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Systematic Review (Pages: 3875-3895)

Diagnostic Value of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Detection of Pediatric Acute Kidney Injury; a Systematic Review and Meta-Analysis

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Abstract

Background: Two questions about diagnostic value of urinary neutrophil gelatin associated lipocalin (uNGAL) in detection of acute kidney injury (AKI) in children have remained unanswered; first, which cut-off point of uNGAL has the highest value in detection of AKI; and second when is the best time for measuring this biomarker in a patient? Accordingly, the present study aimed to conduct a systematic review and meta-analysis to provide evidence on the diagnostic and prognostic value of uNGAL in detection of AKI in children.

Materials and Methods: An extensive search in the electronic databases up to the end of August 2016 was performed. Data were summarized and then the diagnostic performance characteristics of uNGAl in AKI were evaluated.

***Results* :** Data from 37 articles were summarized. Analyses based on area under the curve, sensitivity, specificity and diagnostic odds ratio revealed that uNGAL provides the optimum prognostic and diagnostic value in detection of AKI in children when measured during 0 to 6 hours after admission or surgery with a cut-off point of 50 mg/dL. In this setting, area under the curve, sensitivity, specificity and diagnostic odds ratio of uNGAL are 0.97 (95% CI: 0.95 to 0.98), 0.92 (95% CI: 0.84 to 0.97), 0.92 (95% CI: 0.83 to 0.97) and 148.14 (95% CI: 32.13 to 683.10), respectively.

***Conclusion*:** Based on these results, measuring uNGAL during the first 6 hours after admission or surgery with a cut-off point of 50 mg/dL, provides the optimum diagnostic value in detection of AKI in children.

Key Words: Acute kidney injury, Biomarker, Pediatrics, Urinary Neutrophil Gelatinase Associated Lipocalin (uNGAL).

*Please cite this article as: Izadi A, Yousefifard M, Nakhjavan-Shahraki B, Baikpour M, Mirzay Razaz J, Hosseini M. Diagnostic Value of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Detection of Pediatric Acute Kidney Injury; a Systematic Review and Meta-Analysis. Int J Pediatr 2016; 4(11): 3875-95. DOI: **10.22038/ijp.2016.7783**

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Received date Jul 19, 2016 ; Accepted date: Aug 12, 2016

1- INTRODUCTION

Various diagnostic methods have been proposed for detection of Acute Kidney Injury (AKI) in children, but none can provide a clear picture of the final outcome in these age group (1). In the last decade, as mentioned by various articles, serum biomarkers have opened a now door to immediate diagnosis of kidney diseases and have shown to be acceptable prognostic tools (2-5). Serum creatinine (SCr) is now considered as the gold standard for detection of kidney injuries in the clinic, but for to some reasons, is not an ideal biomarker for diagnosis of AKI; such as it is an indicator of the renal function, not its injury, a significant change in its level only occur after 25 to 50% of the renal function is lost and finally, SCr level depends on the muscle mass, hydration status of the patient, age, gender, medications and endogenous compounds (6).

Hence, in recent years researchers has been searching for another biomarker to detect AKI and among proposed candidates, serum level of Neutrophil gelatinase-associated lipocalin (NGAL) has drawn a lot of attention to itself (2). Not only this biomarker can help diagnose these patients, but also it can help predict the outcome of the patients (7, 8). Nevertheless, still no consensus has been reached on the value of urine Neutrophil gelatinase-associated lipocalin (uNGAL) (9-11). Two sources exist for measurement of NGAL; serum and uNGAL. Major attention has been drawn to urine biomarkers as diagnostic and prognostic tools for AKIs, since measuring such markers is a non-invasive procedure and also if a biomarker is expressed by the kidney tubules, it can reflect on kidney injury earlier than serum markers such as SCr (6). However, there are still discrepancies between the results of studies on the diagnostic value of uNGAL in detection of AKI. In this regard, various systematic reviews have been carried out, most of which have evaluated the value of this biomarker in detection of AKI in adult patients (7, 12, 13). However, still two questions have remained unanswered; 1) Which cut-off point of uNGAL has the highest value in detection of AKI? 2) When is the best time for measuring this biomarker in a patient? Accordingly, the authors of the present study aimed to conduct a systematic review and meta-analysis to provide evidence on the diagnostic value of uNGAL in detection of AKI in children.

2- MATERIALS AND METHODS

2-1. Search strategy

The present study was carried out based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (14). Search strategy, selection of keywords along with the method of summarization and meta-analysis is presented with minor modifications in the previous publications of the authors (5, 15-26). In summary, using Mesh terms in PubMed database and Emtree terms in Embase, manual search in the titles of articles and using the recommendations of specialists in the field, keywords related to NGAL and AKI were selected and combined together. Subsequently an extensive search was carried out in the electronic databases of Medline, ISI Web of Science, Embase, EBSCO, Cochrane library and Scopus. Queries used for the search in three databases of Medline, Embase and Scopus are presented in **Table.1**.

Moreover, manual search was conducted in the bibliographies of related articles, ProQuest database along with Google and Google scholar search engines in order to obtain the maximum number of articles. Two independent reviewers carried out the search.

