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Value of Plasma/Serum Neutrophil Gelatinase-Associated Lipocalin in Detection of Pediatric Acute Kidney Injury; a Systematic Review and Meta-Analysis

Anahita Izadi[1], Mahmoud Yousefifard[2], Babak Nakhjavan-Shahraki[3], Masoud Baikpour[4], Jalaledin Mirzay Razaz[5], Neamatollah Ataei [6], *Mostafa Hosseini [6,7]

[1]Departments of Pediatric Infectious Diseases, Tehran University of Medical Sciences Tehran, Iran. [2]Physiology Research Center and Department of Physiology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran. [3]Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, Tehran, Iran. [4]Department of Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. [5]Department of Community Nutrition, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [6]Pediatric Chronic Kidney Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran. [7]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Background: Major attention has been drawn to the prognostic value of plasma/serum neutrophil gelatinase-associated lipocalin (NGAL) in detection of acute kidney injury (AKI) in children, but still no consensus has been reached. Accordingly, the present study aimed to assess the diagnostic value of this biomarker in detection of acute kidney injury in children through a systematic review and meta-analysis.

Materials and Methods: Two independent reviewers carried out a comprehensive search in electronic databases up to the end of August, 2016. After summarization of studies, screening performance characteristics of plasma/serum NGAL were evaluated in detection of AKI. The area under the curve of receiver operating characteristics curve, sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratio of NGAL were calculated using a mixed-effects binary regression model. A p-value less than 0.05 was considered as significance threshold in all analyses.

Results **:** Data from 22 studies (2,213 non-AKI children and 1,109 AKI patients) were pooled and analyzed. Analyses revealed that the performance of plasma/seum NGAL is maximal when the level of this biomarker is measured in the first 12 hours after admission or surgery, considering a cut-off level of 100 mg/dL. In this setting the area under the curve, sensitivity, specificity and diagnostic odds ratio of plasma/serum NGAL were 0.94 (95% CI: 0.91-0.95), 0.87 (95% CI: 0.67-0.96), 0.88 (95% CI: 0.65-0.96) and 48.05 (95% CI: 9.20-251.04), respectively.

Conclusion**:** The high diagnostic value in the first few hours is one of the advantages of plasma/serum NGAL, emphasizing its usefulness in clinical evaluations.

Key Words: Adolescents, Aggression, Children, Life Satisfaction, Self-rated Health.

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Corresponding Author:

Prof. Mostafa Hosseini, Department of Epidemiology and Biostatistics School of Public Health, Tehran University of Medical Sciences, Poursina Ave, Tehran, Iran; Fax: +98.2188989127.

Email: mhossein110@yahoo.com

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1- INTRODUCTION

Acute kidney injury (AKI) is defined as a drop in renal filtration that can happen over a period of minutes to a few days. This complication that follows an injury to the renal tissues is considered as one of the main public health issues with a rising prevalence all over the world (1). Various complications are associated with this problem including metabolic acidosis, hyperkalemia, uremia and changes in the balance of body fluids. Long term complications of renal failure also include cardiovascular diseases, stroke and heart failure. Children with renal failure most commonly expire due to cardiovascular diseases and infections (2). The burden of AKI in children and its burden are much more severe than the adult population. However, recent studies have shown that implementing preventive strategies and early diagnosis of AKI can significantly decrease the burden of this disease (3). Early detection and treatment of AKI can prevent progression of this disease and its long lasting complications such as chronic renal failure. Nevertheless, despite the vast improvements in the medical sciences, in some cases diagnosis of AKI cannot be made early in the course of the disease which leads to development of long standing injuries. Accordingly, researchers are currently searching for a new diagnostic method to prevent such cases.

In recent years, serum and urine biomarkers have been proposed as sensitive and specific methods for early diagnosis of renal diseases with a higher prognostic performance compared to other diagnostic techniques (4-6). Few of these factors include serum creatinine, cystatin C, Neutrophil gelatinase associated lipocalin (NGAL) protein and Kidney Injury Molecule 1 (KIM-1) (7-9). NGAL is a membrane protein minimally expressed in blood and kidney cells. During an AKI the plasma/serum concentration of NGAL increases and peaks within two hours. Studies have shown that the level of NGAL in the serum is correlated with the severity of AKI, which makes it a good diagnostic factor in acute injuries of the kidney (10). Much attention has been paid to this biomarker in recent years, but still no comprehensive conclusion has been drawn. One of the main methods to reach such conclusion is implementation of a systematic review and meta-analysis (11-14), an approach that has not yet been taken on the performance of plasma/serum NGAL concentration in detection of AKI in children. Only one meta-analysis has been carried out with a similar aim, the findings of which have shown an acceptable diagnostic value for serum NGAL in detection of AKI (15). The mentioned systematic review has mainly focused on data gathered from adults, and so the need for such meta-analysis on data from children has not been fully met. Multiple meta-analyses other than the mentioned study have also been published on this subject, but similarly all of them have mainly evaluated data from adult patients with a brief notion of findings among children. Moreover, only specific settings have been assess in most these surveys such as post-cardiac surgery or contrast induced nephropathy. They have also not proposed a precise cut-off point or a specific timing of measurement for this biomarker (15-17). Accordingly, we aimed to conduct a systematic review and meta-analysis to provide evidence on the diagnostic performance of plasma/serum NGAL in detection of AKI in children.

2- MATERIALS AND METHODS

2-1. Search strategy

A meta-analysis was designed based on the guidelines of Meta-analysis of Observational Studies in Epidemiology statement (18) to assess the performance of plasma/serum NGAL concentration in detection of AKI in children. As the initial

step two independent reviewers carried out a comprehensive search in the electronic databases of Medline, Embase, Scopus, Cochrane library, ISI web of science and EBSCO until the end of August 2016, with no temporal or linguistic limitations.

The search strategy was based on words related to neutrophil gelatinase-associated lipocalin and acute kidney injury, the combinations of which are presented in **Table.1**. These keywords were selected through three different steps. Initially related terms were extracted from the sources of Mesh (Medline database) and Emtree (Embase database). Then by going through the related articles, further terms missed in the initial step were added to the list. Finally, the extracted terms were discussed with a pediatric specialist and final modifications were made to the list. Eventually the appropriate combinations were used to screen for relevant articles on the subject in the mentioned electronic databases. Further articles were found by conducting a hand-search in the bibliographies of relevant articles, ProQuest database and along with the Google and Google scholar search engines. In cases where data could not be extracted from the articles, corresponding authors were contacted and asked whether they could provide the required information. The search strategy is described in details in our previous publications (11-14, 19-28).

2-2. Selection criteria

In the present study, cohort and prospective cross sectional surveys evaluating the performance of plasma/serum NGAL levels for detection of AKI in children were included. Studies were included if AKI had been established in their subjects by a standard method, the serum level of NGAL had been measured in all their cases and their results had been presented as mean and standard deviation (SD), median with interquartile range of NGAL serum concentration, true and false positive and negative cases or sensitivity and specificity. On the other hand, exclusion criteria included retrospective studies, evaluating chronic renal failure or patients with a definitive diagnosis of AKI before measuring serum NGAL concentration, only evaluating urine level of NGAL and not its serum concentration, repetitive reports and surveys with poor qualities.

2-3. Data extraction and quality control

Two reviewers independently summarized the articles and their titles and abstracts were entered into EndNote X7 (Thomson Reuters: Philadelphia, PA, USA; 2106) software for removing duplicate studies. Two reviewers screened the remaining articles and selected potentially relevant studies. Then full-text of each article was studied and if met the inclusion and exclusion criteria, it was summarized into a predesigned checklist based on the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (29). Finally the summarized articles by the two reviewers were compared and their discrepancies were solved through discussion with a third researcher (inter-rater reliability=0.93).

