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Neutrophil-lymphocyte Ratio as a Bio- Inflammatory Prognostic Marker of Fetomaternal Outcomes of Preeclampsia: A Narrative Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Background: Preeclampsia & its related problems have potential contribution to maternal mortality & morbidity. Early diagnosis & appropriate management of preeclampsia can prevent antenatal, intranatal & postnatal complications associated with preeclampsia. The neutrophil to lymphocyte ratio (NLR) which is derived from a complete blood count & dedifferentiation, is a straightforward inflammatory index (1). Pre-existing studies have shown that NLR is indicator of Preeclampsia.
Objective of this Narrative Review: In this we summarized the evidence regarding the clinical utility of NLR in preeclampsia & its related complications.
Methods: A comprehensive systematic search from PubMed, Embase, Cochrane Library, VIP database for relevant literature. Sensitivity, specificity & other measures of accuracy of NLR for the diagnosis of PE were pooled.

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Keywords: NLR; preeclampsia; fetomaternal outcomes; biomarker.

1. INTRODUCTION: WHY THERE IS NEED TO PREDICT FETOMATERNAL OUTCOME?

Preeclampsia affects 2–5% of births in the developed world, but it can affect up to 10% of pregnancies in underdeveloped nations, where emergency care is often insufficient or non-existent [1]. As a result, we require a universally applicable & cheap test that would allow for pre-symptomatic identification in order to identify & monitor patients at risk, allowing us to offer the best prenatal care possible for these women & their children. A test like this would also be useful for confirming a confusing clinical diagnosis & future investigations looking into preventative or temporizing medications.

A screening test must be sensitive & specific, as well as have a high positive predictive value, in order to be successful. Several intriguing markers, alone or in combination, have been developed recently that may meet these criteria. These statistics, on the other h&, were frequently derived from tiny case studies involving a limited number of people.

Before these promising indicators may be used in therapeutically relevant screening tests, large-scale prospective studies around the globe are needed to validate their sensitivity & specificity, as well as to assess their value in different subtypes of preeclampsia.

1.1 What is "PREECLAMPSIA"?

Preeclampsia is a pregnancy-related multi-system disorder characterised by new onset hypertension (systolic & diastolic blood pressure of 140 & 90 mm Hg, respectively, on two occasions, at least 6 hours apart) & proteinuria (protein excretion of 300 mg in a 24-hour urine collection, or a dipstick of 2+) that appears after 20 weeks of pregnancy in previously normotensive women [2].

Edema, haemostasis disturbances, renal or hepatic failure, & the HELLP syndrome (hemolysis, increased liver enzymes, & low platelet counts) can all complicate the clinical picture, depending on the systemic involvement. Preeclampsia can have a mild or severe onset (systolic blood pressure 160 mmHg or diastolic blood pressure 110 mmHg, proteinuria >5 g/24 hours, oliguria, neurological symptoms, other clinical symptoms such as deranged liver function, thrombocytopenia 100 000 mm3, HELLP syndrome) & can progress to eclampsia in the most severe cases [3]. It can also appear as a maternal illness with normal foetal growth, or as a growth-restricted foetus (IUGR) or acute foetal distress.

2. PATHOPHYSIOLOGY

Although the exact cause of preeclampsia is unknown, it is thought to be complex. The placenta's important involvement in disease is a foregone conclusion.

Preeclampsia is thought to occur as a result of immunological maladaptation between the mother & the foetus during the initial weeks of pregnancy, resulting to a two-step problem development (Fig. 1.) that can be summarized as following: in a first – asymptomatic – step, local aberrant fetomaternal immune interactions within the uterine wall lead to impaired tissue & arterial invasion by trophoblast cells. This causes the uterine spiral arteries to fail to convert, resulting in poor placental perfusion.

