Review Article

The clinical utility of neutrophil to lymphocyte ratio in pregnancy related complications: a mini-review

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Contributions: (I) Conception and design: ZD Hu; (II) Administrative support: L Hai; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Pregnancy-related complications (PRCs) are potent contributors to mortality and morbidity in pregnant women. Prediction and early recognition of PRCs are crucial to improve its prognosis. The pathogenesis of PRCs is complex and it is well-recognized that inflammation response is involved in several types of PRCs. Therefore, inflammatory markers are usually used as predictors or prognostic factors in PRCs. Neutrophil to lymphocyte ratio (NLR), which is calculated from complete blood count and dedifferentiation, is a simple and easily obtainable inflammatory index. Accumulated studies have shown that NLR is an indicator of PRCs. In this minireview, we summarized the evidence regarding the clinical utility of NLR in PRCs, including preeclampsia, gestational diabetes mellitus, hyperemesis gravidarum, preterm delivery and ectopic pregnancy.

Keywords: Neutrophil to lymphocyte ratio (NLR); pregnancy-related complications (PRCs); inflammation

Received: 25 September 2019; Accepted: 12 October 2019; Published: 20 January 2020.

doi: 10.21037/jlpm.2019.10.03

View this article at: http://dx.doi.org/10.21037/jlpm.2019.10.03

Introduction

Neutrophil to lymphocyte ratio (NLR), which can be easily calculated from complete blood count and leukocyte differential count, is an inexpensive parameter with multiple clinical applications. For example, accumulated evidences have indicated that NLR is a prognostic factor for heart failure (1), adult subarachnoid hemorrhage (2) and gastric cancer (3). One of the possible mechanisms underlying the multiple applications of NLR is inflammation response, which increases circulating neutrophils and decreased lymphocytes (4,5).

Pregnancy related complications (PRCs), such as preeclampsia (PE) and gestational diabetes mellitus (GDM), are potent contributors to mortality and morbidity in pregnant women. Early diagnosis and prediction of PRCs are crucial to improve its outcomes. Interestingly, inflammation response is involved in the pathogenesis of nearly all types of these complications (6-8). Therefore, inflammation indicators, such as C-reactive protein (CRP) and interleukin 6 (IL-6), are associated with the occurrence of PRCs (9-11).

Because NLR is a simple and inexpensive inflammatory indicator, accumulated studies have investigated the clinical utility of NLR during pregnancy. Therefore, we summarized and commented the currently available evidence regarding NLR and PRCs. In this review, we categorized the available studies into the cross-sectional, case-control and cohort studies. This information was not extracted from the original reports, but justified by the author. Cross-sectional design was defined as any studies that measure exposure factors and outcomes simultaneously.

Case-control design was defined as any studies in which outcomes are firstly obtained and exposure factors before the occurrence of outcomes are retrospectively obtained. Cohort design was defined as any studies in which exposure factors are firstly obtained and subjects are followed until the occurrence of outcome.

PE

PE is a major cause of mortality and morbidity for both mother and fetus around the world (12). It is characterized by hypertension and proteinuria after 20 weeks of pregnancy (12). The prevalence of PE is around 1% to 8% (13-15). Although the pathogenesis of PE is largely unknown, animal and clinical studies indicate that inflammation response is critically involved in the occurrence and development of PE (6,16,17). Because NLR is simple indicator of inflammation response, some studies have investigated the clinical utility of NLR in PE.

Two cross-sectional studies published in 2014 (18,19) investigated the relationship between NLR and PE, but the results are inconsistent. One study found that NLR in PE patients was higher than that in normal pregnant woman, and increased NLR was independently associated with PE after adjusting for cofounding factors (19). The other study determined the NLR level before the caesarean delivery but failed to find the increased NLR in PE (18). Subsequently, several cross-sectional studies have investigated the relationship between PE and NLR, and the results varied (20-28). Some studies found that NLR was higher in PE than in normal pregnant women (20-25,28), while one study failed to demonstrate a significant difference (27). In addition, some of the studies indicated that NLR was associated with severity (22-24), outcome (21), and proteinuria (24) of PE.

Currently, four case-control studies investigated the relationship between NLR and PE (20,29-31). Two of these four studies indicated that increased NLR in first (30) and second trimester (31) was a risk factor for PE. But in one study with large sample size (118 PE patients and 1,495 normal pregnant women), the authors failed to found NLR before the twentieth pregnancy week was increased in PE patients (20).

Taken together, the current evidence regarding NLR and PE is not consistent, and majority of the current evidence is cross-sectional or case-control design. Therefore, prospective cohort studies and meta-analyses are needed to provide robust evidence regarding the clinical utility of NLR in PE.