Gathered data included characteristics of the article (the name of the first author, publication year and the country in the study were conducted), age, gender, number of cases with and without AKI (non-AKI), AKI definition, timing of plasma/serum NGAL assessment, cut-off level, true positive (TP), true negative (TN), false positive (FP) and false negative (FN) cases, mean and standard deviation (or standard error) of plasma/serum NGAL concentration in the AKI and non-AKI groups, median and interquartile range this biomarker in the two groups and finally sensitivity and specificity of NGAL in different cut-off points for detection of AKI. Quality assessment of included

studies was done based on the suggested guideline of 14-item Quality Assessment of Diagnostic Accuracy Studies (QUADAS2) tool (30). Details on quality assessment method and possible bias evaluations are presented in previous publications (11, 13, 14, 19-24, 26-28). In summary each article was assigned a score based on the study protocol, patient selection method (consecutive, random, etc.), inclusion and exclusion criteria, blinding status, using the appropriate reference standard, presence of appropriate interval between the index test and reference standard and recruitment of all patients into the study. According to the assigned scores, articles were rated into three levels of good, fair and poor quality.

2-4. Statistical analysis

Two strategies were employed in the STATA version 11.0 (Stata Corporation, College Station, TX) software to analyze the gathered data. In the first strategy a comparison was made between the serum level of NGAL in the two groups of AKI and non-AKI children using standardized mean differences (SMD) with 95% confidence intervals (CIs) based on Hedge g. For cases where the results were presented as median and interquartile range, the method proposed by Hozo et al. was used to estimate the means and standard deviations (31). Heterogeneity between the articles was assessed using I-squared (I^2) test and an I^2 greater than 50% or a p- value less than 0.1 was considered as a positive heterogeneity. If the studies were homogenous, a fixed model effect was used; otherwise random effect model was utilized. Finally the findings of all the studies were pooled and an overall effect size was calculated. In order to identify the sources of heterogeneity, subgroup analysis was carried out based on the main factors affecting interpretation of the results. Publication bias was also evaluated using Egger's and Begg's tests (32). The second strategy aimed to assess the screening performance characteristics of plasma/serum NGAL in detection of AKI in children using mixed-effects binary regression model to calculate area under the curve of receiver operating characteristics curve, sensitivity, specificity along with positive and negative likelihood ratio and diagnostic odds ratio with 95% confidence intervals (95% CI). Similar to the previous strategy, heterogeneity between the articles was assessed based on I^2 and p- value. Publication bias was evaluated by drawing Deeks' funnel plot asymmetry test and presenting the resultant p-value.

It should be mentioned that in both strategies, meta-regression was used for identifying the sources of heterogeneity and a p-value of less than 0.05 was considered as statistically significant in all the analyses performed.

3- RESULTS

3-1. Literature Search and General Characteristics of included studies

Search in electronic databases yielded 3,547 non-repetitive studies, from which full-texts of 115 articles were evaluated and 93 of them were excluded mainly due to measuring the urine level of NGAL instead of the serum concentration, not including children as their study population, presenting repetitive findings and low quality of the article. **Figure.1** depicts the flow diagram of the process through which eventually 22 articles were selected to be included in this meta-analysis (4, 33-53). All these articles were written in English. A total of 8 studies had evaluated patients in the setting of cardiac surgery (4, 34, 39, 42, 43, 46, 47, 49), 5 had assessed patients admitted to the Intensive Care Unit (ICU) (33, 37, 40, 44, 45), 3 had included asphyxiated neonates (36, 48, 50) and 3 had been conducted on children diagnosed with sepsis or septic shock (35, 51, 52). The age of included

subjects ranges from 0 to 218 months (mean age=27.23 ± 20.34 months). A total of 3,322 children had been evaluated in these 22 studies including 2,096 (63.09%) boys and 1,226 (36.91%) girls. 2,213 children were in the non-AKI group and 1,109 subjects were categorized as AKI. **Table.2** presents a summary of the characteristics of included studies.

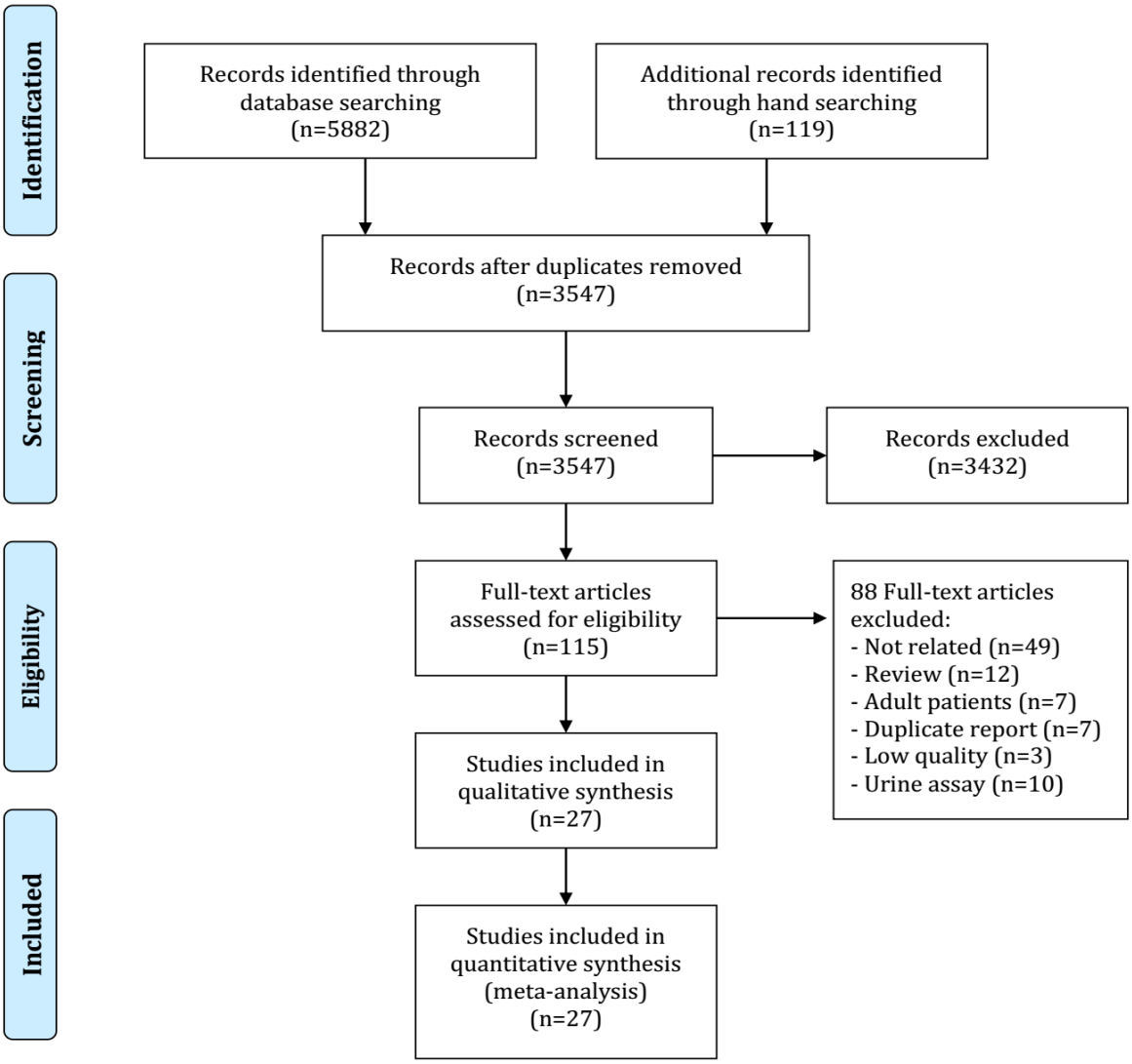


Fig.1: PRISMA flowchart of present study

3-2. Meta-analysis

3-2-1. Comparison the mean plasma/serum level of NGAL between the two AKI and non-AKI groups

