Correlation between neutrophil-to-lymphocyte ratio and soluble FMS-like tyrosine kinase 1 in pregnant women with preeclampsia

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ABSTRACT

Preeclampsia (PE) is a multi-system syndrome in pregnancy that affects 5-10% of pregnancies and is a significant cause of perinatal morbidity and mortality. Therefore, an early and precise diagnosis of PE is needed. Several biomarkers have been used for this diagnosis. The neutrophil-to-lymphocyte ratio (NLR) is a potential biomarker that can be assessed through routine blood tests, but few studies have been conducted to compare NLR with other conventional markers. This study analyzes the correlation between NLR and soluble FMS-like tyrosine kinase 1 (sFLT-1) levels in pregnant women with PE. This study used a cross-sectional design and included 88 patients divided into two groups (normal n=44, PE n=44) by consecutive sampling. All research subjects took venous blood samples and performed routine blood tests and sFLT-1. All statistical analyses were performed using the Statistical Program for Social Sciences (IBM SPSS 24, Chicago, IL, USA). There was no significant difference between the NLR in the control and PE groups, which were 5.45 (0.5) and 5.87 (5.5), respectively. The sFLT-1 marker increased significantly and increased in normal pregnancy and PE, namely 6336 (579) pg/mL and 18,775 (9841) pg/mL. NLR and log sFLT-1 were not correlated in PE (rho=0.11, p=0.451), but they were related in normal pregnancy (rho=0.705, p<0.001). In conclusion, there is a difference in sFLT-1 levels in PE and controls, but no difference in the NLR biomarker. NLR does not correlate with the sFLT-1 biomarker.

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Introduction

Preeclampsia (PE) is a dangerous pregnancy-related disorder that affects 5-10% of pregnancies worldwide, contributing significantly to maternal and perinatal morbidity and mortality.[1] It is characterized by high blood pressure and signs of organ damage, often affecting the liver and kidneys.[2] The early detection of PE is crucial to mitigate severe outcomes such as eclampsia and premature birth, which can lead to maternal and neonatal death.[3,4]

The neutrophil-to-lymphocyte ratio (NLR) is emerging as a cost-effective biomarker for PE due to its availability through routine blood tests. Studies have shown that NLR is significantly elevated in women with PE, suggesting a heightened inflammatory response associated with the condition. Elevated levels of soluble FMS-like tyrosine kinase 1 (sFLT-1), a protein linked to anti-angiogenic processes, have also been associated with PE. The correlation between elevated sFLT-1 and increased NLR suggests a possible interaction between inflammatory and anti-angiogenic pathways in the development of PE.[5-8]

If a significant correlation between NLR and sFLT-1 is confirmed, it could support the use of NLR as a simple, in-

expensive predictive marker for PE. This study aims to explore this relationship, which could pave the way for improved early diagnosis and better clinical management of PE, ultimately reducing the risks of severe maternal and fetal outcomes.

Materials and Methods

Subjects and data collections

A cross-sectional study was conducted on 88 pregnant women, divided into two groups (normal pregnancy n=44; PE n=44) in Dr. Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, Indonesia. This study was approved by the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University (No: 814/UN4.6.4.5.31/PP36/202).

Results

The mean age and gestational age in this study were 30.08 (5.96) years and 37.6 (0.22) weeks (Table 1). There was no significant difference between the NLR in the control and PE groups, which were 5.45 (0.5) and 5.87 (5.5), p=0.455. The sFLT-1 marker significantly increased and increased in normal pregnancy and PE, namely 6336 (579) pg/mL and 18775 (9841) pg/mL, with p<0.001. NLR and log sFLT-1 were not correlated in PE (rho=0.11, p=0.451), but they were related in normal pregnancy (rho=0.705, p<0.001) (Table 2, Figures 1 and 2).

Discussion

The increase in NLR in PE is driven by placental hypoxia and oxidative stress, which trigger systemic inflammation through neutrophil activation, the release of pro-inflammatory cytokines such as interleukin (IL)-1β and IL-18, and NLRP3 inflammasome activation, with potential therapeutic regulation *via* increased *miR-135* or reduced *PCSK6*.[9,10] NLR is significantly higher in preeclamptic patients compared to normal pregnancies, serving as a marker of inflammatory sensitivity and a predictor of disease severity, including distinguishing mild from severe cases.[5,11] Furthermore, placental hypoxia and neutrophil activation produce microvesicles that exacerbate endothelial dysfunction, reinforcing inflammatory mechanisms in PE.[12,13]