Hemolysis, elevated liver enzymes, low-platelet count (HELLP) syndrome

HELPP syndrome is characterized by hemolysis, liver injury, and decreased platelet count in the third trimester of pregnancy (32,33). To present, two studies from the one group have investigated the clinical utility of NLR in HELLP syndrome (34,35). In a case-control study, the author enrolled 14 HELLP syndrome patients and 14 age-matched normal pregnant women and found that NLR in third trimester was significantly increased in HELPP syndrome patients (35). Contrarily in a cross-sectional study the authors failed to prove that NLR in the third trimester was increased in PE (34). Considering that the sample sizes in these two studies are small and cofounding factors were not fully considered, further studies are needed to investigate the utility of NLR in HELLP syndrome management.

GDM

GDM is defined as glucose metabolism disorder that occurs for the first time during pregnancy, and inflammation is believed to be involved in the pathogenesis of GDM (36). In 2014, a cross-sectional study with 42 GDM and 68 non-GDM indicated that NLR was increased in GDM patients, and NLR was independently associated with GDM in a multivariable logistic regression model (37). However, a subsequent study with large sample size failed to found the increased NLR in GMD (38). The possible reasons for the inconsistency are largely unknown. In a recently published work, the researcher included 114 GDM and 114 well-matched non-GDM and found that NLR was increased in GDM patients (39). Furthermore, NLR was independently associated with HbA1c in a multivariable liner regression model (39). Taken together, current evidence regarding GDM and NLR is controversial, and further studies, especially prospective cohort studies, are needed to illustrate the clinical utility of NLR in GDM.

Ectopic pregnancy (EP)

EP is a complication of pregnancy which is defined as the implantation of the embryo outside the uterine cavity (40). Currently, methotrexate (MTX) and surgery are usually used for EP treatment in clinical practice. MTX is a

noninvasive treatment approach and thus much preferred by obstetricians. However, the benefit and hazard of MTX should be balanced when deciding the treatment approach. Generally, MTX is usually used in patients with stable hemodynamics, smaller pregnancy mass size, lower beta-subunit human chorionic gonadotropin (β-hCG), while surgery is used in the remaining. However, the board line between MTX and surgery is not always clear in clinical practice. For some patients, treatment approach selection is really a challenge for obstetricians.

In a study published in 2017, the researchers compared the clinical and laboratory characteristic of EP patients received MTX (n=93) and surgery (n=60) (41). They found that NLR was significantly increased in patients received surgery, indicating that NLR was helpful in the choice of the EP treatment. This finding was validated by a subsequent study (42). In a study published recently, the researcher found that EP patients with tubal rupture had higher NLR than these without (43), also supports that NLR can assist obstetricians choosing treatment approach. Further, in one study with 78 MTX treatment successful and 37 MTX treatment failure patients, higher NLR was observed in MTX treatment successful patients (44), indicating that NLR is a predictor of MTX treatment efficiency.

Hyperemesis gravidarum (HG)

HG is a serious complication characterized by nausea and vomiting in first trimester of pregnancy. It can lead to dehydration, ketonuria, fluid and electrolyte imbalance, and weight loss (45). Some studies have compared the NLR level between normal pregnant women and HG patients (46-51) and all of them found that NLR was increased in HG patients. One study found that NLR increased as the advance of HG severity (47), indicating that NLR is a useful indicator in estimating the severity of HG. However, this finding was not validated in other two studies (48,51). Notably, all of these studies are cross-sectional and the therefore causality cannot be established. Further prospective cohort studies are needed to verify whether NLR is a risk factor for HG.

Preterm delivery (PD)

PD, defined as birth before 37 weeks' gestation, is the major cause of perinatal morbidity and mortality worldwide. Some pregnant women may present with threatened preterm labor (TPL) on admission, but delivery does not occur after a tocolytics treatment. It is of great value to identify TPL women who will give birth preterm. Some studies have investigated the value of NLR in predicting PD (52-57). In three retrospective cohort studies (52,55,56), NLR was reported to be a risk factor for PD. However, in two case-control studies (54,57), the authors reported that NLR was not a risk factor for PD. In another study, the authors reported that NLR was higher in the patients with preterm premature rupture of membranes and it was a predictor of neonatal sepsis (53).

Conclusions

To date, accumulated studies have investigated the clinical utility of NLR in PRCs (*Table 1*). However, the results were not always consistent. This may be due to the small sample sizes and low statistical power in some studies. Therefore, meta-analysis may be needed to pool the results of available

Table 1 Current evidence on neutrophil to lymphocyte ratio and pregnancy-related complications.

