European Journal of Pediatrics (2018) 177:1425–1434
https://doi.org/10.1007/s00431-018-3221-z

REVIEW

Neutrophil gelatinase-associated lipocalin as predictor of acute kidney injury in neonates with perinatal asphyxia: a systematic review and meta-analysis

Ioannis Bellos[1] · Georgia Fitrou[1] · Georgios Daskalakis[2] · Despina N. Perrea[1] · Vasilios Pergialiotis[1]

Received: 21 June 2018 / Revised: 19 July 2018 / Accepted: 22 July 2018 / Published online: 26 July 2018

Abstract

There is growing evidence that neutrophil gelatinase-associated lipocalin (NGAL) is a promising biomarker of acute kidney injury. The objective of this meta-analysis is to determine the accuracy of serum and urinary NGAL in the detection of acute kidney injury in neonates with perinatal asphyxia. Medline (1966–2018), Scopus (2004–2018), EMBASE (1980–2018), Clinicaltrials.gov (2008–2018), and Google Scholar (2004–2018) databases, along with the reference lists of the electronically retrieved articles, were systematically searched. Eleven studies were included, with a total number of 652 neonates. The summary sensitivity of serum NGAL was 0.818 (95% CI [0.668, 0.909]), the specificity 0.870 (95% CI [0.754, 0.936]), and the area under the curve 0.912. Regarding urinary NGAL, pooled sensitivity was calculated at 0.897 (95% CI [0.829, 0.940]), specificity at 0.729 (95% CI [0.561, 0.850]), and area under the curve at 0.899.

Conclusion: Serum and urinary NGAL represent candidate biomarkers with high performance in the prediction of acute kidney injury in newborns with perinatal asphyxia. Before NGAL can be widely used in clinical practice, future large prospective studies are needed to define the optimal cutoffs and accurately determine which levels are suggestive of post-asphyxial acute kidney injury.

What is Known:
- *Acute kidney injury is a major cause of morbidity and mortality in perinatal asphyxia.*
- *Current markers are insufficient in predicting post-asphyxial acute kidney injury.*

What is New:
- *Area under the curve for serum and urinary neutrophil gelatinase-associated lipocalin is 0.818 and 0.899, respectively.*
- *Neutrophil gelatinase-associated lipocalin is a useful marker for detecting asphyxiated neonates at risk of developing acute kidney injury.*

Keywords Acute kidney injury · Perinatal asphyxia · Neutrophil gelatinase-associated lipocalin · NGAL · Meta-analysis

Communicated by Patrick Van Reempts

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00431-018-3221-z) contains supplementary material, which is available to authorized users.

✉ Ioannis Bellos
bellosg@windowslive.com

Georgia Fitrou
georginf196@gmail.com

Georgios Daskalakis
gdaskalakis@yahoo.com

Despina N. Perrea
dperrea@lessr.eu

Vasilios Pergialiotis
pergialiotis@yahoo.com

[1] Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, Athens University Medical School, National and Kapodistrian University of Athens, 15B, Ag. Thoma str., 115 27 Athens, Greece

[2] First Department of Obstetrics and Gynecology, Alexandra Hospital, National and Kapodistrian University of Athens, Athens, Greece

Abbreviations

95% CI	95% confidence intervals
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
AUC	Area under the curve
DOR	Diagnostic odds ratio
ESS	Effective sample size
GFR	Glomerular filtration rate
KDIGO	Kidney Disease: Improving Global Outcomes
LR	Likelihood ratio
NGAL	Neutrophil gelatinase-associated lipocalin
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBINS	Risk Of Bias In Non-randomized Studies
SROC	Summary receiver operating characteristic

Introduction

Perinatal asphyxia is a major cause of neonatal morbidity and mortality, affecting 5–10 per 1000 live births [27]. Acute kidney injury (AKI) represents a serious complication as it is associated with prolonged hospital stay and mechanical ventilation [25], as well as with adverse neurological outcomes [39]. Its incidence is estimated at 40% of asphyxiated newborns, although presenting wide variance depending on the definitions [40]. The pathophysiology of AKI after a hypoxic insult is multifactorial and it is based on renal hypoperfusion due to diving reflex and increased oxidative damage [45]. Recent research has focused on the potential role of various preventive measures, suggesting the administration of theophylline in neonates at high risk for post-asphyxial AKI [34]. However, the interpretation of creatinine measurements in the early postnatal life is unreliable, since it reflects maternal concentrations and can overestimate the glomerular filtration rate (GFR) due to its unfavorable kinetics [12]. As a result, there is growing interest in the identification of novel biomarkers that would allow early risk stratification and accurate prediction of AKI in neonates with perinatal asphyxia [3].

Neutrophil gelatinase-associated lipocalin (NGAL) is a 178 amino acid protein expressed mainly by neutrophils and by various epithelial tissues at lower levels. It presents bacteriostatic properties, contributing to the innate immunity processes [7]. AKI is followed by a rapid rise of serum and urinary NGAL, as it is able to promote renal tubular recovery due to its anti-apoptotic effects [30]. As indicated by recent meta-analyses, NGAL represents a promising biomarker of AKI with high performance in the settings of sepsis [54] and exposure to contrast medium [52]. Furthermore, there is evidence that it can serve as a useful marker in pediatric populations [18] with high predictive efficiency, especially in AKI after cardiopulmonary bypass [11]. NGAL is also increased in a variety of pediatric urologic conditions and can contribute to the evaluation of renal damage in children with infection [51] or obstruction of the urinary tract [20].

The role of NGAL in the prediction of AKI in asphyxiated neonates has been recently explored in several observational studies; however, no consensus exists regarding its exact efficacy in this population. The present meta-analysis aims to accumulate current literature knowledge in the field in order to determine the pattern of NGAL elevation and assess its performance in the prediction of AKI in newborns with perinatal asphyxia.