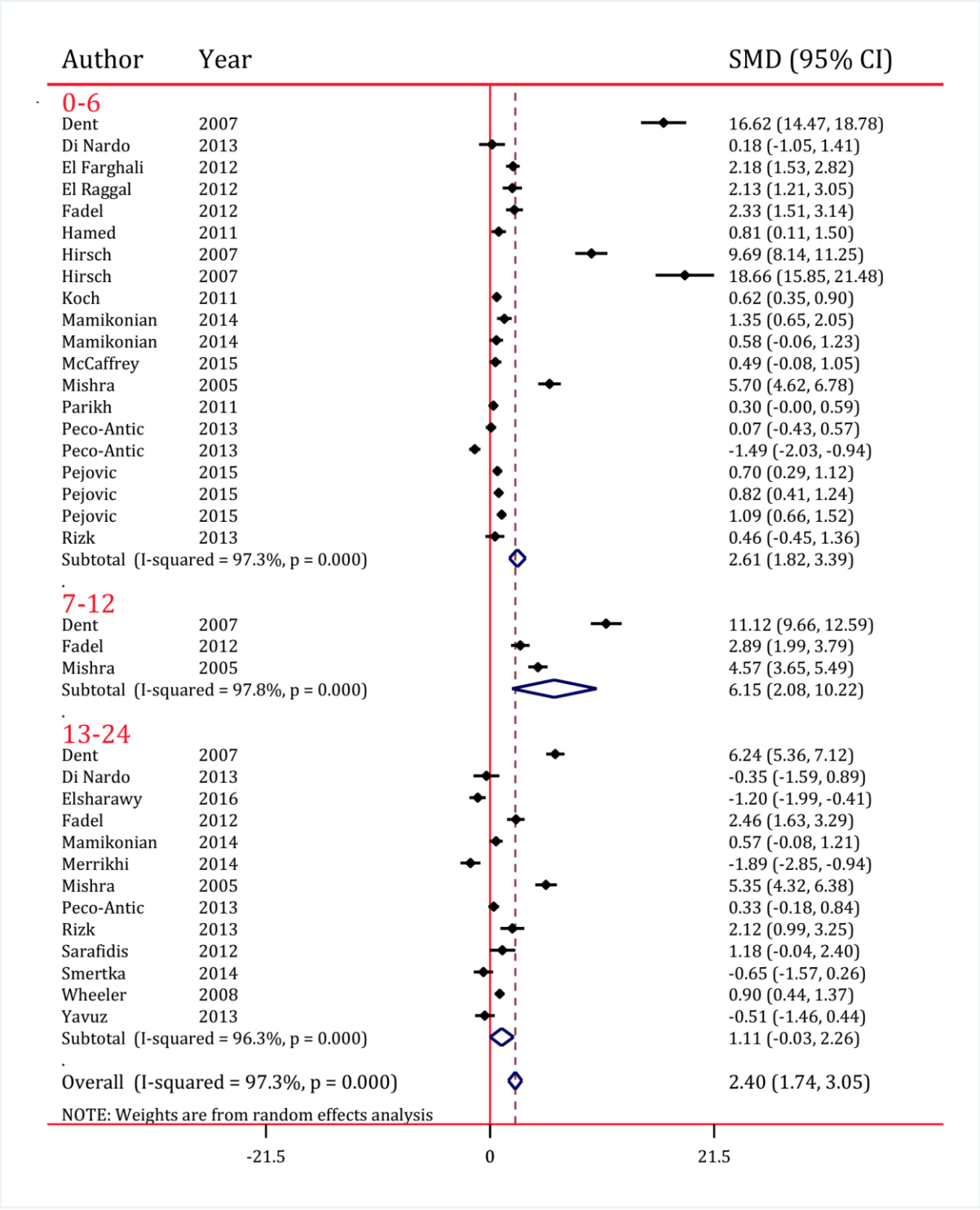
The mean serum concentration of NGAL was found to be significantly higher in AKI children compared to non-AKI subjects (SMD=2.40; 95% CI: 1.74-3.05; P<0.001). No publication bias was found in evaluating the value of plasma/serum NGAL in detection of AKI (P=0.39), however, the heterogeneity between the studies was found to be significant (I2=97.3%; P<0.0001) and so subgroup analysis was performed subsequently. This analysis showed that compared to the non-AKI group, the plasma/serum concentration of this protein was significantly higher in the first 6 hours

(SMD=2.61; 95% CI: 1.82-3.39; P<0.001) and in the first 7-12 hours after admission or surgery (SMD=6.15; 95% CI: 2.08-10.22; P=0.003) in the AKI group; but the difference between the AKI and non-AKI was not statistically significant in measuring the serum level of the biomarker 13-24 hours after admission or surgery (SMD=1.12; 95% CI: -0.03-2.26; P=0.06) (**Figure.2**).

The findings also indicated that the plasma/serum level of NGAL significantly increased in patients who developed AKI after cardiac surgery (SMD=3.09; 95% CI: 2.08-4.11; P<0.001) and in asphyxiated neonates (SMD=1.04; 95% CI: 0.30-1.41; P<0.001), but did not change considerably in subjects diagnosed with sepsis (SMD=0.09; 95% CI: -0.78-1.83; P=0.84). Moreover, when AKI was defined as a 50% increase in serum creatinine (SCr) from baseline, the serum level of NGAL was found to be significantly higher in AKI patients compared to the non-AKI group (SMD=3.97; 95% CI: 2.84-5.09; P<0.001), but the differences between the two groups were non-significant when AKI was defined as a 25% decrease in estimated creatinine clearance (SMD=0.14; 95% CI: -0.63-0.91; P=0.72) or a rise in SCr of at least o.3 mg/dL (SMD=0.54; 95% CI: -0.18-1.27; P=0.14). The findings of this section are presented in **Table.3**. Meta-regression indicated that setting of sepsis (P=0.04) and different AKI definitions (P=0.04) were the main factors affecting the performance value of plasma/serum NGAL (**Table.4**).

3-2-2. The diagnostic value of plasma/serum NGAL level for AKI in children

In order to evaluate the diagnostic value of plasma/serum NGAL level for AKI in children, the screening performance characteristics of this biomarker were assessed based on the time of measurement and the cut-off point. No publication bias was observed in this part of analyses (P=0.14), but the heterogeneity was found to be significant (I2=99.3%; P<0.001). Accordingly, the timing of measurement was categorized into two groups of the first 12 hours and 13-24 hours after admission or surgery. The area under the curve, sensitivity, specificity and diagnostic odds ratio of plasma/serum NGAL in detection of AKI in the first 12 hours group were found to be 0.90 (95% CI: 0.87-0.92), 0.78 (95% CI: 0.66-0.87), 0.93 (95% CI: 0.82-0.98) and 43.48 (95% CI: 15.48-122.18), respectively. The mentioned parameters for measuring plasma/serum NGAL 13-24 hours after admission or surgery were 0.84 (95% CI: 0.81-0.87), 0.83 (95% CI: 0.71-0.91), 0.65 (95% CI: 0.39-0.85) and 9.26 (95% CI: 2.83 -30.32), respectively (**Table.5**). The diagnostic value of plasma/serum NGAL in different cut-off points was also assessed. Optimum performance of this biomarker was found with a cut-off level of 100 mg/dL. The area under the curve, sensitivity, specificity and diagnostic odds ratio of plasma/serum NGAL for the 100 mg/dL cut-off level were 0.95 (95% CI: 0.93-0.97), 0.85 (95 CI%: 0.59-0.96), 0.93(95% CI: 0.73-0.98) and 77.58 (95% CI: 13.08-460.02), respectively (**Table.5**). In order to identify the maximum performance of plasma/serum NGAL, the two factors of measurement timing and cut-off level were assessed simultaneously in the optimum state. Based on the results presented in **Table.6**, the maximum performance of plasma/serum NGAL was achieved when the concentration of the biomarker was measured in the first 12 hours after admission or surgery while considering a cut-off value of 100 mg/dL. In this setting the area under the curve, sensitivity, specificity and diagnostic odds ratio of plasma/serum NGAL were calculated to be 0.94 (95% CI: 0.91-0.95), 0.89 (95% CI: 0.70-0.97), 0.89 (95% CI: 0.68-0.97) and 48.05 (95% CI: 9.20-251.04), respectively (**Figure.3**).