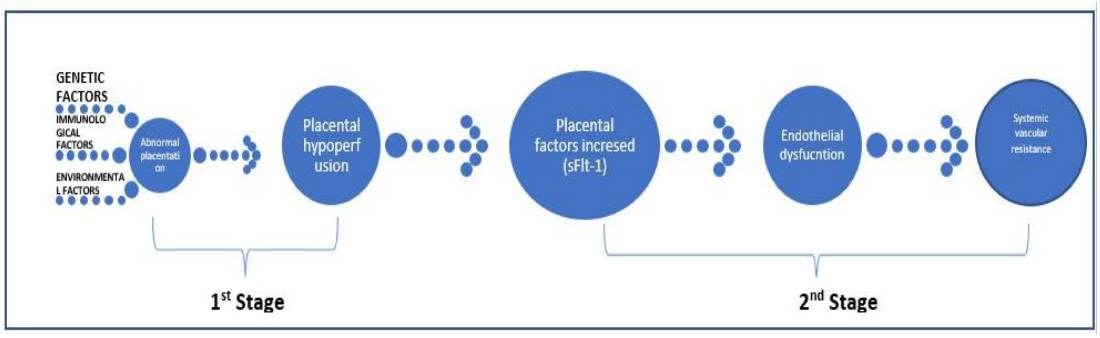

Fig. 1. Chronic hypoxia or alternating periods of hypoxia/reoxygenation inside the intervillous space are likely to enhance placental apoptosis & necrosis by causing tissue oxidative stress

2.1 Two-Stage Theory of Preeclampsia

In 2nd step, the maternal vascular & immune systems become overwhelmed by increased shedding of placental-produced debris, aberrant expression of pro-inflammatory, anti-angiogenic, & angiogenic factors, & monocyte & neutrophil activation, resulting in systemic endothelial cell dysfunction & an exaggerated inflammatory response [4-6]. In the pathophysiology of PE, the neutrophil plays a significant role. When neutrophils move through the intervillous gap, they are exposed to oxidised lipids produced by the placenta [7-9].

This causes thrombocyte activation, vasoconstriction, hypertension, endothelial dysfunction, and end-organ ischemia. As a result, the clinical stage of PE is defined by hypertension, proteinuria, edema, headache, scotoma, coagulopathy, and renal & hepatic dysfunction. Pregnancy can result in systemic inflammation. In normal pregnancies, a shift toward Th2 (suppressor T-helper) cells leads to suppression of Th1 cytokines, permitting maternal immunological tolerance of the foetus; however, in PE, there is a shift toward the Th1 response, immune maladaptation, and hyper-inflammatory state.

Intrinsic failure in trophoblast differentiation (Fig. 2) at various phases of ontogeny was thought to cause either a modest disease with a late start or IUGR worsened or not by maternal symptoms.

Preeclampsia, on the other hand, may be caused by underlying maternal constitutional factors such as heredity, obesity, a faulty maternal clearance system, or, in rare cases, inflammatory systems [10].

Preeclampsia is characterised by shallow trophoblast invasion and aberrant vascular remodelling, which leads to a reduction in maternal blood supply and, as a result, a decrease in foetal growth. The disease's development might be aided by the incapacity of decidual natural killer (NK) cells and macrophages (MΦ) to attract trophoblast cells and drive angiogenesis. EVT is a kind of extravillous trophoblast.

3. MATERIALS AND METHODS

3.1 Study Search

The present study was conducted following the criteria of Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA).

We conducted a literature search using PubMed, The Cochrane Library, EMbase, Chinese National Knowledge Infrastructure (CNKI), Wanfang Medical Network, VIP (VIP), and China Biomedical Literature Database (CBM) without language limitation. The search time limitation was from the establishment of the database to May 31, 2018. The index words were as follows: “Preeclampsia” “neutrophil to lymphocyte” “neutrophil lymphocyte” “NLR” “Neutrophil/ lymphocyte ratio”. All searches used a combination of subject words and free words. All search strategies were determined by multiple pre-searches, and the search formulas were adjusted according to the characteristics of each database.