2-2. Selection criteria

Cohort and cross sectional studies evaluating the diagnostic value of uNGAL in detection of AKI in children were included in the present survey. Inclusion criteria were as follows: confirmation of AKI via the gold standard method; having performed blood chemistry analysis in all the patients; having presented the sensitivity and specificity with a confidence interval of 95% or true positive, true negative, false positive and false negative figures (within the article or obtained from the authors by contacting them). Studies in which chronic renal failure were evaluated or patients with a definitive diagnosis of AKI were assessed before measuring the uNGAL level, duplicate reports and studies with low qualities were excluded from the study.

2-3. Quality assessment and data extraction

After compiling the articles and eliminating repetitive reports, two separate researchers performed initial screening of the articles base on articles' titles and abstracts. Then data were gathered using a checklist designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (27). Collected information included name of the first author and publication year, study setting, number of included patients, age, gender, number of patients diagnosed with AKI and the number non-AKI cases, AKI definition, timing of uNGAL assessment and cut-off point of uNGAL. In case of disagreements, a third reviewer studied the article and solved the problem through discussion (inter-rater reliability=0.93). Where reported findings were repetitive, the article with the highest number of evaluated patients was included. In case the data could not be extracted from the article, the corresponding author was contacted and asked to provide the data. If the results were presented as charts, the data extraction method proposed by Sistrom and Mergo was used (28). In cases where only sensitivity and specificity were presented in the article, reliable online software (clinical calculator 1) were used for calculation of true and false, positive and negative figures. The quality of the articles was assessed based on the guidelines proposed by the 14-item Quality Assessment of Diagnostic Accuracy Studies (QUADAS2) tool (29). Quality assessment was based on the criteria needed for designing diagnostic surveys which included various biases such as selection, performance, recording and reporting bias. Only articles with good and fair quality rates were included in the analysis.

2-4. Statistical analysis

Data were analyzed using STATA version 11.0 (Stata Corporation, College Station, TX) statistical software. Data were presented as mean and standard deviation, true positive (TP), true negative (TN), false positive (FP) and false negative (FN). For the few studies that had presented their findings as median and interquartile range, the method proposed by Hozo et al. was used to estimate mean and standard deviation (30). Heterogeneity was evaluated using the I-squared test and considering a p value of less than 0.1 as statistically significant (positive heterogeneity). Given the articles were homogeneous, fixed effect model was used otherwise random effect model was applied. Eventually, the results of the studies were pooled and an overall effect size was presented. Standardized mean difference (SMD) with a 95% confidence interval (95% CI) was calculated according to the Hedges' g, in order to compare the level of uNGAL in the two groups of AKI and non-AKI patients. Egger's and Begg's tests were used to evaluate publication bias (31). For this section the 'metan' command was used in the STATA software. Afterwards, sensitivity, specificity, positive diagnostic likelihood ratio, negative likelihood ratio

and diagnostic odds ratio were calculated with a 95% CI in order to assess the diagnostic value of uNGAL level in detection of AKI based on TP, TN, FP and FN. For this section, 'midas' command was used to apply a mixed-effect binary regression model, which is a type of random effect model. Publication bias was evaluated based on the Deek's funnel plot asymmetry test. Finally, subgroup analyses were performed according to the timing of measurement, cut-off point of uNGAL level and setting of the study. The timing of measurement was classified into three groups of less than 6 hours, 7-12 hours and 13 to 24 hours after admission or surgery. The cut-off points used for evaluation of uNGAL included 50 mg/dL, 100 mg/dL, 150 mg/dL and 250 mg/dL. In all analyses a p value of less than 0.05 was considered as the significance threshold.