CI: Confidence interval; SMD: Standardized mean difference.

Fig.2: Standardized mean difference of plasma/serum neutrophil gelatinase-associated lipocalin between acute kidney injured and non-injured children

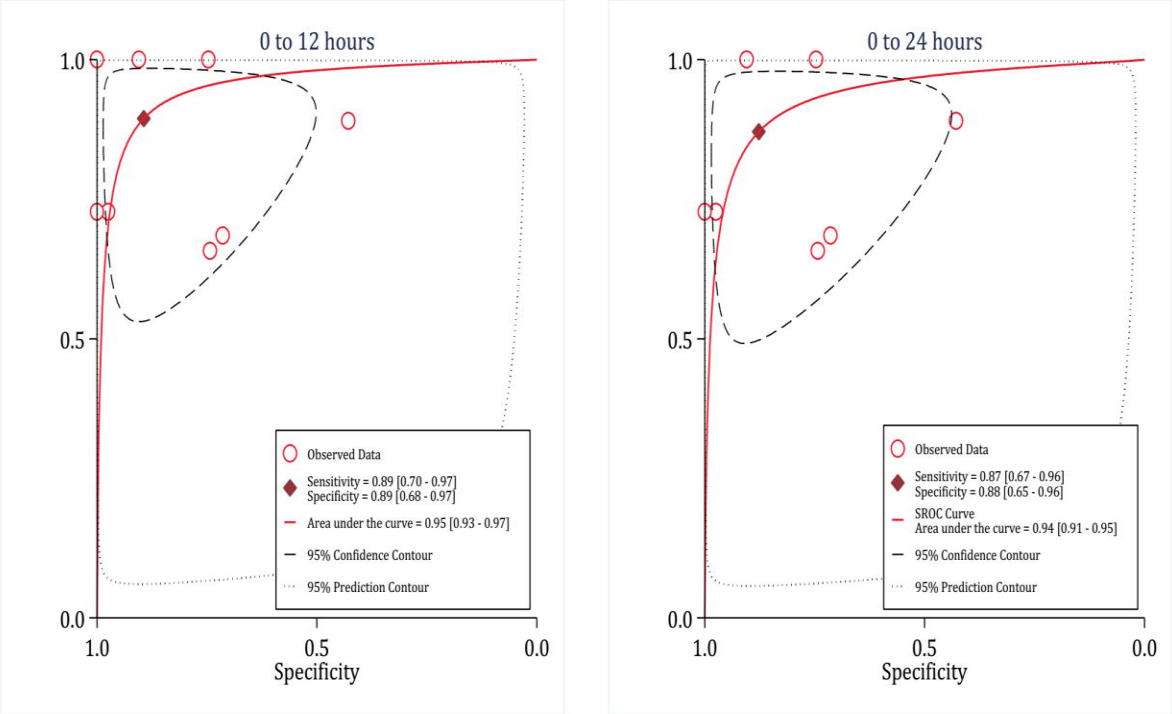


Fig.3: Summary receiver operating characteristic (SROC) plot of plasma/serum neutrophil gelatinase-associated lipocalin (assessment time: 0-12 hours and 0-24 after admission or surgery) in detection of acute kidney injury in children

3-2-2. The diagnostic value of plasma/serum NGAL level for AKI in children

In order to evaluate the diagnostic value of plasma/serum NGAL level for AKI in children, the screening performance characteristics of this biomarker were assessed based on the time of measurement and the cut-off point. No publication bias was observed in this part of analyses (P=0.14), but the heterogeneity was found to be significant (I2=99.3%; P<0.001). Accordingly, the timing of measurement was categorized into two groups of the first 12 hours and 13-24 hours after admission or surgery. The area under the curve, sensitivity, specificity and diagnostic odds ratio of plasma/serum NGAL in detection of AKI in the first 12 hours group were found to be 0.90 (95% CI: 0.87-0.92), 0.78 (95% CI: 0.66-0.87), 0.93 (95% CI: 0.82-0.98) and 43.48 (95% CI: 15.48-122.18), respectively. The mentioned parameters for measuring plasma/serum NGAL 13-24 hours after admission or surgery were 0.84 (95% CI: 0.81-0.87), 0.83 (95% CI: 0.71-0.91), 0.65 (95% CI: 0.39-0.85) and 9.26 (95% CI: 2.83 -30.32), respectively (**Table.5**). The diagnostic value of plasma/serum NGAL in different cut-off points was also assessed. Optimum performance of this biomarker was found with a cut-off level of 100 mg/dL. The area under the curve, sensitivity, specificity and diagnostic odds ratio of plasma/serum NGAL for the 100 mg/dL cut-off level were 0.95 (95% CI: 0.93-0.97), 0.85 (95 CI%: 0.59-0.96), 0.93(95% CI: 0.73-0.98) and 77.58 (95% CI: 13.08-460.02), respectively (**Table.5**).

In order to identify the maximum performance of plasma/serum NGAL, the two factors of measurement timing and cut-off level were assessed simultaneously in the optimum state. Based on the results presented in **Table.6**, the maximum

performance of plasma/serum NGAL was achieved when the concentration of the biomarker was measured in the first 12 hours after admission or surgery while considering a cut-off value of 100 mg/dL. In this setting the area under the curve, sensitivity, specificity and diagnostic odds ratio of plasma/serum NGAL were calculated to be 0.94 (95% CI: 0.91-0.95), 0.89 (95% CI: 0.70-0.97), 0.89 (95% CI: 0.68-0.97) and 48.05 (95% CI: 9.20-251.04), respectively (**Figure.3**).

4- DISCUSSION

In the recent decade, the need for a diagnostic biomarker for AKI is felt more prominently than before. Although, currently SCr is used for detection of AKI, but various limitations of this biomarker have lead researchers to go after another suitable indicator for this disease. Accordingly, for the first time the present study aimed to gather available evidence on the diagnostic value of plasma/serum NGAL in detection of AKI through an analytic approach. The results of this study showed that measuring the plasma/serum concentration of NGAL in the first 12 hours after admission or surgery while considering a cut-off level of 100 mg/dL provides the highest performance.

The findings of this survey are compatible with the results of previous meta-analyses performed on data gathered from adult subjects. For instance, in their evaluation of 19 studies, Haase et al. confirmed that the plasma/serum NGAL has an acceptable diagnostic value for detection of AKI (15); however, their study had some limitations which included the few number of included articles, not evaluating publication bias, high heterogeneity, simultaneous inclusion of adults and children and finally having passed 7 years from their publication. Zhou et al. also reported that plasma/serum NGAL provides an acceptable diagnostic value for detection of post-cardiac surgery AKI in children (17). Their study was also subject to limitations similar to that of Haase et al.'s survey. Only 7 of their included articles had been conducted on children and they briefly mentioned their results pertaining to children. In another study Tong et al. showed the acceptable diagnostic value of NGAL in detection of contrast induced nephropathy (16).