Although NLR is often elevated, some studies have shown its diagnostic value as insignificant. This variation may be attributed to the heterogeneity of patient groups, differences in blood sample collection times, and other factors such as infections or non-obstetric complications affecting systemic inflammation. Additionally, in mild PE, inflammation may be lower than in its severe form, reducing the differences in NLR compared to normal pregnancies.[14,15] These differences may also be caused by fluctuating levels of hormones or cytokines during pregnancy, which are not always directly correlated with the severity of PE.[7]

The significant increase in sFLT-1 levels in PE is primarily driven by placental hypoxia and oxidative stress, which trigger the overexpression of anti-angiogenic factors. sFLT-1 binds to vascular endothelial growth factor (VEGF) and placental growth factor, sequestering them and impairing angiogenesis, leading to endothelial dysfunction and maternal hypertension.[16,17] Elevated sFLT-1 disrupts vascular remodeling by limiting trophoblast invasion into maternal spiral arteries, exacerbating placental ischemia, and perpetuating the cycle of anti-angiogenic dominance.[18,19] This imbalance in angiogenic factors correlates with disease severity and maternal organ dysfunction, making sFLT-1 a reliable biomarker for identifying high-risk preeclamptic pregnancies.[20,21]

Studies have confirmed that sFLT-1 levels are significantly higher in PE compared to normal pregnancies, and this elevation is particularly pronounced in severe and early-onset cases.[22,23] For example, a study demonstrated that sFLT-1 levels above a certain threshold predict adverse maternal and fetal outcomes with high sensitivity and specificity, solidifying its role in clinical risk stratification.[24,25]

The lack of correlation between NLR and sFLT-1 levels may stem from their differing mechanistic roles in PE. sFLT-1 levels are primarily driven by placental hypoxia and the release of antiangiogenic factors like VEGF receptor decoys, which impair vascular endothelial repair and promote hypertension.[16,17] Meanwhile, NLR reflects systemic inflammation through neutrophil activation and lymphocyte suppression, processes influenced by systemic rather than localized placental factors.[18,25] Additionally, PE's heterogeneous presentation means that sFLT-1 levels may be elevated even in cases without significant systemic inflammation, reducing the correlation between NLR and sFLT-1.[26]

Table 1. Subjects' characteristics.

Variable	Normal n (%)	Preeclampsia n (%)
Age		
Low risk	42 (47.7)	23 (26.1)
High risk	2 (2.3)	21 (23.9)
Gestational age		
Preterm	0 (0.0)	31 (35.2)
Aterm	44 (50.0)	13 (14.8)
Body mass index		
<24.9 kg/m^2	8 (9.1)	0 (0.0)
≥24.9 kg/m^2	35 (41.0)	44 (50.0)
Parity		
Primigravida	14 (15.9)	10 (11.4)
Multigravida	30 (35.1)	34 (38.6)

Table 2. Neutrophil-to-lymphocyte ratio and soluble FMS-like tyrosine kinase 1 among subjects

Variable	Normal, mean (SD)	Preeclampsia, mean (SD)	p
NLR	5.45 (0.5)	5.87 (5.5)	0.455
sFLT-1, pg/mL	6336 (579)	18775.38 (9481)	**<0.001**

Mann-Whitney, bold significant. SD, standard deviation; NLR, neutrophil-to-lymphocyte ratio; sFLT-1, soluble FMS-like tyrosine kinase 1.

The strong correlation between NLR and sFLT-1 in normal pregnancies likely reflects a coordinated physiological response. As gestation progresses, the gradual rise in sFLT-1 contributes to subtle shifts in maternal vascular dynamics and may trigger mild inflammatory responses, evidenced by increased NLR.[27,28] Unlike PE, where inflammation is often decoupled from angiogenic dysregulation, normal pregnancies balance angiogenic and inflammatory signals, leading to a proportional relationship.[22,29] This connection suggests a more integrated regulatory mechanism in normal pregnancies compared to the pathological disruptions observed in PE.[30,31]