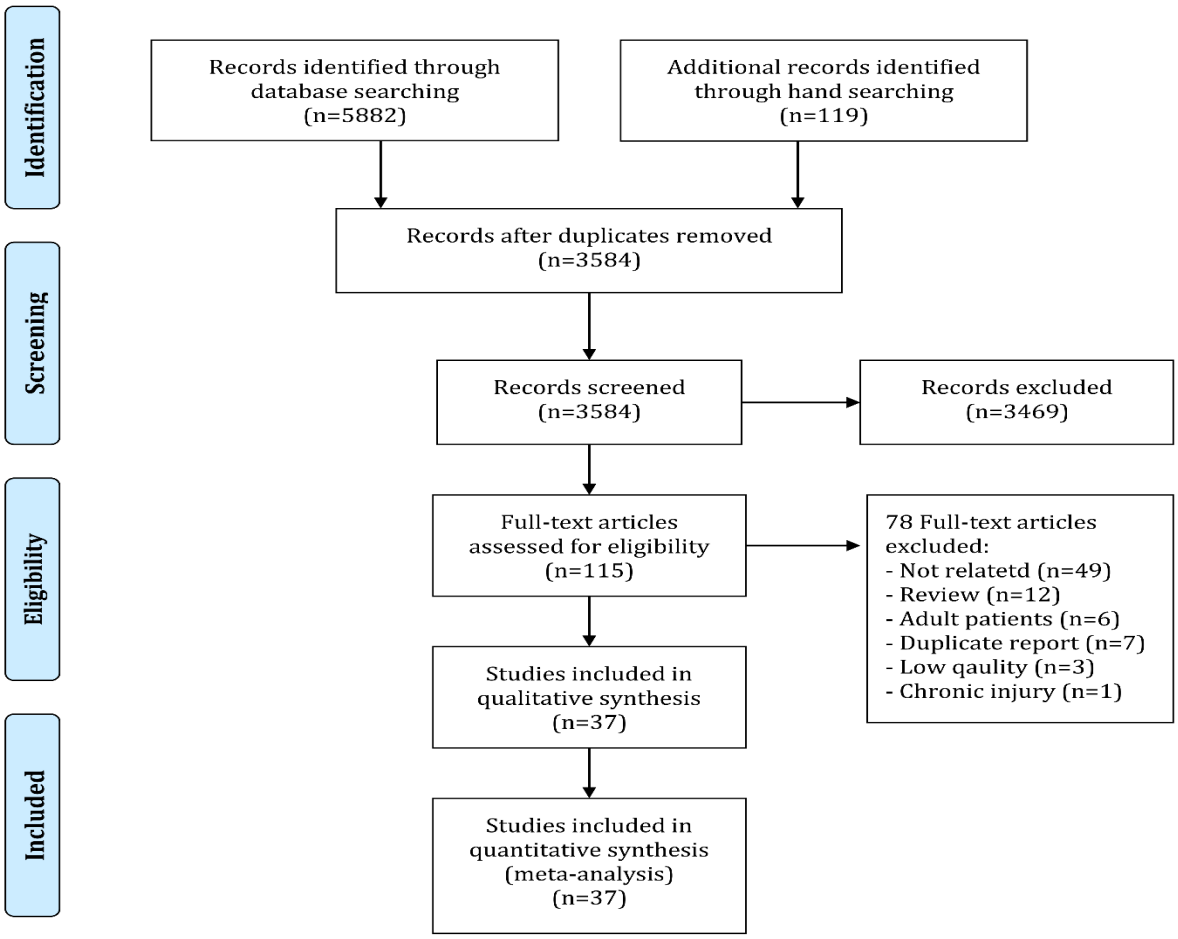


Fig.1: PRISMA flowchart of present study

3- RESULTS

3-1. Characteristics of included articles

The systematic search in electronic databases yielded 3,584 non-duplicate articles. The initial screening eliminated 3,469 articles and only 115 full-texts remained. Eventually, data from 37 articles were summarized and included in the meta-analysis (2, 32-67). Thirty-five articles were written in English (2, 32-36, 38-40, 42-67), one in Czech (37) and another one in Chinese language (41). These studies included data from 2,745 non-AKI and 1,074 AKI children with a mean age of 31.9 ± 36.6 months (range: 0 to 137 months). The majority of children (59.8%) were boys. Cardiac surgery (32, 36-38, 49, 52, 56, 57, 60, 65, 66) and

critically ill patients (34, 43, 46, 47, 50, 51, 53, 54, 63, 67) were the most common settings in these studies. The basic characteristics of these articles are presented in **Table.2**.

3-2. Heterogeneity and publication bias

Analyses performed in both sections including: 1) comparing the mean level of uNGAL between AKI and non-AKI patients (I-squared=98.0%; p<0.001) and 2) evaluating the diagnostic value of this biomarker in detection of AKI (I-squared=97.0%; p<0.001) were indicative of a significant- heterogeneity between the studies. However, no publication bias was observed between the studies according to Egger's test (p=0.985) and Deeks' funnel plot (p=0.66).