Materials and methods

Study design

The present systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. Eligibility criteria were predetermined by the authors. Date or language restrictions were not applied during the literature search to avoid language bias. The studies were selected in three consecutive stages. Firstly, the titles and abstracts of all electronic articles were screened to evaluate their eligibility. Subsequently, the articles that met or were presumed to meet the criteria were retrieved as full texts. In the final stage, all observational studies (both prospective and retrospective) that reported serum or urinary levels of NGAL among asphyxiated newborns that developed AKI were selected. Case reports, review articles, and animal studies were excluded. Any discrepancies regarding the methodology, retrieval of articles, and statistical meta-analysis were resolved through the consensus of all authors.

Literature search and data collection

Literature search was primarily conducted using the Medline (1966–2018), Scopus (2004–2018), EMBASE (1980–2018), and Clinicaltrials.gov (2008–2018) databases, along with the reference lists of the electronically retrieved full-text papers. Google Scholar (2004–2018) database was also searched in order to identify possible additional sources. The date of the last search was set at 12 April 2018. The search strategy included the following terms: "NGAL, neutrophil gelatinase, lipocalin, perinatal, neonatal, birth, asphyxia, encephalopathy, acute kidney injury, renal failure" and is schematically presented in the PRISMA flowchart (Fig. 1).

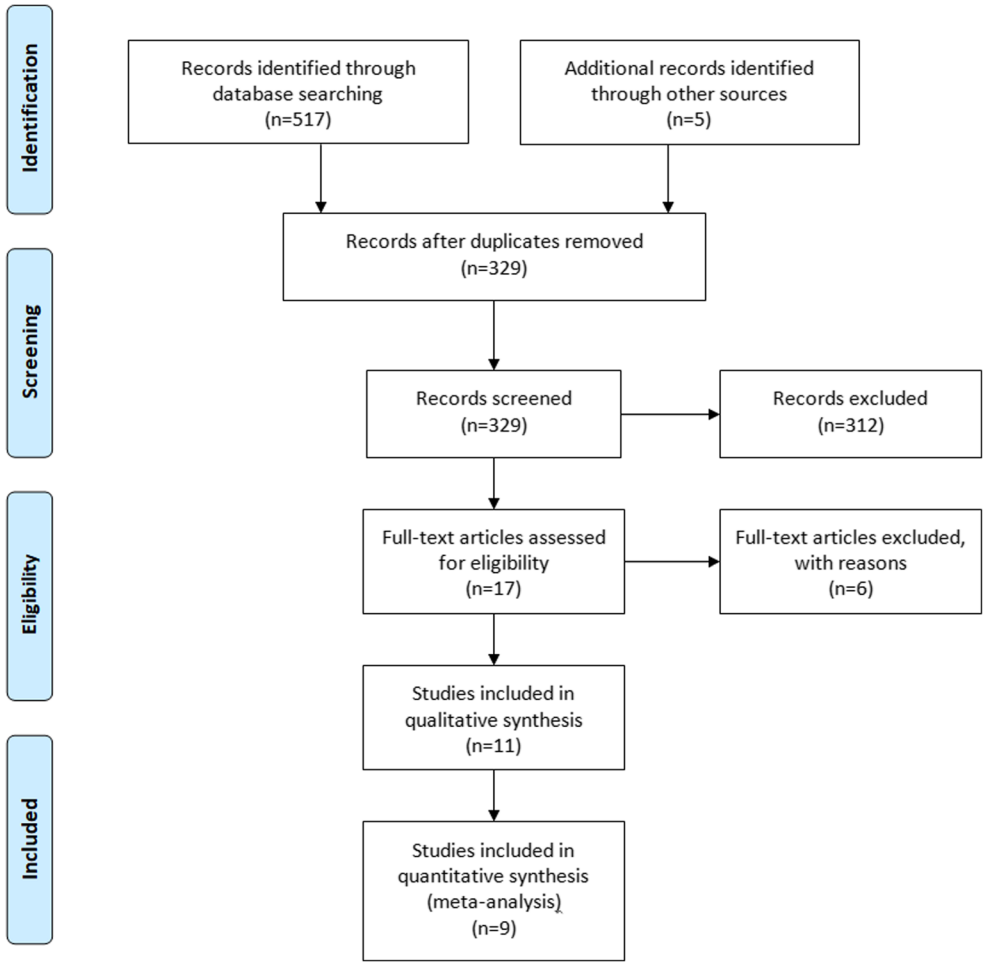

Fig. 1 Search plot diagram

Quality assessment

The quality of all included studies was evaluated with the Risk Of Bias In Non-randomized Studies (ROBINS-I) assessment tool, which assesses the potential bias due to confounding, selection, classification, deviation from intended intervention, missing data, measurement, and reporting of the outcomes [42]. Moreover, the methodological quality of the studies included in the diagnostic accuracy analysis was also judged with the QUADAS-2 tool, which consists of four domains: patient selection, index test, reference standard, and flow and timing [53].

Definitions

Perinatal asphyxia was defined on the basis of Apgar score, fetal distress, pH, metabolic acidosis, hypoxic event, and need for neonatal resuscitation. Acute kidney injury was diagnosed with creatinine criteria (serum creatinine ≥ 1.5 mg/dl) or according to AKIN (Acute Kidney Injury Network) [28] and KDIGO (Kidney Disease: Improving Global Outcomes) [23] guidelines. The definition of AKI in each study is provided in Suppl. Table 1.

Statistical analysis

The statistical meta-analysis of diagnostic accuracy was carried out in R (3.4.3 version), using the MADA package [10]. A bivariate model was fitted to calculate summary estimates of sensitivity and specificity, since it takes into consideration the potential correlations between these two quantities, due to threshold effect [35, 36]. Summary receiver operating characteristic (SROC) curves were constructed and the area under the curve (AUC) for serum and urinary NGAL were separately estimated. Confidence intervals (CI) were set at 95%. Subgroup analysis was performed regarding the following variables: cutoff values, AKI definition, study design, and location. Additionally, as a secondary analysis, a univariate approach was implemented to provide pooled estimates of likelihood ratios (LR) and diagnostic odds ratio (DOR) of the two tests. A Fagan's nomogram was drawn, which determines the post-test probability, according to the calculated positive and negative likelihood ratios [5]. The pre-test

probability was set at 30%. The possibility of publication bias was assessed using Deeks' funnel plot, which is constructed by plotting the inverse of square root of the effective sample size (ESS) against the ln(DOR) [8].

