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THE COMPREHENSIVE SYSTEMATIC REVIEW OF NEUTROPHIL GELATINASE–ASSOCIATED LIPOCALIN AS A PREDICTOR OF PRE-ECLAMPSIA

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ABSTRACT

Background: *The use of NGAL for preeclampsia and eclampsia prediction looks appealing, but one has to understand that NGAL levels increase in the state of inflammatory conditions associated with epithelial cell injury like pelvic inflammatory disease, chronic obstructive pulmonary disease, malignancies of breast, lungs, and colon. NGAL is also released from maternalfetal interface and is thought to be released when there is uterine vasoconstriction as happens in preeclampsia.*

The aim: *This study aims to show about the comprehensive of neutrophil gelatinase-associated lipocalin as a peredictor of pre-eclampsia.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 143 articles, whereas the results of our search on SagePub brought up 24 articles. The results of the search conducted for the last year of 2014 yielded a total 70 articles for PubMed and 15 articles for SagePub. The result from title screening, a total 10 articles for PubMed and 12 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.*

Conclusion: *The utility of NGAL for diagnosing and assessing the severity of preeclampsia. The increase in NGAL due to preeclampsia is attributed to the presence of endothelium dysfunction and systemic inflammation.*

Keyword: *Neutrophil gelatinase–associated lipocalin (NGAL), pre-eclampsia, eclampsia.*

INTRODUCTION

Neutrophil gelatinase–associated lipocalin (NGAL), also called lipocalin-2 (LCN2) or oncogene 24p3, is a 25-kDa protein composed of 198 amino acids. In humans, NGAL is encoded by the LCN2 gene on chromosome 9 and is excreted in the extracellular space, where it exercises its function. The neutrophils, kidneys, salivary glands, esophagus, vagina, and stomach are the main cells and tissues that express NGAL in the human body. Several animal and human studies have highlighted the key role of NGAL in the immune and inflammatory response. NGAL binds to iron and prevents its use by bacteria, regulates cell migration and apoptosis, and plays a role in epithelial cell injury. NGAL is also produced by the kidneys during development and tubular regeneration after injury.[1]

NGAL has been associated with Klebsiella infection, acute pyelonephritis, urinary tract obstruction, hepatorenal syndrome, acute kidney failure, pelvic inflammatory disease, chronic obstructive pulmonary disease, malignancies, and vasculitis.In obstetrics, NGAL has been mostly associated with pre-eclampsia. Indeed, several studies have found that maternal blood and urine levels of NGAL could predict the development of pre-eclampsia in the first trimester.[1]

Preeclampsia is a commonly encountered hypertensive disorder of pregnancy, in both developed as well as developing countries (incidence of 3–4% and up to 15%, respectively). The disease continues to be associated with maternal as well as fetal mortality. Preeclampsia has multisystemic manifestations, with renal affliction being frequently encountered. Both glomerular as well as tubular renal involvement are known to occur. Preeclampsia can also blunt the pregnancy-induced physiological increase in glomerular filtration rate (GFR), or even decrease it. Lastly, there may be a prerenal contribution as well, following hypoperfusion and blood loss. Due to all of the above reasons, preeclampsia is known to be a risk of development of acute kidney injury (AKI).[2]

PE occurs at a frequency of 5-8% of all pregnancies. Previous preeclampsia, nulliparity, age < 18 years or > 40 years, chronic hypertension, chronic kidney disease, family history of preeclampsia, and obesity are some well-known conventional risk factors for PE development. Preeclampsia is a serious concern of obstetrics because of the bearing of potential worse outcomes. PE-associated outcomes are; i) obstetric-related (intrauterine growth restriction, preterm delivery, abruption placenta, even maternal and fetal deaths), ii) long-term maternal risk (chronic hypertension, cardiovascular disease [CVD], death from CVD, stroke, etc). Although, there is no available standardized predictive laboratory test that could assist in diagnosing the disease, the utility of such a test like lipcalin-2 (LCN-2) would be valuable, at least in managing the obstetric course of pregnants with a higher risk for PE development.[3]

