection between inflammation and insulin resistance is well known. This is also supported by clinical as well as epidemiologic data. Women with GDM have even higher inflammatory markers such as tumor necrosis factor (TNF)-α and interleukin-6 (IL-6) compared to women with a normal pregnancy (8).

Recently, several new WBC-based inflammatory markers have been introduced as prognostic markers: the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR) and the systemic immune-inflammation index (SII index) and they have been considered systemic inflammatory response markers. These are also defined as WBC-based inflammatory biomarkers and calculated from complete blood count (CBC). They have been reported to be useful in the diagnosis, follow up and survey of many systemic inflammatory processes and as a markers of increased immune response with chronic inflammation (9).

In this study, we evaluate for any low-grade systemic inflammation presence in GDM at normal pregnancy WBC range and whether white blood-cell-based inflammatory markers that are simple, accessible and cost-effective have any value in the prediction of gestational diabetes.

METHODS

This retrospective case-control study was conducted in Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey, with the approval of the Local Ethics Committee (decision no: 2019-08-04, date: 22.04.2019) in compliance with the Helsinki Declaration.

The study was designed as a retrospective, laboratory information system (LIS) based study of pregnant women who underwent their GDM screening by oral glucose tolerance test (oGTT) from August 2015 to January 2018.

A total of 690 subjects age within 18-47 years were included in the study. GDM was defined according to the criteria of the international association of diabetes and pregnancy study groups (IADPSG) (10). Four hundred seventy six pregnant women with normal glucose tolerance (NGT) and 214 pregnant women with GDM were included in the control and case groups, respectively.

The inclusion criteria were 1. Pregnant women who completed all tests required in this study and applied by 3-point 75 g of glucose 2-h oGTT between 24th and 28th week of pregnancy.

Exclusion criteria were as 1. Unavailable at least a data which planned to work from LIS, 2. Pregestational type 1 diabetes mellitus, 3. Pregestational T2DM, 4. Pregnant women evaluated as having overt diabetes mellitus according to the IADPSG criteria, 5. Pregnant women with systemic diseases or any gestational disease throughout the pregnancy period (preeclampsia, eclampsia) and with acute or chronic infections, 6. Total blood WBC count <6x10^9/L and >16x10^9/L (4).

All pregnant women who included in this study were screened for GDM using a 3-point 75 g of glucose 2-h oGTT between 24th and 28th week of pregnancy. The oGTT used standard procedures (2). Briefly, the test was performed in the morning after a 12 h overnight fast and collected fasting, 1-hour and 2-hour samples were from an antecubital vein in a sitting position. Cut-offs of IADPSG criteria are as follows:

Fasting plasma glucose (FPG)≥92 mg/dL, 1-hr post-load glucose: ≥180 mg/dL, 2-hr postload glucose: ≥153 mg/dL. A pregnant woman with one abnormal value was diagnosed with GDM using the IADPSG criteria.

The CBC parameters such as WBC, neutrophil count, lymphocyte count, hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), PLT, mean platelet volume (MPV), and the screening test glucose results were obtained from LIS. CBC parameters were the results measured in fasting samples taken just before the oGTT test was performed at the same time as which between 24th and 28th week of pregnancy. Glucose was measured by hexokinase-based enzymatic method using Roche Cobas C501 chemistry analyzer and commercial reagents (Roche Diagnostics GmbH, Mannheim, Germany) and calculated plasma level. CBC was performed using CELL-DYN RUBY analyzer (Abbott Diagnostic, Abbott Park, IL, USA).

The NLR was calculated on the basis of absolute peripheral neutrophil (N×10^9/L) and lymphocyte (L×10^9/L) blood counts, using the formula: NLR=N/L. The PLR was calculated on the basis of peripheral PLT (P×10^9/L) and lymphocyte (L×10^9/L) blood counts, using the formula: PLR=P/L. The SII index was calculated on the basis of peripheral PLT (P×10^9/L), neutrophil (N×10^9/L) and lymphocyte (L×10^9/L) blood counts, using the following formula: SII=P×N/L (9).

Statistical Analysis

All the data were collected in a computerized database for statistical analysis. Error control was done. Descriptive statistics [mean, standard deviation (SD), median, minimum, maximum, number] were generated for the two groups then monitored for conformity to the normal distribution by the Kolmogorov-Smirnov test. Mean SD was used for parameters that were normally distributed. Median was used for groups that were not distributed normally. The Mann-Whitney U test was used for the comparison of two groups in the variables that did not realize the normal distribution. Independent t-test analysis was used to determine correlational relationships between variables that provided the normal distribution. Spearman correlation analysis was used to determine correlational relationships between variables that did not provide the normal distribution. Receiver operating characteristic (ROC) curve analysis was performed to find the sensitivity and specificity of NLR, PLR and SI index in the prediction of normal pregnancy and GDM results.