3-3. Meta-analysis

3-3-1. Comparing the level of uNGAL between AKI and non-AKI children

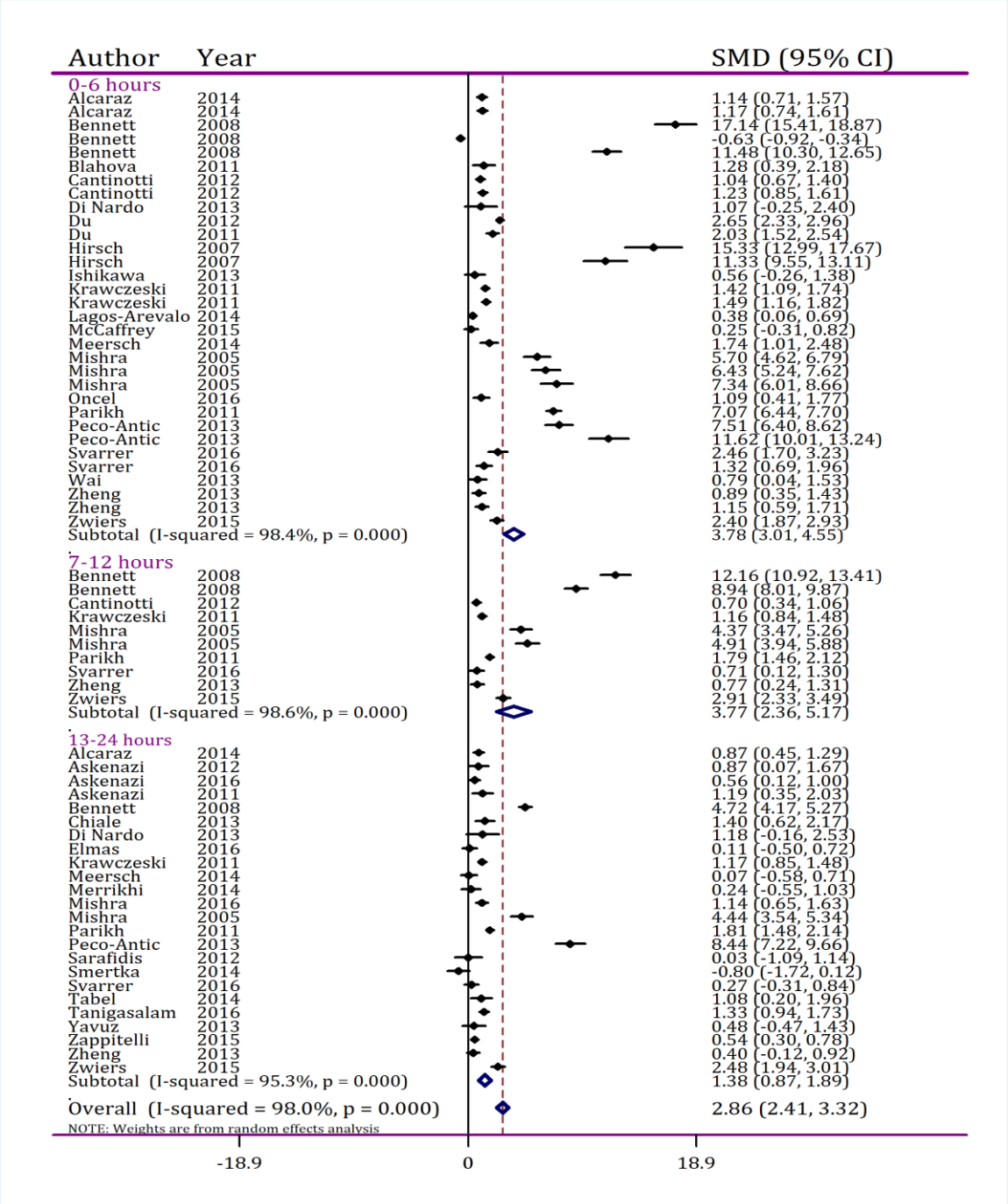
A total of 34 studies had compared the uNGAL levels between the two groups of AKI and non-AKI patients (2, 32-43, 45, 47, 49-67). Based on the performed analyses, the mean level of uNGAL in children with AKI was significantly higher than non-AKI patients (SMD=2.86; 95% CI: 2.41 to 3.32; p<0.0001) (**Figure.2**).

Subgroup analysis was carried out due to the significant heterogeneity between the studies, the results of which revealed that measuring the level of uNGAL in patients in the first 6 hours (SMD=3.78; 95% CI:3.01 to 4.55; p<0.0001) or 7-12 hours (SMD=3.77; 95% CI:2.36 to 5.171; p<0.0001) after admission or surgery provides a higher diagnostic value compared to when the level is checked 13-24 hours (SMD=1.38; 95% CI:0.87 to 1.89; p<0.0001) after admission or surgery (coefficient= -1.22; 95% CI: -2.24 to -0.21; p=0.017). Furthermore, measuring the level of uNGAL was found to have no diagnostic value in children who developed AKI after sepsis, but on the other hand its diagnostic value was found to significantly increase in detection of AKI developed due to cardiac surgery and asphyxia in neonates or in critically ill patients (coefficient= -2.56; 95% CI: -5.16 to -0.04; p=0.043) (**Tables 3 and 4**).

3-3-2. Diagnostic value of uNGAL in detection of AKI

A total of 21 articles had evaluated the diagnostic value of uNGAL in detection of AKI based on different cut-off points ranging from 50 mg/dL to 1544 mg/dL (32, 36-39, 43-46, 48, 53-56, 58, 61-64, 66, 67). Since only one study had used a cut-off point greater than 250 mg/dL, it was excluded from this part of our analysis (63). Analyses were also performed considering the timing of measurement, i.e. 0-6 hours, 7-12 hours and 13-24 hours after admission or surgery. As presented in **Table.5**, the best performance of uNGAL in detection of AKI was observed when the level had been measured in the first 6 hours after admission or surgery, providing the highest area under the curve (AUC=0.93; 95% CI: 0.91 to 0.95) and diagnostic odds ratio (diagnostic OR=97.99; 95% CI: 51.28 to 187.25). Considering the best cut-off level, the best performance of the biomarker was observed with the 50 mg/dL cut-off (AUC=0.94; 95% CI: 0.92 to 0.96 and diagnostic odds ratio [OR]=61.45; 95% C: 20.86 to 181.07), which was similar to that of the 100 mg/dL cut-off (AUC=0.90; 95% CI: 0.87 to 0.92 and diagnostic OR=86.18; 95% CI: 33.91 to 219.04). In order to find the best cut-off level and timing of measurement, the effects of these two factors were simultaneously assessed. In other words, the diagnostic value of uNGAL, measured in the first 6 hours was assessed twice with both cut-off levels of 50 mg/dL and 100 mg/dL. The results of these analyses are presented in **Table.6** and **Figure.3**. As can be seen, based on the area under the curve, sensitivity, specificity and diagnostic odds ratio, when

uNGAL level is measured in the first 6 hours after admission or surgery, the cut-off level of 50 mg/dL provides the optimum diagnostic and prognostic performance of this biomarker for AKI in children. In this setting the area under the curve, sensitivity, specificity and diagnostic odds ratio of uNGAL were calculated to be 0.97 (95% CI: 0.95 to 0.98), 0.92 (95% CI: 0.84 to 0.97), 0.92 (95% CI: 0.83 to 0.97) and 148.14 (95% CI: 32.13 to 683.10), respectively.