First author's name	Year	Country	Population	Design	Major findings	Ref.
PE						
Örgül	2019	Turkey	21 EOPE, 42 LOPE, 123 NP	Case-control	NLR in the first trimester was not predictive for EOPE	(29)
Panwar	2019	India	376 NP, 49 MPE, 15 SPE	Case-control	NLR at the second trimester of pregnancy was a predictor of occurrence and severity of PE The AUCs of NLR for predicting PE and SPE were 0.84 and 0.95, respectively	(31)

Table 1 (*continued*)

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First author's name	Year	Country	Population	Design	Major findings	Ref.
Mannaerts	2019	Belgium	118 PE, 1,495 NP	Case-control	NLR obtained before the 20th pregnancy week was not increased in PE	(20)
Gezer	2016	Turkey	209 PE, 221 NP	Case-control	NLR in first trimester was increased in PE	(30)
					Increased NLR was an independent factor for PE after adjusting for other risk factors, with an OR of 1.43 (95% CI: 1.21–1.76)	
					The AUC of NLR for predicting PE was 0.716 (95% CI: 0.666–0.766)	
Wang	2019	China	162 MPE, 205 SPE, 172 NP, 170 non-pregnancy	Cross-sectional	NLR on admission was increased in PE patients	(21)
					Increased NLR was significantly associated with severe maternal morbidity, adverse neonatal outcome, and preterm delivery after adjustment for potential confounders	
					The AUCs of NLR for predicting PE and MPE were 0.70 (95% CI: 0.66–0.75) and 0.71 (95% CI: 0.66–0.77)	
Gogoi	2019	India	67 NP, 38 MPE, 29 SPE	Cross-sectional	NLR before labor was increased in PE	(26)
					Difference between MPE and SPE is not statistically significant	
Mannaerts	2019	Belgium	59 PE, 138 NP	Cross-sectional	NLR before primary caesarean section was increased in PE	(20)
					The AUC of NLR for predicting PE was 0.863 (95% CI: 0.783–0.944)	
Sitotaw	2018	Ethiopia	66 NP, 33 MPE, 30 SPE	Cross-sectional	NLR was increased in PE	(22)
					SPE had higher NLR than MPE	
Jeon	2017	Korea	68 PE, 86 NP, 33 GH	Cross-sectional	NLR was increased in PE	(28)
					The AUC of NLR for predicting PE was 0.652 (95% CI: 0.550–0.744)	
Cakmak	2017	Turkey	40 NP, 55 MPE, 45 SPE	Cross-sectional	NLR was increased in PE	(23)
					SPE had higher NLR than MPE	
					Increased NLR was independently associated with PE after adjusting for other risk factors	
					The AUC of NLR for predicting PE was 0.930 (95% CI: 0.887–0.973)	
					The OR of NLR was 8.161 (95% CI: 3.091–21.548)	
Yücel	2017	Turkey	110 NP, 27 MPE, 82 SPE	Cross-sectional	NLR on admission to emergency department was not increased in PE	(27)
					NLR in SPE was not significantly higher than that in MPE	
Serin	2016	Turkey	30 NP, 37 MPE, 40 SPE	Cross-sectional	NLR was increased in PE	(24)
					SPE had higher NLR than MPE	
					NLR was positively associated with proteinuria in PE	

Table 1 (*continued*)

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First author's name	Year	Country	Population	Design	Major findings	Ref.
Kurtoglu	2015	Turkey	73 NP, 23 MPE, 107 SPE	Cross-sectional	NLR was increased in PE with an AUC of 0.596 for predicting PE	(25)
Oylumlu	2014	Turkey	54 NP, 54 PE	Cross-sectional	NLR was increased in PE with an AUC of 0.925 (95% CI: 0.878–0.973) for predicting PE	(19)
					Increased NLR was independently associated with PE after adjusting for other risk factors, with an OR of 2.740 (95% CI: 1.354–5.544)	
Yavuzcan	2014	Turkey	30 SPE, 36 NP, 35 non-pregnancy	Cross-sectional	NLR was not significantly increased in PE before the caesarean delivery	(18)
HELLP						
Sisti	2019	USA	10 HELLP, 10 NP	Cross-sectional	NLR in first trimester was comparable to that in NP	(34)
Sisti	2019	USA	14 HELLP, 14 NP	Case-control	NLR in third trimester was significantly higher than that in NP	(35)
GDM						
Basu	2018	India	114 GDM, 114 non-GDM	Cross-sectional	GDM patients had significantly higher NLR than non-GDM	(39)
					NLR was independently associated with HbA1c	
Sargın	2016	Turkey	144 GDM, 76 IGT, 238 OSP, 304 NGT	Cross-sectional	Differences of NLR in GDM, IGT, OSP, and NGT was not statistically significant	(38)
Yilmaz	2014	Turkey	42 GDM, 68 non-GDM	Cross-sectional	GDM patients had significantly higher NLR than non-GDM	(37)
					NLR was independently associated with GDM with an OR 5.512 (95 % CI: 1.352–22.475)	
					The AUC of NLR for predicting GDM was 0.798	
EP						
Kan	2019	Turkey	72 rupture EP patients. 70 non-rupture EP patients	Case-control	NLR can predict tubal rupture in ampulla EP patients	(43)
Kanmaz	2018	Turkey	134 MTX treatment successful, 27 MTX treatment failure	Case-control	NLR was helpful in the choice of the EP treatment (MTX or surgery)	(42)
Akkaya	2017	Turkey	60 surgery treated EP patients and 93 MTX treated EP patients	Case-control	NLR was helpful in the choice of the EP treatment (MTX or surgery)	(41)
Cekmez	2016	Turkey	78 MTX treatment successful, 37 MTX treatment failure	Case-control	MTX treatment successful EP patients had significantly higher NLR than MTX treatment failure EP patients	(44)