Diagnostic performance (sensitivity, specificity, and positive and negative predictive values) at the best cut off point for NLR, PLR and SI index was calculated.

The analysis were performed using the NCSS11 (Number Cruncher Statistical System, 2017 Statistical Software) program and Med Calc Statistical Software version18 (Med Calc Software bvba, Ostend, Belgium; http://www.medcalc.org;2018).

A p-value ≤0.05 was set as statistically significant.

RESULTS

Characteristics of 690 pregnant women who were included in this study are shown in Table 1. According to the criteria of the IADPSG, pregnant women with NGT and with GDM were included in the control (n=476) and case (n=214) groups, respectively.

We found a significantly higher level of the GDM group compared to age matched NGT groups 31 (18-45), 29 (18-47) respectively; (p=0.030).

Hb levels were significantly higher in the NGT group, compared to GDM group 11.5 (8.4-15.0) g/dL, 11.4 (7.3-14.1) g/dL respectively; (p=0.024). Also, the mean Hct level in the NGT group was significantly higher, compared to GDM group 34.39±2.81% (mean ± SD), 33.75±3.16% respectively; (p=0.008).

Compared with the GDM group, MCV levels were statistically significantly higher in NGT group 87 (56-98) fL, 89 (62-105) fL, respectively; (p<0.001).

FPG levels were significantly higher in the GDM group than NGT group 97 (65-133) mg/dL, 83 (50-91) mg/dL, respectively; (p<0.001).

Post 75 g load glucose (oGTT); 1 h plasma glucose levels were significantly higher in the GDM group, compared to NGT group 151 (62-196) mg/dL, 141 (64-179) mg/dL, respectively; (p<0.001). Also, 2 h plasma glucose levels were significantly higher in the GDM group, compared to NGT group 135 (51-198) mg/dL, 116 (50-152) mg/dL, respectively; (p<0.001).

No statistically significant differences in WBC count, neutrophil count, lymphocyte count, PLT count, MPV value, NLR value, PLR value and SII Index value were found between the two groups (p>0.05).

The results of the ROC curve analysis for the diagnostic performance of gestational diabetes with NLR, PLR and SII index are presented in Figure 1 and in Table 2.

At a cut-off level of 3.6, NLR accurately diagnosed GDM [area under the curve (AUC)=0.538, 95% confidence interval 0.500-0.575, p=0.098] with sensitivity and specificity rates of 64% and 47% and positive and negative predictive values of 35.6% and 74.8%, respectively. At a cut-off level of 132 PLR,

Table 1. Characteristics of study subjects

	NGT n= 476	GDM n=214	p
Age	29 (18-47)	31 (18-45)	0.030
WBC count, (x10^9/L)	10.31 (6-16)	10.46 (6.34-16)	0.911
Neutrophil count, (x10^9/L)	7.45 (3.87-12.9)	7.64 (4.12-12.8)	0.513
Lymphocyte count, (x10^9/L)	2 (0.97-4.25)	1.95 (0.86-3.96)	0.317
Haemoglobin (g/dL)	11.5 (8.4-15.0)	11.4 (7.3-14.1)	0.024
Haematocrit (%)	[34.39±2.81]**	[33.75±3.16]**	0.008*
MCV (fL)	89 (62-105)	87 (56-98)	<0.001
Platelet count (x10^9/L)	236 (104-547)	236 (106-459)	0.933
MPV (fL)	8.54 (4.93-15.8)	8.61 (5.29-15.6)	0.645
NLR	3.73 (1.73-7.91)	3.94 (1.94-6.29)	0.113
PLR	114 (49-238)	118 (44-253)	0.257
SII	850 (297-1959)	897 (331-1898)	0.193
oGTT (24-28th week of gestation)			
FPG (mgL/dL)	83 (50-91)	97 (65-133)	<0.001
1-h post 75 g load	141 (64-179)	151 (62-196)	<0.001
2-h post 75 g load	116 (50-152)	135 (51-198)	<0.001

Data expressed as a median (IQR) or proportions. Differences evaluated by nonparametric Mann-Whitney U test or *Independent t-test, respectively. **[mean ± SD], p-value ≤0.05 was accepted as statistically significant.