CI: Confidence interval; SMD: Standardized mean difference.

Fig.2: Standardized mean difference of urinary neutrophil gelatinase-associated lipocalin between acute kidney injured and non-injured children. CI: confidence interval.

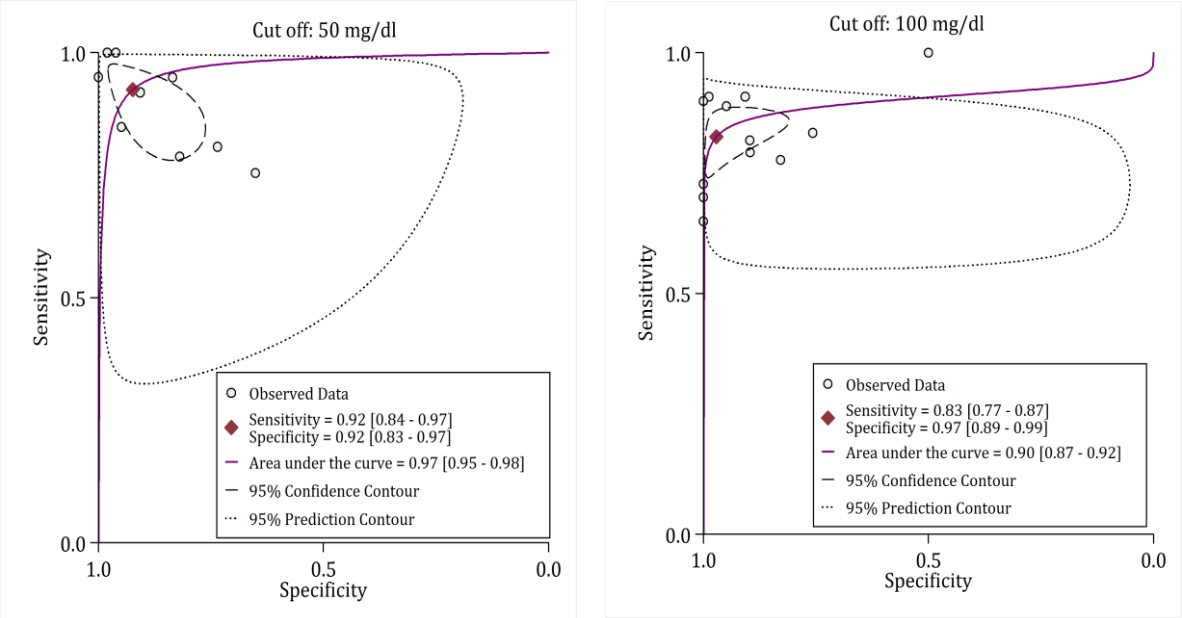


Fig.3: Summary receiver operating characteristic (SROC) plot of urinary neutrophil gelatinase-associated lipocalin (assessment time: 0-6 hours after admission or surgery) in detection of acute kidney injury in children.

4- DISCUSSION

The present meta-analysis aimed to reach a conclusion on the diagnostic value of uNGAL in detection of AKI in children and adolescents and present the optimum cut-off level for this biomarker. Findings showed that when uNGAL concentration is measured in the first 6 hours after admission or surgery, a cut-off level of 50 mg/dL can provide the optimum diagnostic performance in detection of AKI in children. The present study also revealed that uNGAL does not have an acceptable performance in detection of sepsis-induced AKI. In a similar attempt, Haase et al. carried out a systematic review in 2009 to determine the diagnostic value of NGAL in detection of renal failure. Having included data from 19 studies in their meta-analysis, these researchers found an acceptable diagnostic value for NGAL in detection of AKI (7). However, the study had some limitations. Haase et al. included few number of articles their study, they did not assess publication bias and pooled data gathered from children and adults together. Therefore, the need for conducting a more NGAL is a 20-kilodalton protein expressed in different tissues including the kidney tubules. Measuring the urine level of this biomarker can appropriately reflect the status of kidney injury (68). On the contrary to SCr, an increase in the level of NGAL is indicative of kidney injury, not its function. Current evidence also suggests that kidney injury affects both the serum and urine level of NGAL much earlier than it does the concentration of SCr. On the other hand, measuring the urine level of NGAL is a completely non-invasive procedure that does not impose any pain to the children, which is another advantage of this method (6).

In the field of pediatrics, finding such reliable non-invasive method for detection of AKI is of utmost great value. Our study also showed that the level of uNGAL provides a high diagnostic value in detection of AKI developed after cardiac surgery, in critically ill patients and neonates with asphyxia. Only its use in sepsis-induced AKI is not reliable.

Considering the fact that only two of the included articles had evaluated children with sepsis-induced AKI, further investigations are required to reach a solid conclusion on sepsis induced AKI (40, 59). Zou et al. also reported that uNGAL level has a high diagnostic value in detection of AKI developed after cardiac surgery, but these researchers did not perform subgroup analysis based on the timing of measuring the biomarker concentration, a negligence that was addressed in the present survey (13). Contrast-induced nephropathy is another setting in which AKI can develop, but only one of the included articles in our meta-analysis had evaluated such cases (45). So subgroup analysis could not be performed for this setting. But as of current literature, Tong et al. have shown that NGAL has an acceptable diagnostic value in detection of contrast-induced nephropathy in adults (12).