Sensitivity analysis

Leave-one-out analyses were performed to explore the effect of individual studies on the overall outcome. One study was sequentially omitted at a time and pooled estimates of sensitivity, specificity, and AUC were calculated. This analysis was also performed in R (MADA package) [10].

Results

Included studies

Eleven studies [1, 4, 13, 16, 31, 33, 38, 44, 46, 48, 49] were finally included in the present review, with a total number of 652 asphyxiated neonates. Among them, 257 developed AKI, while the rest 395 served as the control group. The methodological characteristics of the included studies (country, study design, patient exclusion criteria, asphyxia and AKI definition, type of sample, assay method, prematurity, and NGAL cutoff value) are presented in Suppl. Table 1. The most important patients' characteristics that were extracted included number, gender, gestational age at delivery, birth weight, nature of birth, Apgar score, and baseline serum creatinine levels (Suppl. Table 2). Nine studies [1, 4, 13, 16, 31, 33, 38, 48, 49] were eligible for the diagnostic accuracy meta-analysis, as they provided adequate data for the construction of the 2×2 table. Sensitivity and specificity of the included studies are illustrated in forest plots (Suppl. Figure 1).

Excluded studies

Six studies [6, 14, 17, 19, 41, 43] were excluded after reading the full text. Four of them [14, 17, 19, 41] did not report the outcome of interest, while the population of one study [43] did not consist exclusively of newborns with perinatal asphyxia. Moreover, one study was not included, since it contained less than five AKI cases [6].

Quality assessment

The outcomes of ROBINS-I tool show that the overall risk of bias was evaluated to be moderate (Suppl. Table 3). The results of the QUADAS-2 tool are illustrated in Fig. 2. Higher risk was identified in the section of index test, since all studies did not use pre-specified cutoff values but the optimal ones. Furthermore, risk of bias in the domain of patient selection was pointed out in two studies [31, 38] due to case-control design, while applicability concerns were acknowledged in one study as a result of differentiations in the applied definitions [49].

Qualitative synthesis

The results of all studies were assessed qualitatively (Suppl. Table 4). Serum levels of NGAL were assessed in six studies [1, 4, 13, 33, 38, 44]. All studies reported significantly higher serum NGAL concentrations in the AKI group, when measured both in the first and third days of life. However, this effect was not observed in measurements in postnatal days 7 and 10 [33, 38]. Pejovic et al. [33] discriminated AKI cases in two stages according to the AKIN criteria, finding higher NGAL in both subgroups. Interestingly, stage 2 was associated with significantly greater NGAL values compared to stage 1. Urinary NGAL was explored in seven studies [1, 16, 31, 38, 46, 48, 49]. In six of them, NGAL was significantly increased in the urine of asphyxiated newborns with AKI, while this was not observed in one case-control study including 13 neonates [38]. More specifically, elevated urinary NGAL was reported in five out of seven studies in the first day of life and in three out of four studies in days 3–4. In addition, Tanigasalam et al. [48] revealed significant differences of urinary NGAL in all stages of AKI compared to the control group, with higher values in stage 3.

Quantitative synthesis

The summary ROC (SROC) curves of serum and urinary NGAL are depicted in Fig. 3. The summary sensitivity and specificity of serum NGAL for the detection of post-asphyxial AKI were calculated at 0.818 (95% CI [0.668, 0.909]) and 0.870 (95% CI [0.754, 0.936]), respectively, while AUC was 0.912. The pooled DOR was estimated at 34.880 (95% CI [7.068, 172.122]), while the positive LR at 5.8 (95% CI [2.618, 12.849]) and the negative LR at 0.213 (95% CI [0.095–0.479]). Pooled estimates of sensitivity, specificity, and AUC for urinary NGAL were 0.897 (95% CI [0.829, 0.940]), 0.729 (95% CI [0.561, 0.850]), and 0.899, respectively. The summary DOR was calculated at 33.183 (95% CI [13.508, 81.518]), with the positive LR to be 3.339 (95% CI [2.060–5.414]) and the negative LR 0.141 (95% CI [0.084, 0.236]). The outcomes of the subgroup analysis are shown in Table 1. Of note, serum NGAL presented higher AUC values in cohort studies, using the AKIN definition, with cutoff > 100 ng/ml, while urinary NGAL appeared to be more specific in studies with lower thresholds. Fagan's nomogram for serum NGAL indicated that the post-test probability was increased to 71.3% and decreased to 8.4%, when the pre-test probability was 30%. Respectively, the post-test probabilities for urinary NGAL were 58.9 and 5.7% (Fig. 4). Deeks' funnel plot revealed no evidence of publication bias (p value > 0.05) (Suppl. Figure 2).