The results of the present study showed the timing of measuring plasma/serum NGAL to be an important factor affecting its diagnostic value for AKI. Measuring the concentration of this biomarker in the first 12 hours after admission or surgery was found to provide a higher prognostic value. This finding can be attributed to the early rise in the level of this biomarker after and acute injury (within the first 2 hours) and its relatively low half-life (10, 54). The immediate increase in the serum level of NGAL can be considered as one of the merits of this diagnostic method which helps the health care team of the patient to provide immediate treatments against AKI, leading to a decrease in the rate of its complications.

The different cut-off values proposed by various studies ranged from 50 to 315 mg/dL, with each providing a specific prognostic performance. The present study found the best cut-off level to be 100 mg/dL, granting the best balance in the sensitivity and specificity of the diagnostic method. To the best of our knowledge, this is the first study presenting the optimum cut-off level for plasma/serum NGAL concentration for applying in the diagnosis of AKI in children.

Another factor that can affect the diagnostic value of plasma/serum NGAL, was found to be the setting in which the patients had been evaluated. The main settings in the included studies were cardiac surgery, intensive care admitted patients, asphyxia and sepsis. The results of the present study found the diagnostic

value of plasma/serum NGAL to be higher in the settings of cardiac surgery and asphyxia compared to other settings. This finding was congruent with the reports of Zhou et al. confirming the high diagnostic value of plasma/serum NGAL in patients developing AKI after cardiac surgery (17).

4-1. Limitation

One of the main limitations of this survey was the difference in definition of AKI between the included studies, which lead to a significant heterogeneity between the articles. Subgroup analysis was performed to minimize the effect of this cofactor on the results. Furthermore, the few number of studies with sepsis and contrast-induced nephropathy settings, lead to reaching unreliable results considering the diagnostic value of plasma/serum NGAL in these settings. All the included articles were observational studies, which increases the risk of selection bias; an entity that can affect the results of the survey.

5- CONCLUSIONS

For the first time, the present meta-analysis aimed to employ an analytic approach to gather information on the diagnostic value of plasma/serum NGAL concentration in detection of AKI in children. The results of the study indicated that measuring the plasma level of NGAL in the first 12 hours after admission or surgery while considering a cut-off level of 100 mg/dL provides the best prognostic performance for detection of AKI in children. The high diagnostic value of this biomarker in the first hours after admission is one of the strengths of this method and increases its applicability in the clinical settings.

6- CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

7- ACKNOWLEDGMENTS

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8- REFERENCES

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298(17):2038-47.

2. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau J-L, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. New England Journal of Medicine 2004;351(13):1285-95.

3. Devarajan P. Biomarkers for the early detection of acute kidney injury. Current opinion in pediatrics 2011;23(2):194.

4. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. The Lancet 2005;365(9466):1231-38.

5. Mitsnefes MM, Kathman TS, Mishra J, Kartal J, Khoury PR, Nickolas TL, et al. Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in children with chronic kidney disease. Pediatric Nephrology 2007;22(1):101-8.

6. Nickolas TL, Barasch J, Devarajan P. Biomarkers in acute and chronic kidney disease. Current opinion in nephrology and hypertension 2008;17(2):127-32.

7. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney international 2002;62(1):237-44.

8. Sabbisetti VS, Waikar SS, Antoine DJ, Smiles A, Wang C, Ravisankar A, et al. Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes. Journal of the American Society of Nephrology 2014;25(10):2177-86.

9. Waanders F, van Timmeren MM, Stegeman CA, Bakker SJ, van Goor H. Kidney

injury molecule-1 in renal disease. The Journal of pathology 2010;220(1):7-16.

10. Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, et al. Urine NGAL Predicts Severity of Acute Kidney Injury After Cardiac Surgery: A Prospective Study. Clinical Journal of the American Society of Nephrology 2008;3(3):665-73.

11. Ebrahimi A, Yousefifard M, Kazemi HM, Rasouli HR, Asady H, Jafari AM, et al. Diagnostic accuracy of chest ultrasonography versus chest radiography for identification of pneumothorax: a systematic review and meta-analysis. Tanaffos 2014;13(4):29-40.

12. Hosseini M, Yousefifard M, Aziznejad H, Nasirinezhad F. The Effect of Bone Marrow–Derived Mesenchymal Stem Cell Transplantation on Allodynia and Hyperalgesia in Neuropathic Animals: A Systematic Review with Meta-Analysis. Biology of Blood and Marrow Transplantation 2015;21(9):1537-44.

13. Yousefifard M, Baikpour M, Ghelichkhani P, Asady H, Darafarin A, Esfahani MRA, et al. Comparison of Ultrasonography and Radiography in Detection of Thoracic Bone Fractures; a Systematic Review and Meta-Analysis. Emergency 2016;4(2):55-64.

14. Yousefifard M, Baikpour M, Ghelichkhani P, Asady H, Nia KS, Jafari AM, et al. Screening Performance Characteristic of Ultrasonography and Radiography in Detection of Pleural Effusion; a Meta-Analysis. Emergency 2016;4(1):1-10.

15. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, Bagshaw SM, et al. Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney Injury: A Systematic Review and Meta-analysis. American Journal of Kidney Diseases 2009;54(6):1012-24.

16. Tong J, Li H, Zhang H, Luo Z, Huang Y, Huang J, et al. Neutrophil Gelatinase-associated Lipocalin in the Prediction of Contrast-induced Nephropathy: A Systemic Review and Meta-analysis. Journal of cardiovascular pharmacology 2015;66(3):239-45.

17. Zhou F, Luo Q, Wang L, Han L. Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: A meta-analysis. European Journal of Cardio-thoracic Surgery 2016;49(3):746-55.

18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology. JAMA: the journal of the American Medical Association 2000;283(15):2008-12.

19. Ghelichkhani P, Yousefifard M, Nazemi L, Safari S, Hosseini M, Baikpour M, et al. The Value of Serum B-Subunit of Human Chorionic Gonadotropin Level in Prediction of Treatment Response to Methotrexate in Management of Ectopic Pregnancy; a Systematic Review and Meta-Analysis. International Journal of Pediatrics 2016;4(9):3503-18.

20. Hosseini M, Ghelichkhani P, Baikpour M, Tafakhori A, Asady H, Ghanbari MJH, et al. Diagnostic Accuracy of Ultrasonography and Radiography in Detection of Pulmonary Contusion; a Systematic Review and Meta-Analysis. Emergency 2015;3(4):127-36.

21. Hosseini M, Yousefifard M, Baikpour M, Rahimi-Movaghar V, Nasirinezhad F, Younesian S, et al. The efficacy of Schwann cell transplantation on motor function recovery after spinal cord injuries in animal models: a systematic review and meta-analysis. Journal of Chemical Neuroanatomy 2016;78:102-11.

22. Mostafa H, Mahmoud Y, Heidar A, Farinaz N. The Effect of Bone Mesenchymal Stem Cell Transplantation on Allodynia and Hyperalgesia in Neuropathic Animals: A Systematic Review with Meta-Analysis. Biol Blood Marrow Transplant 2015;21(9):1537-44.

23. Rahimi-Movaghar V, Yousefifard M, Ghelichkhani P, Baikpour M, Tafakhori A, Asady H, et al. Application of Ultrasonography and Radiography in Detection of Hemothorax: a Systematic Review and Meta-Analysis. Emergency 2016;4(3):116-26.

24. Safari S, Yousefifard M, Hashemi B, Baratloo A, Forouzanfar M, Rahmati F, et al. The Role of Scoring Systems and Urine Dipstick in Prediction of Rhabdomyolysis-induced Acute Kidney Injury: a Systematic

Review. Iranian journal of kidney diseases 2016;10(3):101-6.