Timing of measuring uNGAL is another factor that can affect detection of AKI. For the first time, the present study showed that measuring uNGAL in the first 6 hours after admission or surgery provides the optimum diagnostic performance. This is an important advantage for uNGAL, since an ideal biomarker should be able to yield valuable information considering a certain condition in the earliest possible time.

The extensive search in the electronic databases and applying hand-search method, performing subgroup analysis based on two important factors of cut-off level and timing of measurement and absence of publication bias could be mentioned as strengths of the present survey. However, presence of a significant heterogeneity whose source could not be identified was one of the weaknesses of this study. Lack of sufficient data on sepsis-induced AKI and contrast-induced nephropathy made it impossible to reach a reliable conclusion regarding these settings. It should also be mentioned that all the included studies in our meta-analysis were observational, which makes selection bias a possible issue in these articles.

4-1. Limitation

Presence of a significant heterogeneity whose source could not be identified was one of the weaknesses of this study. Lack of sufficient data on sepsis-induced AKI and contrast-induced nephropathy made it impossible to reach a reliable conclusion regarding these settings.

It should also be mentioned that all the included studies in our meta-analysis were observational, which makes selection bias a possible issue in these articles. However, the extensive search in the electronic databases and applying hand-search method, performing subgroup analysis based on two important factors of cut-off level and timing of measurement and absence of publication bias could be mentioned as strengths of the present survey.

5- CONCLUSIONS

For the first time, the present meta-analysis aimed to reach a reliable conclusion on the diagnostic value of uNGAL in detection of AKI in children and adolescents. It also reported the optimum timing of measuring this biomarker in the urine to be the first 6 hours after admission or surgery and the best cut-off level to interpret its results as 50 mg/dL.

6- CONFLICT OF INTEREST

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

7- ACKNOWLEDGMENTS

The authors wish to thank Dr. Hamid Sohanaki for language editing of the article**.**

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Table-1: Queries used for databases searching

Database	Query
PubMed	("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]) AND ("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]).
Embase	['neutrophil gelatinase-associated lipocalin'/exp OR 'LCN2 protein'/exp OR 'neutrophil gelatinase associated lipocalin'/exp OR 'NGAL'/exp AND '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].
Scopus	[(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))) AND ((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)].

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)
Alcaraz *et al.*, 2014; Spain [1]	Cardiac surgery	25	62	70 / 36	50% increase in SCr	-80	Immunoassay	1-15
Askenazi *et al.*, 2011; England [2]	VLBW Infants	Newborn	14	21 / 9	Rise SCr of at least 0.3 mg/dL	-20	Immunoassay	24
Askenazi *et al.*, 2012; England [3]	Critically ill	Newborn	17	24 / 9	Rise SCr of at least 0.3 mg/dL	-20	Immunoassay	24
Askenazi *et al.*, 2016; England [4]	VLBW Infants	Newborn	55	84 / 27	50% increase in SCr	-70	ECL	24
Bennett *et al.*, 2008; USA [5]	Cardiac surgery	48	105	97 / 99	50% increase in SCr	-80	ELISA	2-24
Blahova *et al.*, 2011; Czech [6]	Cardiac surgery		24	10 / 14	50% increase in SCr	-70	Immunoassay	6
Cantinotti *et al.*, 2012; Italy [7]	Cardiac surgery	7	78	83 / 52	50% increase in SCr	-80	Immunoassay	2-12
Chiale *et al.*, 2013; Italy [8]	VLBW Infants	Newborn	NR	41 / 9	50% increase in SCr	-80	ELISA	24
Di Nardo *et al.*, 2013; Italy [9]	Sepsis	30	4	7 / 4	Decrease in eCCl by at least 25%	-80	Immunoassay	0 and 24
Du *et al.*, 2011; USA [10]	Emergency	137	126	234 / 18	Decrease in eCCl by at least 25%	-80	ELISA	0
Du *et al.*, 2012; China [11]	Emergency	102	NR	493 / 59	Decrease in eCCl by at least 25%	-80	ELISA	0
Elmas *et al.*, 2016; Turkey [12]	Critically ill	Newborn	31	51 / 13	Rise SCr of at least 0.3 mg/dL or Scr>1.5 mg/dL	-70	ELISA	24

Essajee *et al.*, 2015; Kenya [13]	Asphyxiated Neonates	Newborn	63	75 / 17	50% increase in SCr	-70	ELISA	24
Hirsch *et al.*, 2007; USA [14]	Contrast induced nephropathy	80.2	52	80 / 11	50% increase in SCr	-80	ELISA	2 and 6
Hoffman *et al.*, 2013; USA [15]	Critically ill	Newborn	21	20 / 15	50% increase in SCr	-70	ELISA	24
Ishikawa *et al.*, 2013; Japan [16]	Critically ill	NR	24	13 / 11	50% increase in SCr	NR	ELISA	0
James *et al.*, 2014; India [17]	Shock	NR		66 / 25	50% increase in SCr	NR	ELISA	24
Krawczeski *et al.*, 2011; USA [18]	Cardiac surgery	30.8	110	160 / 60	50% increase in SCr	-80	ELISA	2-24
Lagos-Arevalo *et al.*, 2014; Canada [19]	Critically ill	56.4	60	90 / 70	50% increase in SCr	-80	ELISA	0
McCaffrey *et al.*, 2015; UK [20]	Critically ill	36	26	25 / 24	50% increase in SCr	-80	Immunoassay	0
Meersch *et al.*, 2014; Germany [21]	Cardiac surgery	28.9	35	39 / 12	50% increase in SCr	-80	ELISA	4 and 24
Merrikhi *et al.*, 2014; Iran [22]	Critically ill	48.06	18	12 / 13	50% increase in SCr	NR	ELISA	24
Mishra *et al.*, 2005; USA [23]	Cardiac surgery	41.6	45	51 / 20	50% increase in SCr	-80	ELISA	2-24
Mishra *et al.*, 2016; India [24]	Critically ill	72	50	30 / 50	50% increase in SCr	-80	ELISA	24
Oncel *et al.*, 2016; Turkey [25]	Asphyxiated Neonates	Newborn	23	26 / 15	Rise SCr of at least 0.3 mg/dL	NR	ELISA	6
Parikh *et al.*, 2011; USA [26]	Cardiac surgery	45.6	171	258 / 53	50% increase in SCr	-80	ELISA	6-18