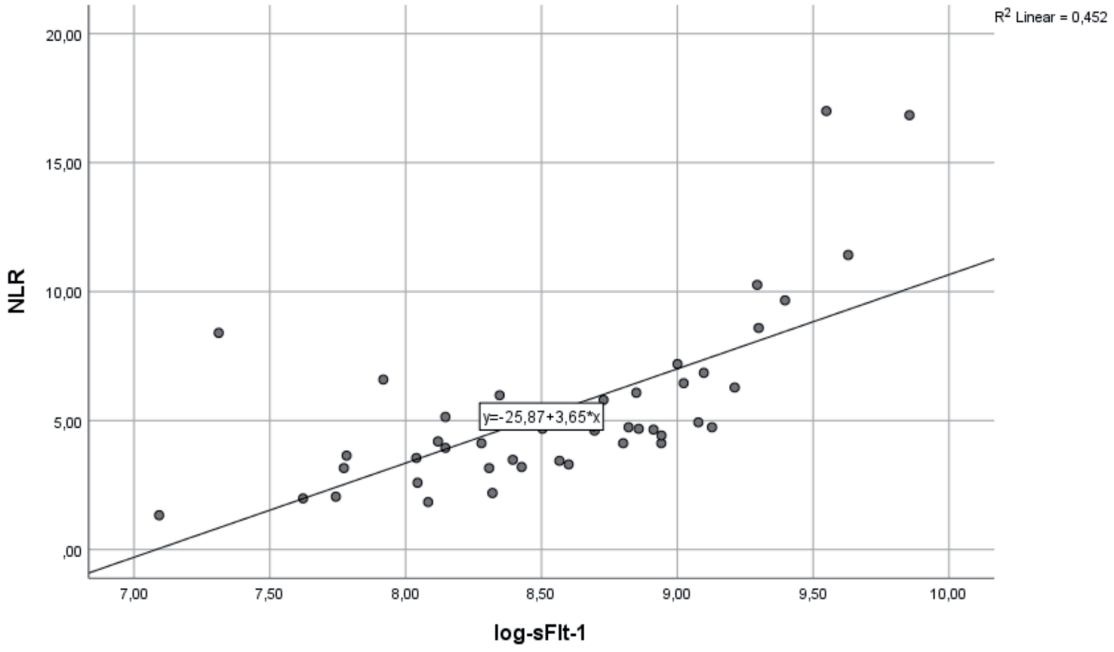

Figure 1. Neutrophil-to-lymphocyte ratio (NLR) correlation with soluble FMS-like tyrosine kinase 1 in normal pregnancy (rho=0.705, p<0.001).

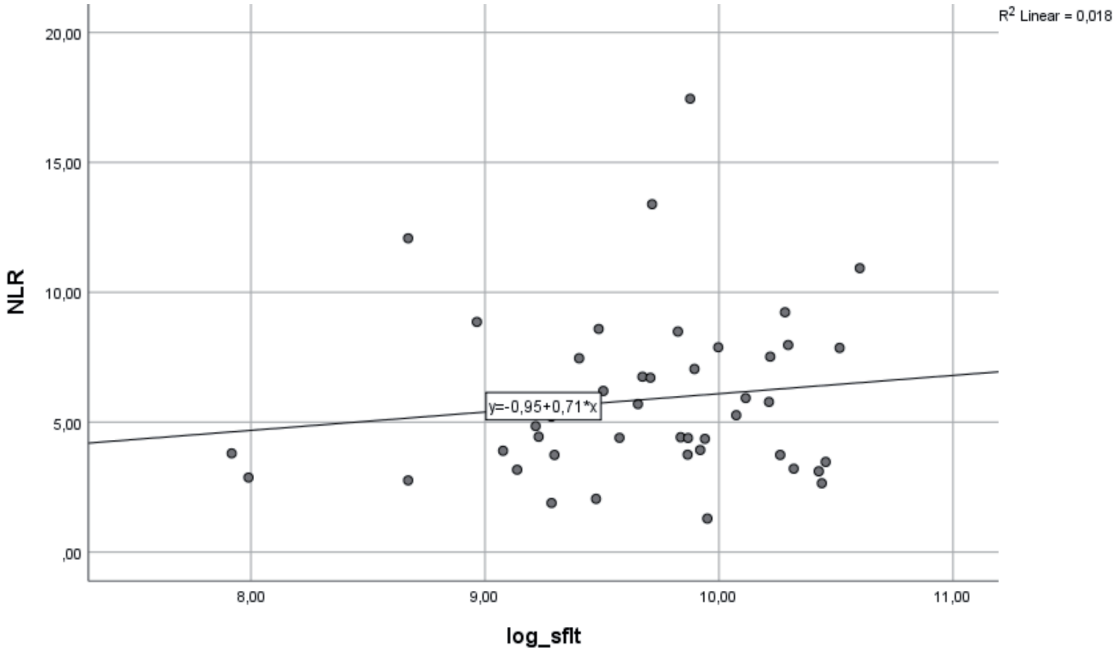

Figure 2. Neutrophil-to-lymphocyte ratio (NLR) correlation with soluble FMS-like tyrosine kinase 1 in preeclampsia (rho=0.117, p=0.451).

Conclusions

The increase in sFLT-1 and the increase in NLR are correlated under normal pregnancy. There is a difference in sFLT-1 levels in PE and controls, but no difference in the biomarker NLR. NLR does not correlate with the biomarker sFLT-1.

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