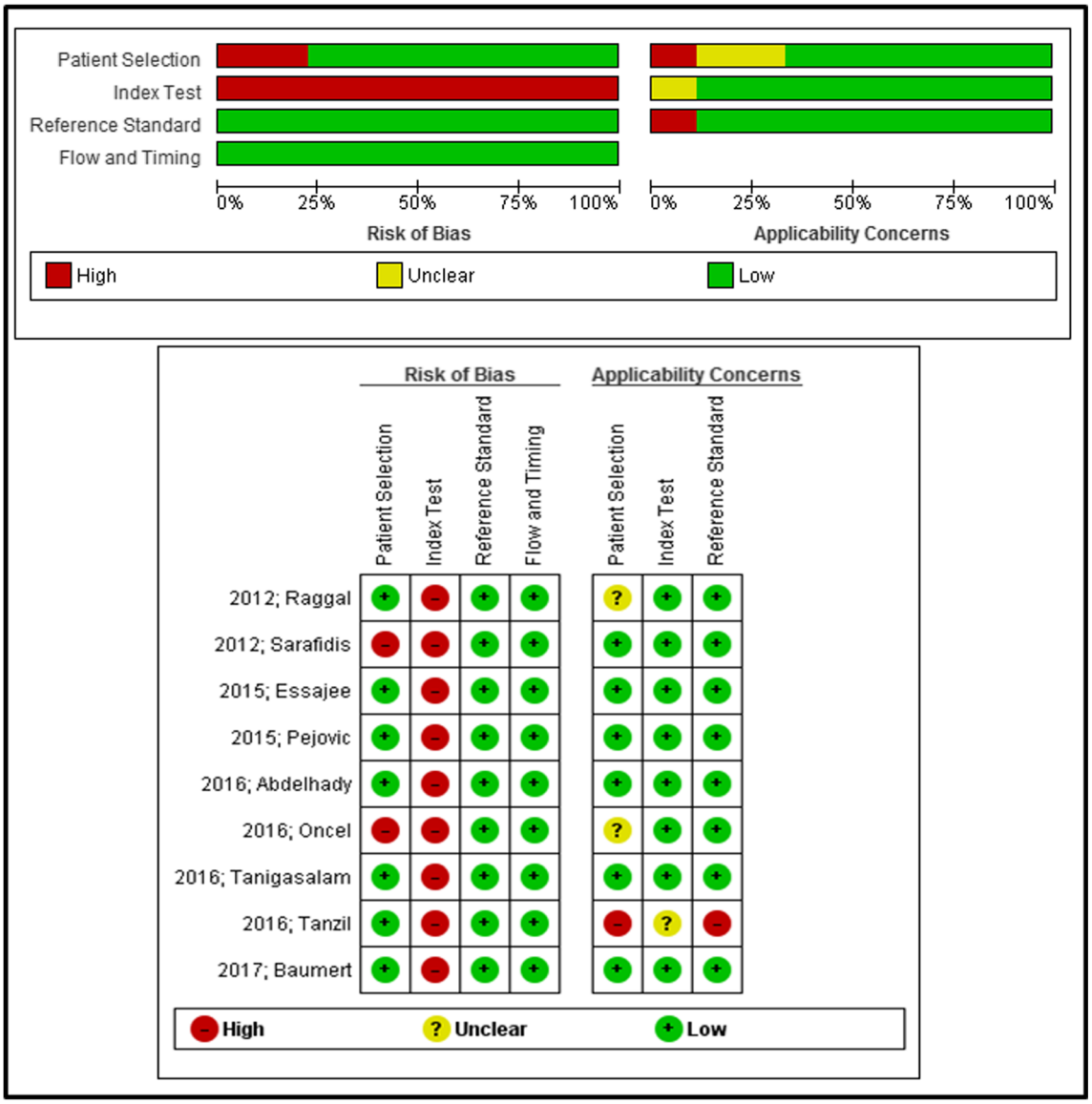

Fig. 2 QUADAS-2 evaluation

Sensitivity analysis

The outcomes of the leave-one-out analysis revealed that no single study was found to significantly affect the overall outcome (Suppl. Table 4). By omitting one study at a time, sensitivity of serum NGAL ranged from 0.766 to 0.874, specificity from 0.845 to 0.906, and AUC from 0.873 to 0.949. Concerning urinary NGAL, sensitivity ranged from 0.887 to 0.927, specificity from 0.674 to 0.781, and AUC from 0.881 to 0.934.

Discussion

Acute kidney injury constitutes a leading cause of neonatal morbidity, especially in the setting of perinatal asphyxia. Early risk stratification is essential to guide clinical management, provide measures of prevention, and improve mortality rates. More specifically, recent research has focused on the potential role of theophylline in preventing post-asphyxial acute kidney injury, since it is able to increase renal blood flow by inhibiting the pre-glomerular vasoconstriction mediated by adenosine [32]. In this context, several clinical trials [15, 21, 29, 34] have investigated the effectiveness of this approach, concluding that the administration of theophylline early after birth is associated with significantly higher urine output and improved glomerular filtration rate. Moreover, there is evidence that therapeutic hypothermia in newborns with perinatal asphyxia is associated with reduced incidence and severity of acute kidney injury, as well as with lower mortality rates [47]. As a result, effective early risk assessment is crucial to identify the group of asphyxiated neonates that

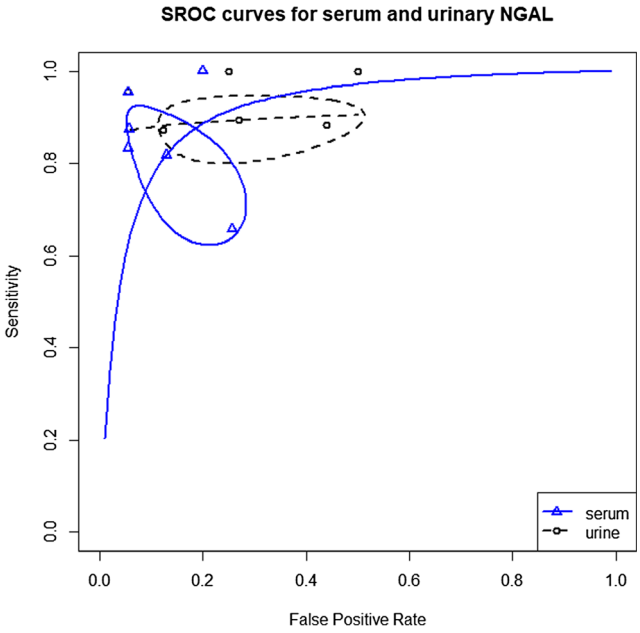

Fig. 3 Summary ROC curve (bivariate model) for the performance of serum and urinary NGAL in the prediction of acute kidney injury in asphyxiated neonates

would benefit the most from the application of the above preventive strategies [40].