NGT: Normal glucose tolerance, GDM: Gestational diabetes mellitus, WBC: White blood cell, MCV: Mean corpuscular volume, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune index, oGTT: Oral glucose tolerance test, FPG: Fasting plasma glucose

Table 2. Diagnostic performance of gestational diabetes with NLR, PLR and SII

Group	Cut-off	Sensitivity %	Specificity %	AUC	p-value	CI	PPV	NPV
NLR	3.6	64	47	0.538	0.098	0.500-0.575	35.6	74.8
PLR	132	37	71	0.527	0.267	0.489-0.565	37	71.7
SII	831	62	47	0.531	0.191	0.493-0.569	34.3	73.1

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune index, CI: Confidence interval, AUC: Area under the curve, PPV: Positive predictive values, NPV: Negative predictive values

accurately diagnosed GDM [AUC=0.527, 95% confidence interval 0.489-0.565, p=0.267] with sensitivity and specificity rates of 37% and 71% and positive and negative predictive values of 37% and 71.7%, respectively. At a cut-off level of 831 SII index accurately diagnosed GDM [AUC=0.531, 95% confidence interval 0.493-0.569, p=0.191] with sensitivity and specificity rates of 62% and 47% and positive and negative predictive values of 34.3% and 73.1%, respectively.

DISCUSSION

In this retrospective case-control study, WBC-based inflammatory markers were evaluated at normal gestational WBC range for any low-grade systemic inflammation presence in GDM. Maternal age has been found to be a risk factor for GDM in many studies (11,12). The mean age of the pregnant women with GDM was significantly higher than the pregnant women with NGT in this study.

The total blood volume increases by about 1.5 L to supply the needs of the new vascular bed during pregnancy. Red cell mass also increases by 10%-20% but the net result is that Hb concentration falls (13). Consequently, Hb concentrations and Hct values decrease in pregnancy. In addition MCV is normally slightly increased (4). In this study, the levels of Hb, Hct and MCV were statistically significantly higher in the pregnant women with NGT, compared with the pregnant women with GDM.

The IADPSG criteria was developed based on the results of the Hyperglycemia and Adverse Pregnancy Outcomes study, which is a large multinational and multicenter study.

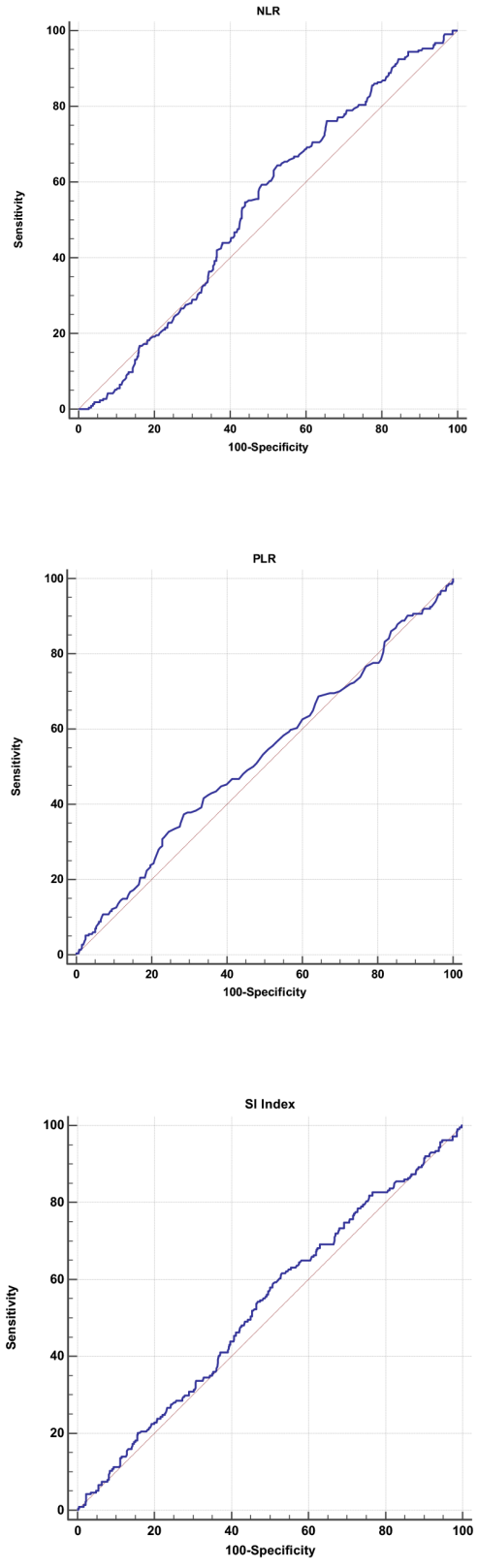

Figure 1. ROC curves of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index
PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, SI: Systemic immune-inflammation, ROC: Receiver operating characteristic

In accordance with the criteria of the IADPSG, independent of the other two values of the 75 g oGTT FPG≥92 mg/dL confirms GDM (10). FPG levels were found to be significantly higher in the GDM group than in the NGT group ($p<0.001$) in this study.