25. Safari S, Yousefifard M, Hashemi B, Baratloo A, Forouzanfar MM, Rahmati F, et al. The value of serum creatine kinase in predicting the risk of rhabdomyolysis-induced acute kidney injury: a systematic review and meta-analysis. Clinical and experimental nephrology 2016;20(2):153-61.

26. Yousefifard M, Movaghar VR, Baikpour M, Ghelichkhani P, Hosseini M, Jafari AM, et al. Early versus Late Decompression for Traumatic Spinal Cord Injuries; a Systematic Review and Meta-analysis. Emergency 2016;4:[In press].

27. Yousefifard M, Rahimi-Movaghar V, Nasirinezhad F, Baikpour M, Safari S, Saadat S, et al. Neural stem/progenitor cell transplantation for spinal cord injury treatment; A systematic review and meta-analysis. Neuroscience 2016;322:377-97.

28. Hassanzadeh-Rad A, Yousefifard M, Katal S, Asady H, Fard-Esfahani A, Moghadas Jafari A, et al. The value of 18F-fluorodeoxyglucose positron emission tomography for prediction of treatment response in gastrointestinal stromal tumors: a systematic review and meta-analysis. Journal of gastroenterology and hepatology 2016;31(5):929-35.

29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine 2009;151(4):264-9.

30. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155(8):529-36.

31. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Medical Research Methodology 2005;5(1):13.

32. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-34.

33. Basu RK, Wang Y, Wong HR, Chawla LS, Wheeler DS, Goldstein SL. Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. Clin J Am Soc Nephrol 2014;9(4):654-62.

34. Dent CL, Ma Q, Dastrala S, Bennett M, Mitsnefes MM, Barasch J, et al. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Critical care (London, England) 2007;11(6):R127.

35. Di Nardo M, Ficarella A, Ricci Z, Luciano R, Stoppa F, Picardo S, et al. Impact of severe sepsis on serum and urinary biomarkers of acute kidney injury in critically ill children: an observational study. Blood purification 2013;35(1-3):172-6.

36. El Raggal NM, Khafagy SM, Mahmoud NH, El Beltagy SA. Serum neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury in asphyxiated neonates. Indian Pediatrics 2013;50(5):459-62.

37. El-Farghali O, El-Raggal N, Mahmoud N, Zaina G. Serum neutrophil gelatinase-associated lipocalin as a predictor of acute kidney injury in critically-ill neonates. Pakistan Journal of Biological Sciences 2012;15(5):231-7.

38. Elsharawy S, Raslan L, Morsy S, Hassan B, Khalifa N. Plasma neutrophil gelatinase-associated lipocalin as a marker for the prediction of worsening renal function in children hospitalized for acute heart failure. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 2016;27(1):49-54.

39. Fadel FI, Abdel Rahman AMO, Mohamed MF, Habib SA, Ibrahim MH, Sleem ZS, et al. Plasma neutrophil gelatinase-associated lipocalin as an early biomarker for prediction of acute kidney injury after cardio-pulmonary bypass in pediatric cardiac surgery. Archives of Medical Science 2012;8(2):250-5.

40. Hamed HM, Awad S, Barakat NAA, Rasheed EA, Thabet EH, Lebedy DE. Neutrophil gelatinase-associated lipocalin in critically ill septic children with and without acute kidney injury. Australian Journal of Basic and Applied Sciences 2011;5(11):659-66.

41. Hirsch R, Dent C, Pfriem H, Allen J, Beekman Iii RH, Ma Q, et al. NGAL is an

early predictive biomarker of contrast-induced nephropathy in children. Pediatric Nephrology 2007;22(12):2089-95.

42. Koch AM, Dittrich S, Cesnjevar R, Rüffer A, Breuer C, Glöckler M. Plasma neutrophil gelatinase-associated lipocalin measured in consecutive patients after congenital heart surgery using point-of-care technology. Interactive Cardiovascular and Thoracic Surgery 2011;13(2):133-6.

43. Mamikonian LS, Mamo LB, Smith PB, Koo J, Lodge AJ, Turi JL. Cardiopulmonary bypass is associated with hemolysis and acute kidney injury in neonates, infants, and children*. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2014;15(3):e111-9.

44. McCaffrey J, Coupes B, Chaloner C, Webb NJA, Barber R, Lennon R. Towards a biomarker panel for the assessment of AKI in children receiving intensive care. Pediatric Nephrology 2015;30(10):1861-71.

45. Merrikhi A, Gheissari A, Mousazadeh H. Urine and serum neutrophil gelatinase-associated lipocalin cut-off point for the prediction of acute kidney injury. Advanced biomedical research 2014;3(1):66.

46. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. Journal of the American Society of Nephrology 2011;22(9):1748-57.

47. Peco-Antic A, Ivanisevic I, Vulicevic I, Kotur-Stevuljevic J, Ilic S, Ivanisevic J, et al. Biomarkers of acute kidney injury in pediatric cardiac surgery. Clinical biochemistry 2013;46(13-14):1244-51.

48. Pejovic B, Eric-Marinkovic J, Pejovic M, Kotur-Stevuljevic J, Peco-Antic A. Detection of acute kidney injury in premature asphyxiated neonates by serum neutrophil gelatinase-associated lipocalin (sNGAL)--sensitivity and specificity of a potential new biomarker. Biochemia medica 2015;25(3):450-9.

49. Rizk MM, Abu El Kassem AS, Hashad D, Abo Taleb E. Neutrophil gelatinase - Associated lipocalin (NGAL) as a biomarker for acute kidney injury, morbidity and mortality after pediatric cardiac surgery. Biochimica Clinica 2013;37:S236.

50. Sarafidis K, Tsepkentzi E, Agakidou E, Diamanti E, Taparkou A, Soubasi V, et al. Serum and urine acute kidney injury biomarkers in asphyxiated neonates. Pediatric nephrology (Berlin, Germany) 2012;27(9):1575-82.

51. Smertka M, Wroblewska J, Suchojad A, Majcherczyk M, Jadamus-Niebroj D, Owsianka-Podlesny T, et al. Serum and urinary NGAL in septic newborns. BioMed research international 2014;2014:717318.

52. Wheeler DS, Devarajan P, Ma Q, Harmon K, Monaco M, Cvijanovich N, et al. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. Critical care medicine 2008;36(4):1297-303.

53. Yavuz S, Anarat A, Acarturk S, Dalay AC, Kesiktas E, Yavuz M, et al. Neutrophil gelatinase associated lipocalin as an indicator of acute kidney injury and inflammation in burned children. Burns : journal of the International Society for Burn Injuries 2014;40(4):648-54.

54. Axelsson L, Bergenfeldt M, Ohlsson K. Studies of the release and turnover of a human neutrophil lipocalin. Scandinavian journal of clinical and laboratory investigation 1995;55(7):577-88.