Nevertheless, current criteria for AKI detection have important shortcomings, since creatinine represents a late biomarker due to its constant rate of generation by muscle tissue and varies widely, as it is influenced by maternal renal function and GFR alterations in the early postnatal life [2]. Consequently, it is necessary to find out an optimum marker that combined with clinical factors would maximize the ability to promptly predict AKI in asphyxiated neonates [50].

The findings of the present meta-analysis suggest that NGAL is elevated in newborns with perinatal asphyxia complicated with AKI and may serve as a promising biomarker, given its high diagnostic performance. Urinary levels presented greater sensitivity (89.7%), while serum levels turned out to be more specific (specificity: 87%). As indicated by the subgroup analysis, the predictive accuracy of serum NGAL was superior when thresholds ranged from 140 to 157 ng/ml. On the contrary, the used cutoff values of urinary levels presented wide variation (18–652 ng/ml), rendering thus the interpretation of the test problematic. It is important to mention

Table 1 Outcomes of the subgroup analysis

Subgroup	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	AUC
Serum NGAL				
Cutoff value				
< 100 ng/ml	2	0.669 (0.557–0.764)	0.738 (0.586–0.849)	0.766
≥ 100 ng/ml	3	0.889 (0.738–0.958)	0.944 (0.859–0.979)	0.969
AKI definition				
AKIN	2	0.925 (0.745–0.981)	0.943 (0.839–0.982)	0.973
Other	3	0.743 (0.558–0.869)	0.809 (0.639–0.91)	0.845
Study design				
Cohort	3	0.889 (0.738–0.958)	0.944 (0.859–0.979)	0.969
Other	2	0.669 (0.557–0.764)	0.738 (0.586–0.849)	0.766
Location				
Egypt	2	0.894 (0.715–0.966)	0.944 (0.803–0.986)	0.948
Europe	3	0.763 (0.555–0.892)	0.835 (0.647–0.933)	0.867
Urinary NGAL				
Cutoff value				
< 100 ng/ml	3	0.917 (0.796–0.969)	0.783 (0.475–0.935)	0.931
≥ 100 ng/ml	2	0.916 (0.667–0.983)	0.649 (0.448–0.808)	0.849
AKI definition				
AKIN	3	0.917 (0.796–0.969)	0.783 (0.475–0.935)	0.931
Other	2	0.916 (0.667–0.983)	0.649 (0.448–0.808)	0.849
Study design				
Cohort	2	0.925 (0.730–0.982)	0.796 (0.239–0.980)	0.936
Other	3	0.935 (0.804–0.980)	0.731 (0.478–0.889)	0.927
Location				
Asia	3	0.935 (0.804–0.980)	0.731 (0.478–0.889)	0.927
Africa	2	0.925 (0.730–0.982)	0.796 (0.239–0.980)	0.936

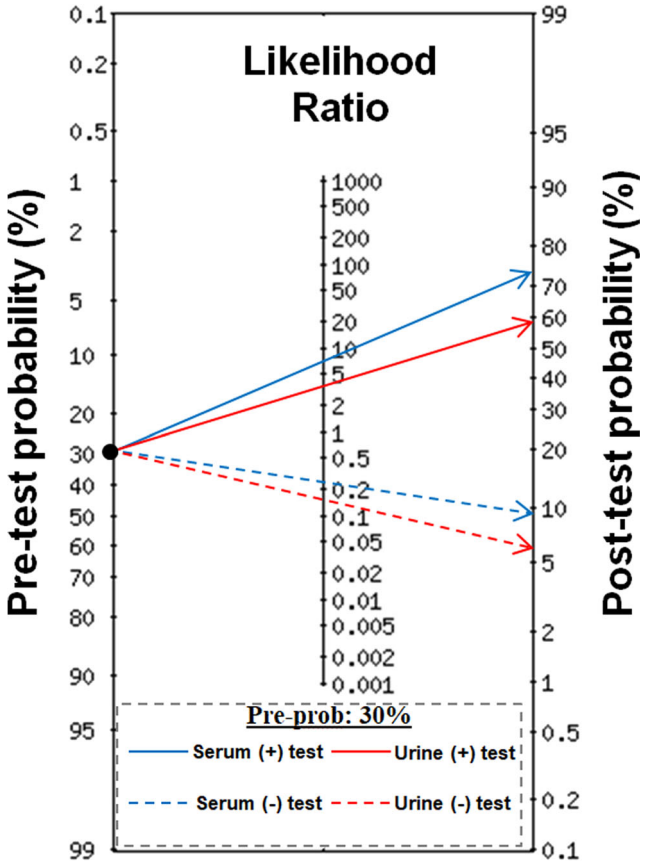

Fig. 4 Fagan's nomogram for the calculation of the post-test probability of acute kidney injury

that NGAL levels showed a significant rise early in the postnatal period, while this effect was attenuated after the first week of life, highlighting the potential role of this marker in the follow-up of AKI cases. Furthermore, severe forms of AKI were associated with increased levels of both serum and urinary NGAL [33, 48], while a positive correlation with Sarnat stages of hypoxic-ischemic encephalopathy was noted [1]. As reported in two studies, the utility of NGAL in the prediction of perinatal asphyxia severity is also supported by its linear correlation with Apgar score ($r = -0.41$, p value < 0.05) [4], umbilical lactate concentration ($r = 0.57$, p value < 0.05), and pH ($r = -0.55$, p value < 0.05) [44].