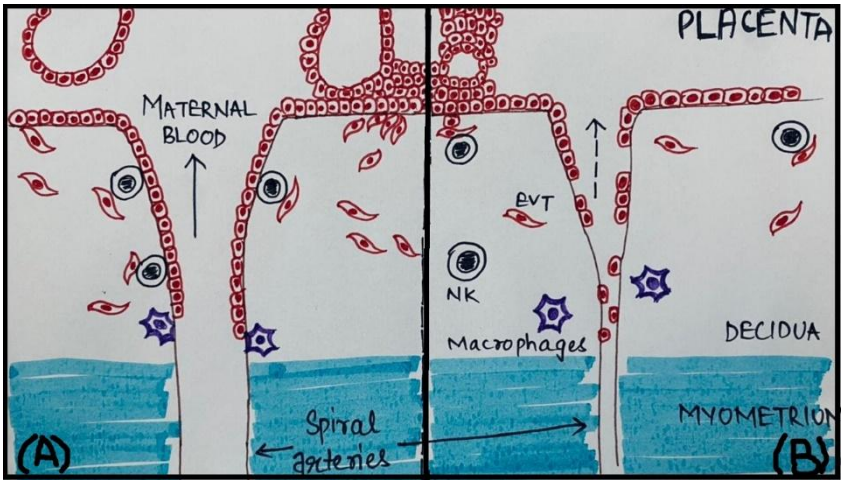

Fig. 2. Spiral arteries & trophoblast invasion in *healthy* (A) & *preeclamptic* (B) pregnancy

3.2 Study Selection

A total of 102 related articles were obtained in the initial inspection. According to inclusion and exclusion criteria, 32 studies were excluded due to duplication, 50 studies were excluded as irrelevant study. After reading full-text articles, 6 studies were excluded for lacking necessary data. At last, 14 studies were determined to be eligible for meta-analysis (Fig. 1).

Neutrophil-Lymphocyte Ratio as a Predictive Biomarker of Preeclampsia: The neutrophil-to-lymphocyte ratio (NLR) is a new metric for assessing the systemic inflammatory response (SIR). NLR's predictive value for a multitude of diseases, including cancer and heart disease, has gained a lot of press. The amount of leukocytes in PE is greater than in a normal pregnancy. A decrease in lymphocytes and an increase in neutrophils induce increased NLR in PE. In women with PE, neutrophils are likely to get activated when they migrate through the intervillous area and are exposed to oxidised lipids produced by the placenta [1,11]. Oxidized lipids, which are potent neutrophil activators, induce the formation of COX-2, which controls the release of thromboxane, TNF, and superoxide (Vaughan et al., 2006; Vaughan & Walsh, 2005). The neutrophils of preeclamptic women generate far more COX-2 than the neutrophils of healthy pregnant or non-pregnant women [12].