Table-1: Queries used for databases searching

Database	Query
PubMed	1- ("Acute Kidney Injury"[Mesh] OR "Acute Kidney Injuries"[TIAB] OR "Kidney Injuries, Acute"[TIAB] OR "Kidney Injury, Acute"[TIAB] OR "Acute Renal Injury"[TIAB] OR "Acute Renal Injuries"[TIAB] OR "Renal Injuries, Acute"[TIAB] OR "Renal Injury, Acute"[TIAB] OR "Renal Insufficiency, Acute"[TIAB] OR "Acute Renal Insufficiencies"[TIAB] OR "Renal Insufficiencies, Acute"[TIAB] OR "Acute Renal Insufficiency"[TIAB] OR "Kidney Insufficiency, Acute"[TIAB] OR "Acute Kidney Insufficiencies"[TIAB] OR "Kidney Insufficiencies, Acute"[TIAB] OR "Acute Kidney Insufficiency"[TIAB] OR "Kidney Failure, Acute"[TIAB] OR "Acute Kidney Failures"[TIAB] OR "Kidney Failures, Acute"[TIAB] OR "Acute Renal Failure"[TIAB] OR "Acute Renal Failures"[TIAB] OR "Renal Failures, Acute"[TIAB] OR "Renal Failure, Acute"[TIAB] OR "Acute Kidney Failure"[TIAB] OR "Acute Kidney Tubule Necrosis"[TIAB]). 2- ("neutrophil gelatinase-associated lipocalin"[Mesh] OR "neutrophil gelatinase-associated lipocalin"[TIAB] OR "LCN2 protein"[Mesh] OR "LCN2 protein"[TIAB] OR "neutrophil gelatinase associated lipocalin"[TIAB] OR "NGAL"[TIAB]). 3- (#1 AND #2).
Embase	1- 'Acute kidney injuries' OR 'kidney injuries, acute' OR 'kidney injury, acute' OR 'acute renal injury'/exp OR 'acute renal injuries' OR 'renal injuries, acute' OR 'renal injury, acute' OR 'renal insufficiency, acute'/exp OR 'acute renal insufficiencies' OR 'renal insufficiencies, acute' OR 'acute renal insufficiency'/exp OR 'kidney insufficiency, acute'/exp OR 'acute kidney insufficiencies' OR 'kidney insufficiencies, acute' OR 'acute kidney insufficiency'/exp OR 'kidney failure, acute'/exp OR 'acute kidney failures' OR 'kidney failures, acute' OR 'acute renal failure'/exp OR 'acute renal failures' OR 'renal failures, acute' OR 'renal failure, acute' OR 'acute kidney failure'/exp OR 'acute kidney tubule necrosis'/exp. 2- 'neutrophil gelatinase-associated lipocalin'/exp OR 'LCN2 protein'/exp OR 'neutrophil gelatinase associated lipocalin'/exp OR 'NGAL'/exp. 3- (#1 AND #2).
Scopus	1- [(TITLE-ABS-KEY (acute kidney injury) OR TITLE-ABS-KEY (acute kidney injuries) OR TITLE-ABS-KEY (acute renal injury) OR TITLE-ABS-KEY (acute renal injuries) OR TITLE-ABS-KEY (acute renal insufficiency) OR TITLE-ABS-KEY (acute renal insufficiencies) OR TITLE-ABS-KEY (acute kidney failure) OR TITLE-ABS-KEY (acute kidney failures) OR TITLE-ABS-KEY (acute kidney tubule necrosis)]. 2- [(TITLE-ABS-KEY (neutrophil gelatinase-associated lipocalin) OR TITLE-ABS-KEY (lcn2 protein) OR TITLE-ABS-KEY (neutrophil gelatinase associated lipocalin) OR TITLE-ABS-KEY (ngal)]. 3- (#1 AND #2).

Table-2: Characteristics of included studies

Author, year; country	Setting	Mean age (month)	Gender (boys, n)	No. of patients Non-AKI / AKI	AKI definition	Storage degree*	Assay method	Timing (hour)
Basu *et al.*, 2014; USA (1)	ICU admitted	42	134	185 / 29	Decrease in eCrCl > 50%	NR	ELISA	24
Dent *et al.*, 2007; USA (2)	Cardiac surgery	21.4	105	75 / 45	50% increase in SCr	-80	ELISA	2-24
Di Nardo *et al.*, 2013; Italy (3)	Sepsis	30	4	7 / 4	Decrease in eCCl > 25 %	-80	ELISA	0 and 24
El Raggal *et al.*, 2012; Egypt (4)	Asphyxiated Neonates	Newborn	17	18 / 12	Elevation of SCr >1.5 mg/dL	NR	ELISA	6
El Farghali *et al.*, 2012; Egypt (5)	ICU admitted	Newborn	34	26 / 34	Rise SCr of > 0.3 mg/dL	-20	ELISA	6
Elsharawy *et al.*, 2016; Egypt (6)	Heart failure	8	15	13 / 17	Rise SCr of > 0.3 mg/dL	-20	ELISA	24
Fadel *et al.*, 2012; Egypt (7)	Cardiac surgery	20.75	20	21 / 19	50% increase in SCr	NR	ELISA	2-24
Hamed *et al.*, 2011; Egypt (8)	ICU admitted	11.1	19	20 / 15	50% increase in SCr	-20	ELISA	0
Hirsch *et al.*, 2007; USA (9)	CIN	80.2	52	80 / 11	50% increase in SCr	-80	ELISA	2 and 6
Koch *et al.*, 2011; Germany (10)	Cardiac surgery	60	126	96 / 122	50% increase in SCr	NR	ELISA	0
Mamikonian *et al.*, 2014; USA (11)	Cardiac surgery	15.5	17	24 / 16	50% increase in SCr	-80	ELISA	2-24
McCaffrey *et al.*, 2015; UK (12)	ICU admitted	36	26	25 / 24	50% increase in SCr	-80	ELISA	0
Merrikhi *et al.*, 2014; Iran (13)	ICU admitted	48.06	18	12 / 13	50% increase in SCr	NR	ELISA	24
Mishra *et al.*, 2005; USA (14)	Cardiac surgery	41.6	45	51 / 20	50% increase in SCr	-80	ELISA	2-24

Parikh *et al.*, 2011; USA (15)	Cardiac surgery	45.6	171	258 / 53	50% increase in SCr	-80	ELISA	6
Peco-Antic *et al.*, 2013; Serbia (16)	Cardiac surgery	19.2	65	94 / 18	Decrease in eCCl > 25 %	-80	ELISA	2-24
Pejovic *et al.*, 2015; Serbia (17)	Asphyxiated Neonates	Newborn	66	35 / 73	Rise SCr > 0.3 mg/dL	-80	ELISA	2-6
Rizk *et al.*, 2013; Egypt (18)	Cardiac surgery	49	9	12 / 8	Decrease in eCCl > 25 %	-80	ELISA	6 and 24
Sarafidis *et al.*, 2012; Greece (19)	Asphyxia	Newborn	10	5 / 8	50% increase in SCr	-80	ELISA	24
Smertka *et al.*, 2014; Poland (20)	Sepsis	Newborn	47	68 / 5	Rise SCr > 0.3 mg/dL	NR	ELISA	24
Wheeler *et al.*, 2008; USA (21)	Sepsis	35.4	83	121 / 22	Scr>2 mg/dL	-80	ELISA	24
Yavuz *et al.*, 2013; Turkey (22)	Burn	30.5	12	16 / 6	50% increase in SCr	-80	ELISA	24

*Celsius; AKI: Acute kidney injury; CIN: contrast induced nephropathy; Cr: Creatinine; eCCl: Estimated creatinine clearance; ELISA: Enzyme-linked immunosorbent assay; ICU: Intensive care unit; NR: Not reported; SCr: Serum creatinine.