Strengths and limitations of the study

The present study constitutes a systematic review combining, for the first time, current literature in the field of NGAL utility on the prediction of AKI among asphyxiated neonates. A recent meta-analysis [22] has also shown the potential efficacy of NGAL in AKI among critically ill neonates; however, the present meta-analysis includes a significantly greater number of studies (11 vs. 5) and focused only in cases with perinatal asphyxia in order to determine the accuracy of NGAL in this specific population. Statistical meta-analysis was performed using a bivariate model, which is a random effects model that overcomes the limitations of the conventional Moses-Littenberg method [9]. The methodological quality of the studies was evaluated by two independent tools (ROBINS-I and QUADAS-2), in order to reveal possible sources of systematic bias. Potential confounders were identified and subgroup analysis was conducted. Also, sensitivity analysis was performed to assess if a single study exerted significant effect on the overall outcome and the results remained stable. It is necessary to note that omitting the study [49] with the higher risk of bias did not significantly alter the net diagnostic accuracy (AUC 0.885 vs. 0.899). A Fagan's nomogram was finally drawn, since it is a clinically useful tool that allows the rapid determination of post-test probability, using one of the two NGAL tests.

However, this meta-analysis is based on the results of nine studies, including a moderate number of patients. Since the majority of them reported their outcomes in terms of median and range, a quantitative synthesis regarding the differences of the absolute NGAL values between the two studied groups was impossible to be performed. Moreover, the variability of the applied cutoffs was conspicuous, while the tendency of studies to use the optimal ones may have overestimated the calculated diagnostic accuracy of the test. Possible sources of heterogeneity that could contribute to the wide variability of NGAL measurements include differentiations in patient eligibility criteria and definition of perinatal asphyxia, as well as in the laboratory assay used for the detection of the marker. In addition, the population of seven out of nine studies consisted exclusively of term neonates; therefore, evidence regarding NGAL utility in premature newborns remains insufficient. Most measurements were performed in the first 3 days of life and thus the role of this marker in AKI follow-up is uncertain. It is also important to state that the use of creatinine as the gold standard test constitutes an inherent limitation of all studies investigating the accuracy of novel biomarkers, due to its unreliable nature in the perinatal period, as earlier discussed.

Implications for current clinical practice and future research

The present meta-analysis suggests that NGAL represents a promising marker in neonates and may serve as a candidate test to detect perinatal asphyxia complicated by AKI. Effective stratification of AKI risk would allow intervening early in the disease process by offering prophylactic measures and guide clinical management regarding fluid balance and the avoidance of nephrotoxic medications. However, several aspects need to be elucidated before NGAL use can be applied in the clinical setting. Future large-scale multi-center prospective studies should be conducted in order to accurately calculate the diagnostic efficacy of NGAL and to determine the range of its concentration in asphyxiated neonates with and without AKI, as well as in healthy

controls. The AKIN [28] and KDIGO [23] criteria should be used as the reference test, while definitions based on single creatinine measurements should be avoided. Furthermore, studies should pre-determine their cutoffs based on the values proposed in the present review, in order to achieve a more realistic estimation of NGAL accuracy. The effect of possible confounders, especially severity of perinatal asphyxia, stage of AKI, and prematurity should be taken into consideration and analyzed separately. Other perinatal factors able to modify NGAL levels, such as congenital infections and neonatal sepsis [24, 37], should not be ignored. Also, sequential measurements of NGAL would allow defining the optimal timing of sampling and assessing its utility as a marker of recovery from renal injury. Head-to-head comparison of serum and urinary levels should be performed to find out which of the two is the most useful test. In this context, NGAL should be evaluated in conjunction with other novel biomarkers and clinical factors in order to construct a combined predictive model that would maximize the accuracy of AKI detection among newborns with perinatal asphyxia. Finally, randomized clinical trials are needed to assess if NGAL constitutes a useful tool in guiding decisions regarding clinical management and preventive strategies, especially the administration of theophylline early after birth.

Conclusions

The outcomes of the present meta-analysis suggest that serum and urinary NGAL present high performance in the detection of post-asphyxial AKI. However, since the available evidence comes from a limited number of studies, future large cohorts are needed to confirm its diagnostic efficacy, as well as to determine the optimal timing of measurement and the cutoff values to be applied in the clinical practice.

Authors' contributions Ioannis Bellos conceived the idea and designed the analysis.

Georgia Fitrou performed the literature search and tabulated the data.

Georgios Daskalakis performed the statistical analysis and wrote the manuscript.

Despina N. Perrea performed the quality assessment and the sensitivity analysis.

Vasilios Pergialiotis contributed to the quality assessment and revised the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent The present systematic review and meta-analysis is based on aggregated data that were retrieved from studies already retrieved. We did not collect individual patient data and did not have direct contact with patients included.