Peco-Antic *et al.*, 2013; Serbia [27]	Cardiac surgery	19.2	65	94 / 18	Decrease in eCCl by at least 25%	-80	ELISA	2-24
Sarafidis *et al.*, 2012; Greece [28]	Asphyxia	Newborn	10	5 / 8	50% increase SCr	-80	ELISA	24
Smertka *et al.*, 2014; Poland [29]	Sepsis	Newborn	47	68 / 5	Rise SCr of at least 0.3 mg/dL or Scr>1.5 mg/dL	NR	ELISA	24
Svarrer *et al.*, 2016; Denmark [30]	Cardiac surgery	86.6	28	25 / 22	50% increase or rise SCr of at least 0.3 mg/dL	-80	ELISA	2-24
Tabel *et al.*, 2014; Turkey [31]	Preterm infant	Newborn	29	44 / 6	Rise of Scr>1.5 mg/dL	-70	ELISA	24
Tanigasalam *et al.*, 2016; India [32]	Asphyxiated Neonates	Newborn	68	65 / 55	50% increase or rise SCr of at least 0.3 mg/dL	NR	ELISA	24
Wai *et al.*, 2013; USA [33]	Critically ill	103.4	19	20 / 12	Decrease in eCCl by at least 50%	-80	ELISA	0
Yavuz *et al.*, 2013; Turkey [34]	Burn	30.5	12	16 / 6	50% increase or rise SCr	-80	ELISA	24
Zappitelli *et al.*, 2015; USA [35]	Cardiac surgery	47.5	159	154 / 133	50% increase or rise SCr of at least 0.3 mg/dL	-80	ELISA	24
Zheng *et al.*, 2013; China [36]	Cardiac surgery	8.65	39	29 / 29	50% increase or rise SCr of at least 0.3 mg/dL	-80	ELISA	4-24
Zwiers *et al.*, 2015; Netherlands [37]	Critically ill	Newborn	66	65 / 35	50% increase or rise SCr of at least 0.3 mg/dL	-80	ELISA	6-24

*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 of urine 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	0.99	REM	<0.001 (98.0%)	2.86 (2.41-3.32)	<0.001
a) Timing of NGAL assessment					
0-6 hours	0.78	REM	<0.001 (98.4%)	3.78 (3.00-4.55)	<0.001
7-12 hours	>0.99	REM	<0.001 (98.6%)	3.77 (2.36 -5.17)	<0.001
13-24 hours	0.42	REM	<0.001 (95.3%)	1.38 (0.87-1.89)	<0.001
b) Setting					
Cardiac surgery	0.80	REM	<0.001 (98.5%)	3.56 (2.92-4.21)	<0.001
Critical ill patients	0.99	REM	<0.001 (92.4%)	1.11 (0.49-1.73)	<0.001
Sepsis	0.30	REM	0.016 (75.8%)	0.41 (-0.98-1.81)	0.561
Asphyxia	0.30	FEM	0.094 (57.7%)	1.00 (0.39-1.60)	0.001
Other	0.13	REM	<0.001 (97.4%)	3.58 (2.21-4.95)	<0.001
c) AKI definition					
50% increase in SCr	0.61	REM	<0.001 (98.1%)	2.87 (2.37-3.37)	<0.001
Decrease in eCCl by at least 25%	0.81	REM	<0.001 (97.9%)	4.87 (2.84-6.91)	<0.001
Rise SCr of at least 0.3 mg/dL	0.31	REM	0.004 (74.3%)	0.51 (-0.16-1.18)	0.14

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	-0.002-0.02	0.13
Time of assessment			
0-6 hours	*Ref.*	*Ref.*	*Ref.*
7-12 hours	-0.09	-2.82-2.63	0.94
13-24 hours	-2.51	-4.53- -0.47	0.017
Setting			
Cardiac surgery	*Ref.*	*Ref.*	*Ref.*
Critical ill patients	-3.16	-7.78-1.42	0.17
Sepsis	-2.56	-5.16- -0.04	0.043
Asphyxia	-2.84	-7.41-1.73	0.22
Other	0.20	-2.63-3.034	0.89
AKI definition			
50% increase in SCr	*Ref.*	*Ref.*	*Ref.*
decrease in eCCl by at least 25%	-2.52	-6.14-1.10	0.17
rise SCr of at least 0.3 mg/dL	1.89	-1.24-5.02	0.23
Other	-1.93	-9.74-5.89	0.62
Storage degree (Celsius)			
-20	*Ref.*	*Ref.*	*Ref.*
-70	-0.27	-7.16-6.62	0.94
-80	2.42	-3.30-8.15	0.40