Table-3: Primary meta-analyses level of Neutrophil gelatinase-associated lipocalin (NGAL) in children

Characteristics	P for publication bias	Model	P for heterogeneity (I^2)	Effect size (95% CI)	P for effect size
Overall	0.39	REM	<0.001 (97.3%)	2.40 (1.74-3.05)	<0.001
a) Timing of NGAL assessment					
0-6 hours	0.30	REM	<0.001 (97.8%)	2.61 (1.82-3.39)	<0.001
7-12 hours	>0.99	REM	<0.001 (96.3%)	6.15 (2.08 -10.22)	0.003
13-24 hours	0.76	REM	<0.001 (97.3%)	1.12 (-0.03-2.26)	0.06
b) Setting					
Cardiac surgery	0.09	REM	<0.001 (98.0%)	3.09 (2.08-4.11)	<0.001
ICU admitted patients	0.35	REM	<0.001 (93.9%)	0.43 (-0.98-1.83)	0.55
Sepsis	0.18	REM	0.01 (72.8%)	0.09 (-0.78-0.96)	0.84
Asphyxia	0.19	FEM	0.07 (53.4%)	1.04 (0.30-1.41)	<0.001
Other	0.21	REM	<0.001 (99.0%)	6.52 (0.30-12.74)	0.04
c) AKI definition					
50% increase in SCr	0.18	REM	<0.001 (98.2%)	3.97 (2.84-5.09)	<0.001
Decrease in eCCl by at least 25%	0.35	REM	<0.001 (86.7%)	0.14 (-0.63-0.91)	0.72
Rise SCr of at least 0.3 mg/dL	0.42	REM	0.02 (90.7%)	0.54 (-0.18-1.27)	0.14
Other	>0.99	REM	<0.001 (81.7%)	1.45 (0.25-2.65)	0.02

AKI: Acute kidney injury; CI: Confidence interval; eCCl: Estimated creatinine clearance; FEM: Fixed effect model; ICU: Intensive care unit; REM: Random effect model; SCr: Serum creatinine.

Table-4: Meta-regression analysis for assessment of source of heterogeneity

Variables	Coef.	95% CI	P-value
Sample size	0.01	-0.01-0.04	0.37
Time of assessment			
0-6 hours	*Ref.*	*Ref.*	*Ref.*
7-12 hours	3.12	-2.48-8.73	0.27
13-24 hours	-1.93	-5.15- 1.30	0.23
Setting			
Cardiac surgery	*Ref.*	*Ref.*	*Ref.*
Critical ill patients	-2.82	-7.76-2.11	0.25
Sepsis	-3.20	-8.15- -1.75	0.04
Asphyxia	-2.04	-6.55-2.48	0.22
Other	3.14	-1.86-8.15	0.21
AKI definition			
50% increase in SCr	*Ref.*	*Ref.*	*Ref.*
Decrease in eCCl by at least 25%	-3.63	-7.71-0.44	0.08
Rise SCr of at least 0.3 mg/dL	-3.94	-7.80--0.09	0.04
Other	-2.61	-9.13-3.91	0.42
Storage degree (Celsius)			
-20	*Ref.*	*Ref.*	*Ref.*
-80	2.66	-3.56-8.87	0.39

AKI: Acute kidney injury; Coef: Meta-regression coefficient; CI: Confidence interval; eCCl: Estimated creatinine clearance; Ref.: Reference category; SCr: Serum creatinine.

Table-5: Diagnostic performance characteristics of Neutrophil gelatinase-associated lipocalin (NGAL) in detection of acute kidney injury

Characteristics	P for publication bias	Model	P for heterogeneity (I^2)	Effect size (95% CI)
Timing of NGAL assessment				
0-12 hours				
Area under the curve	0.08	REM	<0.001 (99.0)	0.90 (0.87-0.92)
Sensitivity	0.08	REM	<0.001 (81.6)	0.78 (0.66-0.87)
Specificity	0.08	REM	<0.001 (93.5)	0.93 (0.82-0.98)
Positive likelihood ratio	0.08	REM	<0.001 (88.1)	11.00 (4.19-28.91)
Negative likelihood ratio	0.08	REM	<0.001 (89.3)	0.25 (0.16-0.41)
Diagnostic odds ratio	0.08	REM	<0.001 (100.0)	43.48 (15.48-122.18)
13-24 hours				
Area under the curve	0.10	REM	0.007 (76.0)	0.84 (0.81-0.87)
Sensitivity	0.10	FEM	0.24 (19.9)	0.83 (0.71-0.91)
Specificity	0.10	REM	<0.001 (82.6)	0.65 (0.39-0.85)
Positive likelihood ratio	0.10	REM	<0.001 (61.3)	2.40 (1.19-4.82)
Negative likelihood ratio	0.10	FEM	0.34 (10.2)	0.26 (0.14-0.49)
Diagnostic odds ratio	0.10	REM	<0.001 (89.4)	9.26 (2.83 -30.32)
Cut off				

≥ 50 mg/dl				
Area under the curve	0.14	REM	<0.001 (91.0)	0.87 (0.84-0.90)
Sensitivity	0.14	REM	0.03 (65.5)	0.76 (0.55-0.89)
Specificity	0.14	REM	<0.001 (90.2)	0.87 (0.59-0.97)
Positive likelihood ratio	0.14	REM	<0.001 (75.9)	5.99 (1.82-19.75)
Negative likelihood ratio	0.14	FEM	0.14 (44.7)	0.27 (0.15-0.50)
Diagnostic odds ratio	0.14	REM	0.04 (63.4)	21.92 (7.39-65.07)
≥ 100 mg/dl				
Area under the curve	0.30	REM	<0.001 (98.0)	0.95 (0.93-0.97)
Sensitivity	0.30	REM	<0.001 (94.2)	0.85 (0.59-0.96)
Specificity	0.30	REM	<0.001 (92.9)	0.93 (0.73-0.98)
Positive likelihood ratio	0.30	REM	<0.001 (91.5)	12.12 (2.93-50.16)
Negative likelihood ratio	0.30	REM	<0.001 (97.1)	0.16 (0.05-0.51)
Diagnostic odds ratio	0.30	REM	<0.001 (100.0)	77.58 (13.08-460.02)
≥ 150 mg/dl				
Area under the curve	0.57	REM	<0.001 (94.0)	0.87 (0.83-0.89)
Sensitivity	0.57	FEM	0.52 (0.0)	0.86 (0.79-0.91)
Specificity	0.57	REM	<0.001 (98.1)	0.82 (0.43-0.96)

Positive likelihood ratio	0.57	REM	<0.001 (96.3)	4.74 (1.12-20.05)
Negative likelihood ratio	0.57	FEM	0.14 (16.8)	0.17 (0.11-0.28)
Diagnostic odds ratio	0.57	REM	<0.001 (99.6)	27.67 (4.76-160.88)
≥ 315 mg/dl				
Area under the curve	0.78	REM	<0.001 (95.0)	0.60 (0.55-0.64)
Sensitivity	0.78	FEM	0.19 (37.1)	0.53 (0.42-0.64)
Specificity	0.78	REM	<0.001 (96.7)	0.86 (0.50-0.97)
Positive likelihood ratio	0.78	REM	<0.001 (82.8)	3.80 (0.89-16.32)
Negative likelihood ratio	0.78	FEM	0.23 (30.8)	0.55 (0.43-0.69)
Diagnostic odds ratio	0.78	REM	<0.001 (100.0)	6.97 (1.39-34.96)

CI: Confidence interval; FEM: Fixed effect model; REM: Random effect model.

Table-6: Diagnostic performance characteristics of Neutrophil gelatinase-associated lipocalin (NGAL) assessment during 0-12 hours after admission or operation in detection of acute kidney injury

Characteristics	$P_{\text{for publication bias}}$	Model	$P_{\text{for heterogeneity}}$ (I^2)	Effect size (95% CI)
Cut off ≥ 100 mg/dl				
Area under the curve	0.32	REM	<0.001 (96.0)	0.94 (0.91-0.95)
Sensitivity	0.32	REM	<0.001 (92.7)	0.89 (0.70-0.97)
Specificity	0.32	REM	<0.001 (91.5)	0.89 (0.68-0.97)
Positive likelihood ratio	0.32	REM	<0.001 (89.7)	7.07 (2.19-22.79)
Negative likelihood ratio	0.32	REM	<0.001 (93.1)	0.15 (0.05-0.41)
Diagnostic odds ratio	0.32	REM	<0.001 (199.0)	48.05 (9.20-251.04)

CI: Confidence interval; FEM: Fixed effect model; REM: Random effect model.