References

1. Abdelhady S, Gawad ERA, Haie OMA, Mansour AI (2016) Usefulness of serum and urinary neutrophil gelatinase-associated lipocalin in detecting acute kidney injury in asphyxiated neonates. Int J Med Health Sci 5(4):230–236
2. Askenazi D (2012) Are we ready for the clinical use of novel acute kidney injury biomarkers? Pediatr Nephrol 27(9):1423–1425. https://doi.org/10.1007/s00467-012-2185-x
3. Askenazi DJ, Ambalavanan N, Goldstein SL (2009) Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? Pediatr Nephrol 24(2):265–274. https://doi.org/10.1007/s00467-008-1060-2
4. Baumert M, Surmiak P, Więcek A, Walencka Z (2017) Serum NGAL and copeptin levels as predictors of acute kidney injury in asphyxiated neonates. Clin Exp Nephrol 21(4):658–664. https://doi.org/10.1007/s10157-016-1320-6
5. Caraguel CGB, Vanderstichel R (2013) The two-step Fagan's nomogram: ad hoc interpretation of a diagnostic test result without calculation. Evidence Based Medicine 18(4):25–128. https://doi.org/10.1136/eb-2013-101243
6. Chandrashekar C, Venkatkrishnan A (2016) Clinical utility of serum neutrophil gelatinase associated lipocalin (NGAL) as an early marker of acute kidney injury in asphyxiated neonates. Journal of Nepal Paediatric Society 36(2):121. https://doi.org/10.3126/jnps.v36i2.14985
7. Clerico A, Galli C, Fortunato A, Ronco C (2012) Neutrophil gelatinase-associated lipocalin (NGAL) as biomarker of acute kidney injury: a review of the laboratory characteristics and clinical evidences. Clin Chem Lab Med 50(9):1505–1517. https://doi.org/10.1515/cclm-2011-0814
8. Deeks JJ, Macaskill P, Irwig L (2005) The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 58(9):882–893. https://doi.org/10.1016/j.jclinepi.2005.01.016
9. Dinnes J, Mallett S, Hopewell S, Roderick PJ, Deeks JJ (2016) The Moses-Littenberg meta-analytical method generates systematic differences in test accuracy compared to hierarchical meta-analytical models. J Clin Epidemiol 80:77–87. https://doi.org/10.1016/j.jclinepi.2016.07.011
10. Doebler P, Münster W, Holling H (2015) Meta-analysis of diagnostic accuracy with mada. https://cran.r-project.org/web/packages/mada/vignettes/mada.pdf
11. Dong L, Ma Q, Bennett M, Devarajan P (2017) Urinary biomarkers of cell cycle arrest are delayed predictors of acute kidney injury after pediatric cardiopulmonary bypass. Pediatr Nephrol 32(12):2351–2360. https://doi.org/10.1007/s00467-017-3748-7
12. Durkan AM, Alexander RT (2011) Acute kidney injury post neonatal asphyxia. J Pediatr 158(2):e29–e33. https://doi.org/10.1016/j.jpeds.2010.11.010
13. El Raggal N, Khafagy SM, Mahmoud NH, El Beltagy S (2013) Serum neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury in asphyxiated neonates. Indian Pediatr 50(5):459–462
14. El-Salam MA, Zaher MM, Mohamed RAE-S et al (2014) Comparison of some urinary biomarkers of acute kidney injury in term new born with and without asphyxia. Clinical Medicine and Diagnostics 4(2):23–28. https://doi.org/10.5923/j.cmd.20140402.02
15. Eslami Z, Shajari A, Kheirandish M, Heidary A (2009) Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia. Iran J Kidney Dis 3(4):222–226
16. Essajee F, Were F, Admani B (2015) Urine neutrophil gelatinase-associated lipocalin in asphyxiated neonates: a prospective cohort