PE cannot be predicted by previous obstetric history and risk factors alone, much research has focused on the identification of women at high risk of developing PE. This would allow more intensive monitoring of this high risk group as well as targeted prophylactic intervention, timely diagnosis and treatment. The identification of PE biomarkers in early pregnancy would enable appropriate stratification of a pregnancy into high and low risk, such that a positive predictive test would allow specific therapeutic interventions. Maternal deaths due to PE might thus be avoided more easily as the ultimate long term goal. However, on a pragmatic basis, the identification of PE biomarkers would lead to increased maternal surveillance of high risk pregnancies and improve perinatal outcomes.[4]

Due to the complex pathophysiology and aetiology of PE, a wide range of potential biomarkers have been investigated. These biomarkers can be classified under different categories and many novel biomolecules have been identified. In addition to the predictive value of biomarkers, the identification of these entities (e.g., metabolomic or proteiomic molecules) may elucidate the underlying mechanism for the pathogenesis of PE. Although no single biomarker has been deemed suitable for clinical application at present various novel biomarkers or combinations of biomarkers with other well recognized clinical parameters are promising. To this end, we conducted a systematic review and meta-analyses of biomarkers during the first half of pregnancy for the prediction of PE.[4]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast the comprehensive of neutrophil gelatinase-associated lipocalin as a peredictor of pre-eclampsia. It is possible to accomplish this by researching or investigating the comprehensive of neutrophil gelatinase-associated lipocalin as a peredictor of pre-eclampsia. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the comprehensive of neutrophil gelatinase-associated lipocalin as a peredictor of pre-eclampsia. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " the comprehensive of neutrophil gelatinase-associated lipocalin as a peredictor of pre-eclampsia." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *((*"Neutrophil gelatinase-associated lipocalin *"[MeSH Subheading] OR* "Pre-eclampsia*"[All Fields] OR* "Predictor of Pre-eclampsia*" [All Fields]) AND (*"Mechanism of pre-eclampsia*"[All Fields] OR "* effects of neutrophil gelatinase-associated lipocalin *"[All Fields]) AND (*"Mechanism of gelatinase-associated lipocalin as a peredictor of pre-eclampsia*"[All Fields]) OR (*"Pathogenesis of pre-eclampsia" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