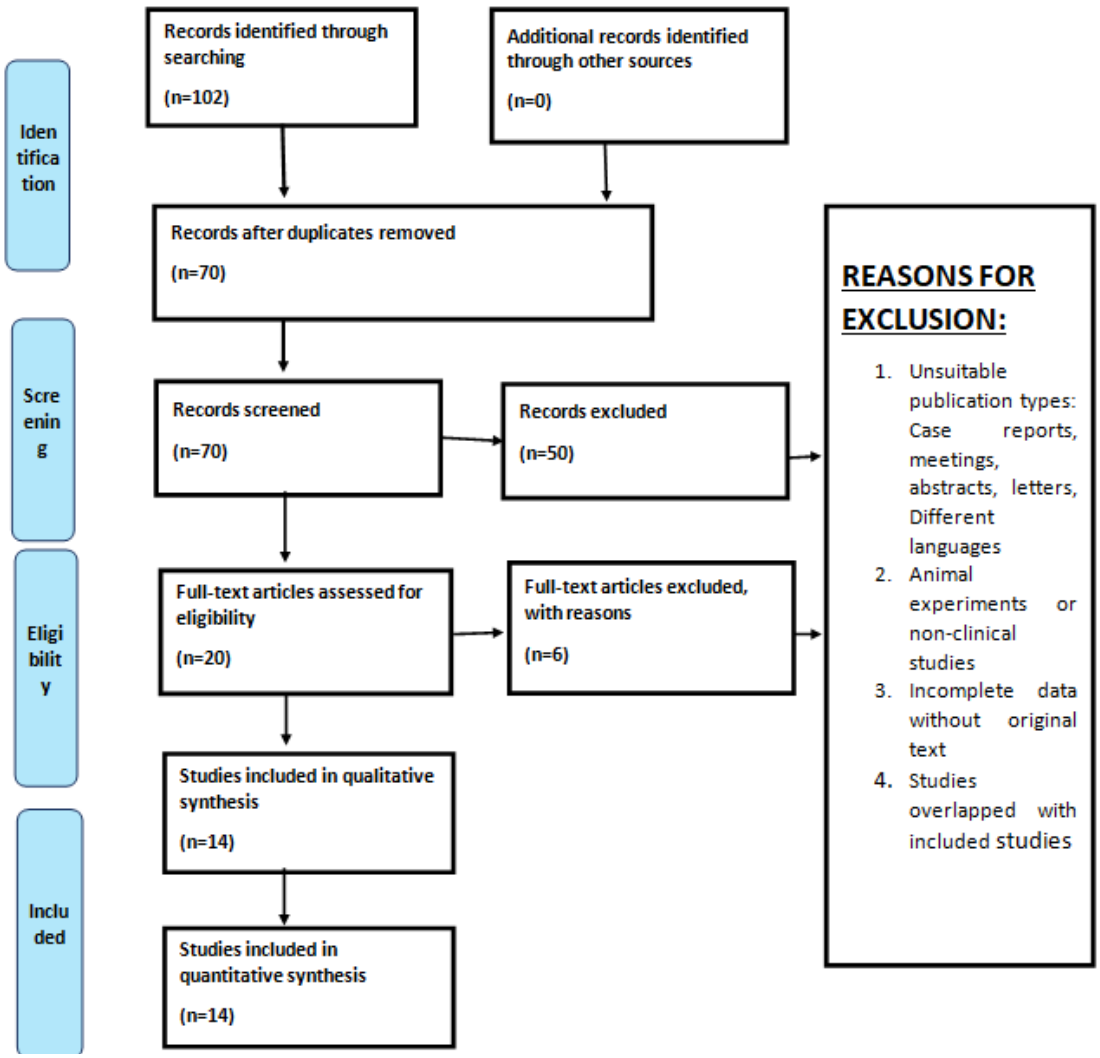

Fig. 3. A block diagram of inclusion and exclusion criteria

Many studies have shown that macrophages have a role in atherosclerotic plaque as foam cells. Lymphocytes are immune cells that assist the body fight illness by producing antibodies. Neutrophils are commonly thought to be the first line of defence against infection at the wound site, however new study has discovered that neutrophils infiltrate systemic vascular tissue in Preeclampsia patients, causing vascular inflammation [13-5]. Other types of leukocytes may enter the maternal vascular system and produce vascular dysfunction in pre-eclamptic mothers.

NLR is a low-cost inflammatory biomarker that has been studied for its therapeutic efficacy during pregnancy in various studies.

Two cross-sectional studies published in 2014 looked at the link between NLR and PE, however the results were equivocal [6,14]. In one study, NLR was shown to be higher in PE patients than in normal pregnant women, and increased NLR was found to be associated to PE independently after correcting for cofounding factors [6]. Another study looked at the NLR level before the caesarean delivery, however the higher NLR in PE was not seen [14]. Following that, other cross-sectional studies looked at the link between PE & NLR, with mixed results [9,10–19]. Some studies found that NLR was higher in PE than in normal pregnant women [9,10,16,19,2], while one study failed to demonstrate a significant difference [20]. In addition, some of the studies indicated that NLR was associated with severity [9,10,18], outcome [19] & proteinuria [9] of PE.

Four case-control studies are presently looking at the link between NLR & PE [17,21–23]. Two of these four studies indicated that increased NLR in first [21] & second trimester [23] was a risk factor for PE. However, the authors of one big research (118 PE patients & 1,495 normal pregnant women) failed to find that NLR was raised in PE patients before the twentieth pregnancy week [15].

NLR is a promising prognostic biomarker, according to *Kang et al.,* 2020, since it is highly raised in pre-eclamptic pregnancies, especially in severe ones [24]. Certain features, however, must be investigated further in order to completely underst& its therapeutic value. To correctly identify the function of NLR in PE, further large-scale prospective cohort studies are required. The start & severity of the condition, as well as the existence of prenatal growth restriction, should all be considered when separating cases. NLR should be assessed in a systematic manner during pregnancy to determine the best gestational age for sampling. In order to examine the prediction usefulness of this marker, cut-off values should be created. These parameters should be predetermined to avoid overestimation of diagnostic performance. Finally, NLR should be examined in combination with traditional PE indicators & put into combined models to provide the most accurate disease prediction.