study. Pediatr Nephrol 30(7):1189–1196. https://doi.org/10.1007/s00467-014-3035-9
17. Fiala M, Baumert M, Surmiak P, Walencka Z, Sodowska P (2016) Umbilical markers of perinatal hypoxia. Ginekol Pol 87(3):200–204
18. Filho LT, Grande AJ, Colonetti T, Della ÉSP, da Rosa MI (2017) Accuracy of neutrophil gelatinase-associated lipocalin for acute kidney injury diagnosis in children: systematic review and meta-analysis. Pediatr Nephrol 32(10):1979–1988. https://doi.org/10.1007/s00467-017-3704-6
19. Firmani ND, Yuniati T, Rachmadi D (2015) The differences of urinary neutrophil gelatinase-associated lipocalin (NGAL) levels between asphyxiated and non-asphyxiated neonates. Open J Pediatr 5(3):185–189. https://doi.org/10.4236/ojped.2015.53028
20. Forster CS, Devarajan P (2017) Neutrophil gelatinase-associated lipocalin: utility in urologic conditions. Pediatr Nephrol 32(3):377–381. https://doi.org/10.1007/s00467-016-3540-0
21. Jenik AG, Cernadas JMC, Gorenstein A et al (2000) A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. Pediatics 105(4):E45
22. Jiang L, Cui H (2015) Could blood neutrophil gelatinase-associated lipocalin (NGAL) be a diagnostic marker for acute kidney injury in neonates? A systemic review and meta-analysis. Clin Lab 61(12):1815–1820
23. Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury. Nephron Clinical practice 120(4):c179–c184. https://doi.org/10.1159/000339789
24. Kisiel A, Roszkowska-Blaim M, Pańczyk-Tomaszewska M, Stelmaszczyk-Emmel A, Górska E, Borszewska-Kornacka M (2017) Effect of perinatal risk factors on neutrophil gelatinase-associated lipocalin (NGAL) level in umbilical and peripheral blood in neonates. Central European Journal of Immunology 3(3):274–280. https://doi.org/10.5114/ceji.2017.70970
25. Kriplani DS, Sethna CB, Leisman DE, Schneider JB (2016) Acute kidney injury in neonates in the PICU. Pediatr Crit Care Med 17(4):e159–e164. https://doi.org/10.1097/PCC.0000000000000668
26. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62(10):e1–e34. https://doi.org/10.1016/j.jclinepi.2009.06.006
27. McGuire W (2007) Perinatal asphyxia. BMJ Clin Evid 2007:0320
28. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury Network (2007) Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 11(2):R31. https://doi.org/10.1186/cc5713
29. Merrikhi AR, Ghaemi S, Gheissari A, Shokrani M, Madihi Y, Mousavinasab F (2012) Effects of aminophyllinein preventing renal failure in premature neonates with asphyxia in Isfahan-Iran. JPMA J Pak Med Assoc 62:S48–S51
30. Mishra J, Mori K, Ma Q, Kelly C, Yang J, Mitsnefes M, Barasch J, Devarajan P (2004) Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol 15(12):3073–3082. https://doi.org/10.1097/01.ASN.0000145013.44578.45
31. Oncel MY, Canpolat FE, Arayici S, Alyamac Dizdar E, Uras N, Oguz SS (2016) Urinary markers of acute kidney injury in newborns with perinatal asphyxia. Ren Fail 38(6):882–888. https://doi.org/10.3109/0886022X.2016.1165070
32. Osswald H, Gleiter C, Mühlbauer B (1995) Therapeutic use of theophylline to antagonize renal effects of adenosine. Clin Nephrol 43:S33–S37
33. Pejović B, Erić-Marinković J, Pejović M, Kotur-Stevuljević J, Peco-Antić A (2015) Detection of acute kidney injury in premature asphyxiated neonates by serum neutrophil gelatinase-associated lipocalin (sNGAL)—sensitivity and specificity of a potential new biomarker. Biochem Medica 25(3):450–459. https://doi.org/10.11613/BM.2015.046
34. Raina A, Pandita A, Harish R, Yachha M, Jamwal A (2016) Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates. Acta Paediatr 105(10):e448–e451. https://doi.org/10.1111/apa.13469
35. Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PM, Zwinderman AH (2005) Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 58(10):982–990. https://doi.org/10.1016/j.jclinepi.2005.02.022
36. Rutter CM, Gatsonis CA (2001) A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med 20(19):2865–2884
37. Saleh NY, Abo El Fotoh WMM, El-Hawy MA (2017) Serum neutrophil gelatinase–associated lipocalin. Pediatr Crit Care Med 18(6):e245–e252. https://doi.org/10.1097/PCC.0000000000001186
38. Sarafidis K, Tsepkentzi E, Agakidou E, Diamanti E, Taparkou A, Soubasi V, Papachristou F, Drossou V (2012) Serum and urine acute kidney injury biomarkers in asphyxiated neonates. Pediatr Nephrol 27(9):1575–1582. https://doi.org/10.1007/s00467-012-2162-4
39. Sarkar S, Askenazi DJ, Jordan BK, Bhagat I, Bapuraj JR, Dechert RE, Selewski DT (2014) Relationship between acute kidney injury and brain MRI findings in asphyxiated newborns after therapeutic hypothermia. Pediatr Res 75(3):431–435. https://doi.org/10.1038/pr.2013.230
40. Selewski DT, Charlton JR, Jetton JG, Guillet R, Mhanna MJ, Askenazi DJ, Kent AL (2015) Neonatal acute kidney injury. Pediatrics 136(2):e463–e473. https://doi.org/10.1542/peds.2014-3819
41. Song Y, Sun S, Yu Y et al (2017) Diagnostic value of neutrophil gelatinase-associated lipocalin for renal injury in asphyxiated preterm infants. Exp Ther Med 13(4):1245–1248. https://doi.org/10.3892/etm.2017.4107
42. Sterne JA, Hernán MA, Reeves BC et al (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355:i4919. https://doi.org/10.1136/BMJ.I4919
43. Suchojad A, Tarko A, Smertka M, Majcherczyk M, Brzozowska A, Wroblewska J, Maruniak-Chudek I (2015) Factors limiting usefulness of serum and urinary NGAL as a marker of acute kidney injury in preterm newborns. Ren Fail 37(3):439–445. https://doi.org/10.3109/0886022X.2014.996109
44. Surmiak P, Baumert M, Fiala M, Sypniewska K, Walencka Z, Łukomska A, Karcz K (2014) Umbilical cord blood NGAL concentration as an early marker of perinatal asphyxia in neonates. Ginekol Pol 85(6):424–427
45. Sweetman DU (2017) Neonatal acute kidney injury—severity and recovery prediction and the role of serum and urinary biomarkers. Early Hum Dev 105:57–61. https://doi.org/10.1016/j.earlhumdev.2016.12.006
46. Sweetman DU, Onwuneme C, Watson WR, O'Neill A, Murphy JFA, Molloy EJ (2016) Renal function and novel urinary biomarkers in infants with neonatal encephalopathy. Acta Paediatr 105(11):e513–e519. https://doi.org/10.1111/apa.13555
47. Tanigasalam V, Bhat V, Adhisivam B, Sridhar MG (2015) Does therapeutic hypothermia reduce acute kidney injury among term neonates with perinatal asphyxia?—a randomized controlled trial. J Matern Fetal Neonatal Med 29(15):2545–2548. https://doi.org/10.3109/14767058.2015.1094785
48. Tanigasalam V, Bhat BV, Adhisivam B, Sridhar MG, Harichandrakumar KT (2016) Predicting severity of acute kidney injury in term neonates with perinatal asphyxia using urinary

neutrophil gelatinase associated lipocalin. The Indian Journal of Pediatrics 83(12–13):1374–1378. https://doi.org/10.1007/s12098-016-2178-z

49. Tanzil WL, Wilar R, Mantik MFJ et al (2017) Comparison of urine neutrophil gelatinase-associated lipocalin to serum creatinine to assess kidney function in neonatal asphyxia. Paediatr Indones 56(6): 356. https://doi.org/10.14238/pi56.6.2016.356-9
50. Treiber M, Gorenjak M, Pecovnik Balon B (2014) Serum cystatin-C as a marker of acute kidney injury in the newborn after perinatal hypoxia/asphyxia. Ther Apher Dial 18(1):57–67. https://doi.org/10.1111/1744-9987.12054
51. Valdimarsson S, Jodal U, Barregård L, Hansson S (2017) Urine neutrophil gelatinase-associated lipocalin and other biomarkers in infants with urinary tract infection and in febrile controls. Pediatr Nephrol 32(11):2079–2087. https://doi.org/10.1007/s00467-017-3709-1
52. Wang K, Duan C, Wu J et al (2016) Predictive value of neutrophil gelatinase-associated lipocalin for contrast-induced acute kidney injury after cardiac catheterization: a meta-analysis. Can J Cardiol 32(8):1033.e19–1033.e29. https://doi.org/10.1016/j.cjca.2015.09.011
53. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, QUADAS-2 Group (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155(8):529–536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009
54. Zhang A, Cai Y, Wang P-F, Qu JN, Luo ZC, Chen XD, Huang B, Liu Y, Huang WQ, Wu J, Yin YH (2016) Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: a systematic review and meta-analysis. Crit Care 20:41. https://doi.org/10.1186/s13054-016-1212-x