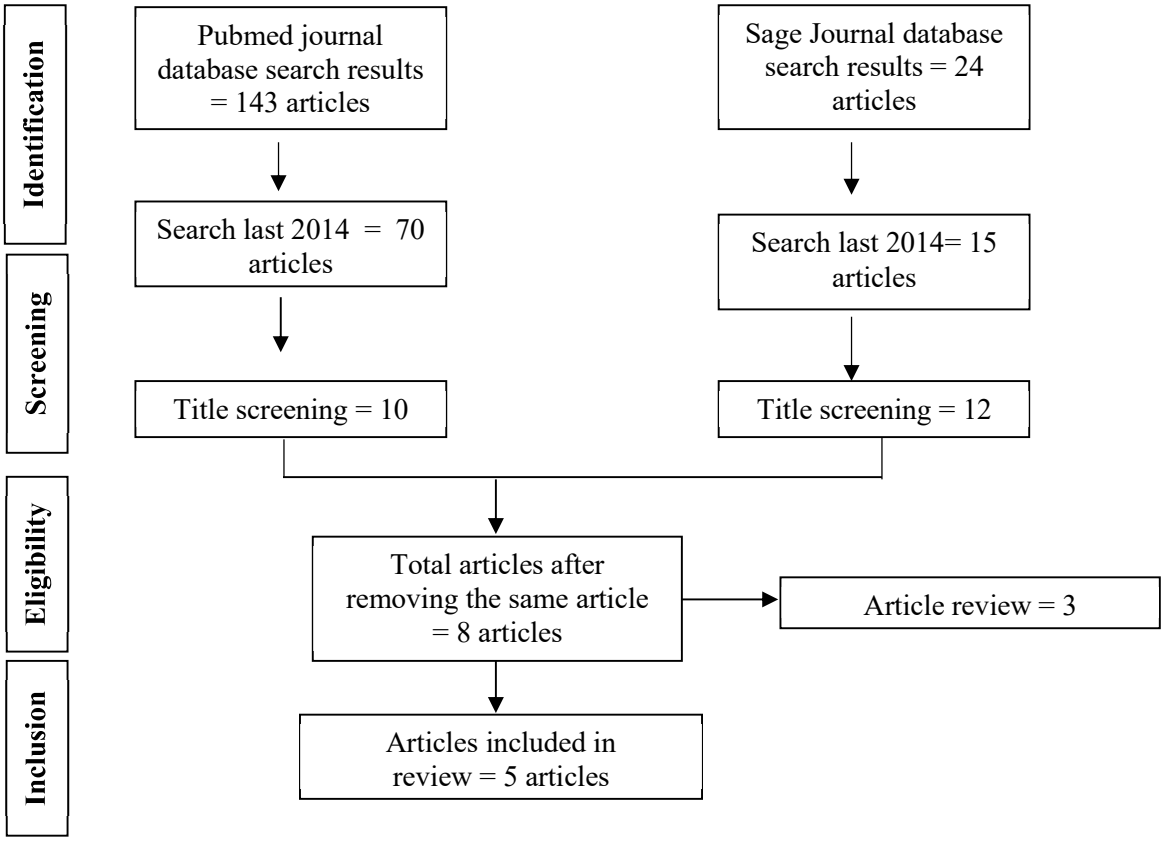

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 143 articles, whereas the results of our search on SagePub brought up 24 articles. The results of the search conducted for the last year of 2014 yielded a total 70 articles for PubMed and 15 articles for SagePub. The result from title screening, a total 10 articles for PubMed and 12 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.

Springer, S *et al* (2022)[5] showed women with twin pregnancies who developed hypertensive disorders showed increased NGAL values at 11–16 weeks of pregnancy. Many issues have to be elucidated in the future, e.g., the definition of normal ranges for NGAL in twin pregnancies and the implementation of this parameter into predictive models for the risk assessment of developing preeclampsia.

Sachan, R *et al* (2014)[6] showed serum NGAL levels were evaluated in normal pregnant women and women suffering with HDP and correlated with severity of disease. Between the two groups, we found a positive correlation of serum NGAL with disease severity and better sensitivity and specificity in the evaluation of HDP as compared with previously reported studies.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Springer,S *et al*., 2022[5]	Germany	A Cohort Study	242	Serum NGAL was evaluated twice during pregnancy and once in the postpartum period. Furthermore, serum NGAL values were compared between women who developed hypertensive disorders and those who had normal blood pressure. In all twin pregnancies, mean NGAL values increased significantly from the first to the second visit (p = 0.004) and, further, after delivery (p < 0.001). NGAL was significantly higher in pregnancies that developed pregnancy hypertension or preeclampsia when compared to the control group at the first visit (109.2 ± 48.9 ng/mL vs. 91.9 ± 29.4 ng/mL, p = 0.04, respectively). The predictive power of first visit NGAL values for development of pregnancy hypertension or preeclampsia was evaluated. When using a cut-off value of 115 ng/mL, we obtained a sensitivity of 45% with a specificity of 77%.
Sachan, R *et al*., 2014[6]	India	Prospective case-control study	1850	Mean serum NGAL value in patients with oliguria was significantly higher when compared with non-oliguric patients (P < 0.001). Serum NGAL had a positive correlation with systolic blood