Table 1 (*continued*)

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First author's name	Year	Country	Population	Design	Major findings	Ref.
HG						
Kan	2019	Turkey	113 HG, 41 NP	Cross-sectional	NLR was increased in HG patients but not correlated with severity of HG	(51)
					The AUC of NLR for predicting HG was 0.714	
Cintesun	2019	Turkey	94 HG, 100 NP	Cross-sectional	HG patients had higher NLR than NP	(49)
Beyazit	2017	Turkey	54 HG, 58 NP	Cross-sectional	HG patients had higher NLR than NP	(50)
					The AUC of NLR for predicting HG was 0.818	
Tayfur	2017	Turkey	433 HG, 160 NP	Cross-sectional	NLR was increased in HG patients but not correlated with severity of HG	(48)
					The AUC of NLR for predicting HG was 0.64	
Caglayan	2015	Turkey	45 HG, 45 NP	Cross-sectional	HG patients had higher NLR than NP	(46)
Kurt	2014	Turkey	55 HG, 50 NP	Cross-sectional	NLR was increased in HG patients and correlated with severity of HG	(47)
PD						
Gezer	2018	Turkey	229 PD, 178 TD	Retrospective cohort	In preterm labor patients, increased NLR was an independent risk factor of PD, with an OR of 1.41 (95% CI: 1.32–1.51)	(56)
					The AUC of NLR for predicting PD was 0.711 (95% CI: 0.662–0.760)	
Daglar	2016	Turkey	30 PD, 25 TPL, 53 TD	Case-control	In preterm labor patients, NLR was not associated with PD	(54)
Bozoklu Akkar	2016	Turkey	35 PD, 44 TD	Prospective cohort	Increased NLR was associated with PD in preterm labor patients	(55)
Isık	2015	Turkey	90 PD, 128 TD	Case-control	NLR at 34 weeks' gestation was not increased in PD patients	(57)
Kim	2011	Korea	102 PD, 73 TD	Retrospective cohort	In preterm labor patients, increased NLR was a risk factor of PD	(52)
					The AUC of NLR was 0.717 (95% CI: 0.610–0.824)	
Ozel	2019	Turkey	60 PPROM, 50 TPL, 47 TD	Cross-sectional	Significantly higher NLR was observed in the PPROM patients	(53)
					NLR is a predictor of neonatal sepsis	

NP, normotensive pregnant woman; PE, preeclampsia; MPE, mild preeclampsia; SPE, severe preeclampsia; NLR, neutrophil to lymphocyte ratio; EOPE, early-onset preeclampsia; LOPE, late-onset preeclampsia; GH, gestational hypertension; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; OSP, only screen positive; NGT, normal glucose tolerance; EP, ectopic pregnancies; MTX, methotrexate; HG, hyperemesis gravidarum; PD, preterm delivery; PPROM, preterm premature rupture of membranes; TPL, threatened preterm labor; TD, term delivery; AUC, area under receiver operating characteristic curve; OR, odds ratio; CI, confidence interval.

results in future. Notably, majority of evidences is case-control or cross-sectional design and multivariable analysis is not performed in large portion of available studies. Therefore, prospective cohort studies with large sample sizes and fully-adjusted analyses are needed to rigorously evaluate the clinical utility of NLR in PRCs.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Laboratory and Precision Medicine* for the series "Laboratory Medicine in Pregnancy". The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/jlpm.2019.10.03). The series "Laboratory Medicine in Pregnancy" was commissioned by the editorial office without any funding or sponsorship. Zhi-De Hu served as an unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Journal of Laboratory and Precision Medicine* from November 2016 to October 2021. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jlpm.2019.10.03
Cite this article as: Hai L, Hu ZD. The clinical utility of neutrophil to lymphocyte ratio in pregnancy related complications: a mini-review. J Lab Precis Med 2020;5:1.