Neutrophil-Lymphocyte Ratio as a Prognostic Biomarker of Preeclampsia: The BMI, the woman's age, uterine & cervical abnormalities, & lifestyle choices have all been connected to pregnancy. Many complications, including gestational diabetes mellitus, hypertensive disorders of pregnancy, & preeclampsia, as well as infectious & systemic pathological conditions like immunological, endocrine, cardiovascular, hematological, metabolic, gastroenterological, oncological, & kidney diseases, can jeopardize pregnancy.

When assessed in the first trimester of pregnancy, the neutrophil to lymphocytes ratio (NLR) has been linked to pregnancy problems, with a higher value indicating underlying inflammatory processes. When compared to normal pregnancies, NLR has been observed to be higher in preeclampsia, especially in its more severe symptoms [9] as a result, it has been proposed that it can be utilized as a valid biomarker for illness detection in the first trimester of pregnancy [21,3].

Women with pregnant diabetes mellitus, intrahepatic cholestasis, & hyperemesis gravidarum have all been found to have higher NLR readings [3].

Apart from pregnancy-related issues such as Preeclampsia, NLR is employed as a predictive biomarker in illnesses such as metastatic gall bladder cancer, sepsis, stroke, metabolic syndrome, & most recently, COVID-19 sickness [25].

NLR is being researched to see if it may be used as a prognostic tool in hypertensive diseases of pregnancy, particularly Preeclampsia. In addition, the influence of a higher NLR ratio on various fetomaternal outcomes in preeclamptic women is being researched extensively.

Table 1. Biomarkers used in conjunction with Preeclampsia

	Plasma Concentrations					
Biochemical Marker	**1^0 Trimester**	**2^0 Trimester**	**Manifest Preeclampsia**	**Reported combinations for prediction**	**Altered levels are also correlated with**	
sFlt-1	---			- sEng, PIGF, VEGF, - Ultrasound	---	
sEng	---			- sFlt-1, PIGF - Ultrasound	- - -	IUGR HELLP SGA
PIGF				- sFlt-1, PIGF,	-	IUGR
PP-13				- Ultrasound	- -	Preterm delivery SGA
P-Selectin				Activin A, sFlt-1	---	
Cell-free fetal DNA				Inhibin A	- - - -	IUGR Polyhydramnios Trisomy 21 Preterm Labour
Cell free DNA	---	---		---	-	Trisomy 21
ADAM12		---	---		- -	Trisomy 18 SGA
PTX3				---	-	IUGR
PAPP-A					-	Birthweight
Visfatin	---				-	Type 2 DM

Various other Biomarkers used for Prediction of Preeclampsia: Biomarkers combined with uterine artery Doppler screening appear to be a promising screening method nowadays.

Various biophysical & biochemical indicators have been studied for many years, based on pathophysiological observations made in cases of preeclampsia, such as placental malfunction, a broad inflammatory response, endothelial dysfunction, & coagulation system activation.

4. DISCUSSION

Despite the inadequacy of existing preventative & therapeutic options for preeclampsia, the hunt for noninvasive blood-borne or urine biomarkers that might forecast the onset or aid in the identification of this life-threatening pregnant condition remains critical. The availability of such indicators might have a significant influence not only on the medical care of pregnant women & their children (for example, referral to a tertiary centre), but also on the health expenses associated with this poor medical state. As a result, identifying pregnant women at risk for preeclampsia as early as possible is critical in order to apply preventative measures.

5. CONCLUSION

PE is a multisystem ailment, & the disease's pathogenetic phases are yet unknown. Because delivery is the sole therapeutic option, early detection & prevention are critical to minimize the fetal & maternal effects, particularly in the case of preterm PE. As a result, there is increased interest in studying the significance of new biomarkers in identifying high-risk pregnant women & shedding insight on the disorder's etiology. Our data imply that the NLR value is greater in PE patients, particularly those with severe cases.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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