				pressure ($r \sim 0.5973$), diastolic blood pressure ($r \sim 0.6195$), blood urea ($r \sim 0.4392$), serum creatinine ($r \sim 0.6112$), serum uric acid ($r \sim 0.3878$). Sensitivity and specificity of serum NGAL using a cut-off value of 545 pg/ml, for the diagnosis of HDP, was 97.89% and 93.55% respectively, using 95% confidence interval.
Ali, EA *et al*., 2021[7]	Iraq	Randomized case-control study	132	The mean serum level of NGL was significantly higher in PE (535.37 ± 158.61 ng / ml for severe PE, 522.5 ± 106.3 ng / ml for non-severe PE, and 161.96 ± 17.48 ng / ml for the control group). The ROC Curve NGL criteria of more than 204.4 ng / ml showed 100% sensitivity and specificity in both severe and non-severe cases versus control. The N / L ratio showed a significant difference (5.81 ± 5.24 for severe PE, 4.1 ± 3.41 for non-severe PE, and 3.89 ± 1.79 for the control group), but the ROC curve criterion was not significant. Both showed a non-significant positive correlation.
Surmiak, P *et al*.,2022[8]	Poland	Prospective, single-centre, case-control study	27	Significant differences in umbilical cord MDA and NGAL concentration between the SGA and AGA groups. Such dependencies were not found in blood samples from neonates collected in the first 12 hours of life for MDA and NGAL concentrations. Additionally, we have observed differences in umbilical MDA and NGAL levels between newborns of preeclamptic or hypertensive mothers compared to healthy ones. A significant correlation between the occurrence of hypertension during pregnancy and umbilical MDA and NGAL concentrations was also found.
Simonazzi, G *et al*., 2015[9]	Italy	Cross-sectional case–control study	18	Linear regression disclosed a positive and significant correlation between urinary NGAL and 24-hour proteinuria. Serum NGAL appeared to be higher, but not significantly different, in severe pre-eclampsia.

Ali, EA *et al* (2021)[7] showed NGL is an excellent diagnostic factor, whereas N/L might have lower diagnostic performance compared with NGL. The two variables are related independently in the pathophysiology of PE.

Surmiak, P *et al* (2022)[8] showed that small for gestational age newborns or born by preeclamptic and hypertensive mothers had significantly elevated MDA and NGAL levels as compared to healthy ones. This may be confirmed by the influence of oxidative stress on the onset of subclinical altered organ function in growth-restricted neonates. Further investigation is needed to understand the pathophysiologic influence of hypertension in pregnancy on developing kidneys of foetuses with growth restriction.

Simonazzi, G *et al* (2015)[9] showed that NGAL correlates with inflammatory renal involvement in cases of severe pre-eclampsia. Further studies on a larger patient population should be useful for better estimating the clinical value of NGAL as a biomarker of severe pre-eclampsia, to minimize the effects of potential bias (*e.g.* chronic hypertension) and potentially help in the evaluation of delivery induction.

DISCUSSION

Preeclampsia (PE) mainly occurs after 20 weeks of pregnancy and manifests as hypertension, proteinuria, and tissue edema, with systemic multiple organ damage. It is a pregnancy-specific complication with an incidence of 3–8 % and is one of the main causes of maternal and neonatal mortality. The etiology of PE has not yet been fully elucidated, and there are no clinically effective treatments other than the termination of pregnancy. It is well established that people with a high risk of PE could take low-dose aspirin during early pregnancy to effectively reduce the risk of PE. The International Federation of Gynecology and Obstetrics (FIGO) recommends that the maternal risk factors, such as maternal age, obesity, and previous or family history of PE, combined with biomarkers can better predict the risk of PE and may prompt increased monitoring and early clinical intervention of PE in high-risk populations to reduce the risk of PE. Therefore, biomarkers validated by extensive clinical research may be formally applied to clinical PE risk prediction, which is of great clinical significance.[10,11]

Hypertension is considered one of the serious medical complications of pregnancy and significantly affects the perinatal morbidity and mortality. Preeclampsia (PE) is a severe complication affecting 5%–7% of all pregnant females. It is considered a widespread multiple organ disorder of unknown cause. The different mechanisms of preeclampsia are still unknown, but are believed to result from an insufficient function of the placenta. The main pathological lesion in PE is the renal lesion named glomerular endotheliosis, which has been regarded as pathognomic for that condition.[12]