The immune system and metabolic system highly interact with each other to keep the body function properly (14). Additionally, studies have showing that metaflammation develops when this interaction is impaired (15). Recently, some evidence suggested that immune system disorders play a key role during the development of inflammation and that chronic low-grade inflammation is a major factor in the etiology of insulin resistance (16). With a general activation of the innate immune system T2DM is a chronic state of low-grade inflammation (17) and during normal pregnancy, the innate immune system is activated likewise (5). According to some authors, GDM represents an early stage in the natural history of T2DM (18). Inflammation may represent the pathophysiological link between GDM and the risk of future T2DM. Recently, some authors have reported that increased early pregnancy leukocyte count was associated with the results of GDM screening tests and increased risk of developing GDM. They also concluded that women who developed GDM display increased inflammation during early pregnancy approximately 20 weeks before the GDM was diagnosed. Physiological increase in insulin resistance associated with normal pregnancy and subclinical inflammation together manifest as GDM probably (19). There was no significant difference between the NGT group and GDM groups concerning WBC count and both neutrophil and lymphocyte counts in this study. In accordance with the purpose of the study, limitation of leukocyte level at normal pregnancy level may have affected the results.

In pregnancy, the PLT count is usually within normal, except during the third trimester when benign gestational thrombocytopenia can be observed (20). PLT volume is measured using MPV is a marker of PLT activation and function. In a study, while no statistically significant difference was observed in the PLT count, mean MPV value of the GDM group was evaluated to be significantly higher than the mean MPV value of the healthy pregnancy group in the last trimester (32-36 weeks) (21). This finding was further supported by another study (22). However in a recent study mean MPV value was observed to be lower in GDM and mean NLR and mean PLR values were statistically not different in patients with GDM as compared with healthy pregnant women (23). No statistically significant differences in PLT count and MPV value were found between the GDM group and NGT groups in this study.

Some studies have been conducted to assess the utility of NLR and PLR as inflammation biomarkers in GDM. In a study the mean NLR level and PLR level were significantly higher in pregnant women with GDM (24) and the other study the mean NLR level was significantly higher in pregnant women with GDM (25). Additionally NLR and PLR were evaluated in association with GDM in a recent study (26). In another study conducted in the first trimester of pregnancy, while mean NLR level and mean PLR level was similar in pregnant women with GDM and healthy pregnant group, mean MPV level was higher in pregnant women with GDM (27). It was shown that there was no relation between NLR and PLR with GDM in another study but the leukocyte counts were significantly higher during the second and early third trimesters in the women with GDM and the authors did not recommend use blood NLR and PLR as biomarkers for GDM screening (28). Similarly, no statistically significant differences in NLR and PLR and SII index were found between the GDM group and NGT group in this study. The results of the ROC curve analysis for the diagnostic performance of gestational diabetes with NLR, PLR and SII index were evaluated. The AUC values of them were considered to have poor predictive capabilities as screening tests and poor diagnostic capabilities as biomarkers according to the cut off values, which determined in this study. There is no literature on the relationship between GDM and the SII index. Here, the current study is the first study to investigate the relationship between GDM and SII index in normal pregnancy WBC reference value.

Screening and management can make better outcomes for women with GDM and their babies. Unfortunately, screening and diagnostic standards are not the same worldwide, so this might lead to underdiagnosis and undermanagement of the disease (29). There is no international consensus on the screening and diagnostic criteria for GDM currently. Additionally it was reported that because of large changes in inflammatory mediators during normal pregnancy, a comparison between studies is challenging. Meanwhile identifying circulating biomarkers that could lead to better tests to predict, diagnose, and monitor the progression of this important disease is essential (30).

This study has some limitations because of its retrospective nature. Due to this retrospective design, we do not have data on some parameters as body mass index and parity of women and data relating to the insulin levels or insulin resistance and inflammatory cytokines as IL-6 and TNF-α.

CONCLUSION

There was no statistically significant difference between WBC-based inflammatory markers in normal pregnancy reference values between pregnant women with gestational diabetes mellitus and pregnant women with NGT in this study. Additionally, they have poor predictive capabilities as screening tests and poor diagnostic capabilities as biomarkers. WBC-based inflammatory markers can be useful in understanding the pathophysiology of GDM and future studies may provide further evidence on the role of WBC-based inflammatory markers as an indicator of subclinical inflammation in GDM.

ETHICS

Ethics Committee Approval: This retrospective case-control study was conducted in Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey, with the approval of the Local Ethics Committee (decision no: 2019-08-04, date: 22.04.2019) in compliance with the Helsinki Declaration.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Z.L.C., N.G., Concept: Z.L.C., Design: Z.L.C., N.G., Data Collection or Processing: Z.L.C., N.G., Analysis or Interpretation: Z.L.C., Literature Search: Z.L.C., Writing: Z.L.C.

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