Hypertension is a frequent medical issue, complicating up to one-tenth of pregnancies globally. Therefore, pregnancy-related hypertensive disorders represent a substantial cause of perinatal and maternal morbidity and mortality worldwide. Numerous clinical studies postulated an increased rate of pregnancy-related hypertensive disorders in multifetal gestations. Approximately 6.5% of all singleton pregnancies, 12.7% of all twin pregnancies, and 20% of all triplet pregnancies are affected by pregnancy-related hypertensive disorders.[5]

Preeclampsia (PE) is characterised by elevated blood pressure values initially diagnosed after the 20th week with new-onset proteinuria, and when proteinuria is absent, by other diagnostic characteristics of typical preeclampsia-induced end-organ dysfunction, which include impaired liver function, thrombocytopenia, severe persistent epigastric pain, renal insufficiency, pulmonary oedema and new-onset of visual disturbances, headache or fetal growth restriction.[5]

The appearance of new novel biomarkers of renal injury has opened a new era for early recognition and prediction of AKI, including urine and plasma NGAL, cystatin C, kidney injury molecule 1, brain natriuretic peptide (BNP), IL6 and IL18, liver fatty acid-binding protein, and homovanillic acid sulfate (HVA SO4). NGAL is a small 25-kDa glycoprotein excreted by activated neutrophils. It was recognized as a matrix protein of specialized granules of human neutrophils.[12]

The potential mechanisms underlying the association between increased circulating NGAL and PE remain to be determined. Since the placenta plays a central role in the pathogenesis of PE, it could be hypothesized that NGAL may interact with the placenta, therefore, participate in the pathogenesis of PE. An early study showed that increased apoptosis of trophoblasts at the maternal-fetal interface might result from an activated NGAL in the nitrofen model of congenital diaphragmatic hernia. Interestingly, increased apoptosis of trophoblasts has been recognized as a key process involved in the pathogenesis and progression of PE. In addition, *via* increasing the activity of matrix metalloproteinase-9, NGAL has been shown to enhance the invasion of extravillous trophoblasts in the placenta, thereby increasing the vulnerability to PE. Studies are warranted in the future to determine the potential molecular pathways underlying the association between NGAL and PE.[11]

PE pathogenesis is considered to be: incomplete infiltration of trophoblasts of the uterine spiral artery that leads to placental ischemia, which finally releases inflammatory factors, immune cell activation and endothelial dysfunction. Besides, it is also related to oxidative stress (OS); because pregnancy will increase OS, it results in large circulating reactive oxygen species (ROS) and reactive nitrogen species (RNS) increase. Therefore, enhancing antioxidant capacity is the way to overcome OS during pregnancy. Vitamin E is a hydrophobic antioxidant, while vitamin A is an essential fat-soluble micronutrient, which has the highest antioxidant potential among all vitamins. What's more, both vitamins A and E are essential micronutrients, which play a vital role in maternal health and fetal development. Some studies have shown that the levels of vitamin A, C and E are all low in PE, and found that vitamin E level is negatively correlated with blood

pressure. In addition, some studies have shown that supplementation of omega-3 fatty acids and vitamin E in PE pregnant women can relieve illness. PE is a common cause of acute kidney injury (AKI) in low- and middle-income countries.[13]

PR-AKI is a serious obstetric complication, which may have devastating effects on mothers, fetuses and newborns. Recently, the morbidity of PR-AKI has increased and it is related to gestational hypertension. The AKI severity depends on the increase of serum creatinine (Scr) level or the decrease of urine output. For a long time, uric acid may induce slight kidney damage, which is the inducing factor of AKI; and urine biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) can also be used for early AKI diagnosis. Other studies have shown that serum vitamin B12 level is negatively correlated with urine markers, and electrolytes in the urine, and kidney injury molecules in children lacking B12 also increase.[13]

CONCLUSION

The utility of NGAL for diagnosing and assessing the severity of preeclampsia. The increase in NGAL due to preeclampsia is attributed to the presence of endothelium dysfunction and systemic inflammation.

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