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	$P_{\text{for publication bias}}$	Model	$P_{\text{for heterogeneity}}$ (I^2)	Effect size (95% CI)
Timing of NGAL assessment				
0-6 hours				
Area under the curve	0.08	REM	<0.001 (77.6)	0.93 (0.91-0.95)
Sensitivity	0.29	REM	<0.001 (50.2)	0.86 (0.83-0.89)
Specificity	0.29	REM	<0.001 (89.6)	0.94 (0.90-0.97)
Positive likelihood ratio	0.29	REM	<0.001 (85.9)	14.40 (8.2-25.0)
Negative likelihood ratio	0.29	REM	<0.001 (59.3)	0.15 (0.12-0.18)
Diagnostic odds ratio	0.29	REM	<0.001 (100.0)	97.99 (51.28-187.25)
7-12 hours				
Area under the curve	0.99	REM	<0.001 (77.0)	0.77 (0.73-0.80)
Sensitivity	0.99	REM	<0.001 (55.0)	0.74 (0.63-0.82)
Specificity	0.99	REM	<0.001 (67.3)	0.67 (0.57-0.76)
Positive likelihood ratio	0.99	REM	<0.001 (64.5)	2.30 (1.70-3.00)
Negative likelihood ratio	0.99	REM	<0.001 (83.5)	0.39 (0.27-0.57)
Diagnostic odds ratio	0.99	REM	<0.001 (69.4)	5.75 (3.17-10.43)
13-24 hours				
Area under the curve	0.48	REM	<0.001 (77.0)	0.85 (0.81-0.87)
Sensitivity	0.48	FEM	0.99 (0.0)	0.80 (0.73-0.85)
Specificity	0.48	REM	<0.001 (56.2)	0.81 (0.71-0.87)
Positive likelihood ratio	0.48	REM	<0.001 (23.0)	4.09 (2.69-6.21)
Negative likelihood ratio	0.48	FEM	0.79 (0.0)	0.25 (0.19-0.34)
Diagnostic odds ratio	0.48	REM	<0.001 (99.9)	16.24 (8.76-30.12)
Cut off				
≥50 mg/dl				
Area under the curve	0.43	REM	0.02 (70.0)	0.94 (0.92-0.96)
Sensitivity	0.43	REM	<0.001 (83.1)	0.88 (0.81-0.94)
Specificity	0.43	REM	<0.001 (95.0)	0.89 (0.81-0.94)

Positive likelihood ratio	0.43	REM	<0.001 (93.8)	8.08 (4.26-15.33)
Negative likelihood ratio	0.43	REM	<0.001 (88.5)	0.13 (0.08-0.22)
Diagnostic odds ratio	0.43	REM	<0.001 (100.0)	61.45 (20.86-181.07)
≥100 mg/dl				
Area under the curve	0.65	REM	<0.001 (96.0)	0.90 (0.87-0.92)
Sensitivity	0.65	REM	<0.001 (53.4)	0.82 (0.77-0.86)
Specificity	0.65	REM	<0.001 (88.5)	0.95 (0.88-0.98)
Positive likelihood ratio	0.65	REM	<0.001 (83.9)	16.58 (6.69-41.12)
Negative likelihood ratio	0.65	REM	<0.001 (60.9)	0.19 (0.15-0.25)
Diagnostic odds ratio	0.65	REM	<0.001 (100.0)	86.18 (33.91-219.04)
≥150 mg/dl				
Area under the curve	0.34	FEM	0.17 (8.0)	0.91 (0.88-0.93)
Sensitivity	0.34	FEM	0.21 (29.1)	0.83 (0.77-0.88)
Specificity	0.34	REM	<0.001 (80.4)	0.89 (0.81-0.93)
Positive likelihood ratio	0.34	REM	<0.001 (65.9)	7.29 (4.12-12.88)
Negative likelihood ratio	0.34	FEM	0.14 (37.2)	0.19 (0.13-0.27)
Diagnostic odds ratio	0.34	REM	<0.001 (98.9)	38.63 (16.21-92.04)

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

Table-6: Diagnostic performance characteristics of Neutrophil gelatinase-associated lipocalin (NGAL) assessment during 0-6 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				
≥50 mg/dl				
Area under the curve	0.09	REM	0.02 (70.0)	0.97 (0.95-0.98)
Sensitivity	0.09	REM	<0.001 (83.1)	0.92 (0.84-0.97)
Specificity	0.09	REM	<0.001 (95.0)	0.92 (0.83-0.97)
Positive likelihood ratio	0.09	REM	<0.001 (95.7)	12.08 (5.19-28.12)
Negative likelihood ratio	0.09	REM	<0.001 (90.7)	0.08 (0.04-0.18)
Diagnostic odds ratio	0.09	REM	<0.001 (100.0)	148.14 (32.13-683.10)
≥100 mg/dl				
Area under the curve	0.30	REM	<0.001 (96.0)	0.90 (0.87-0.92)
Sensitivity	0.30	REM	0.01 (53.1)	0.83 (0.77-0.87)
Specificity	0.30	REM	<0.001 (90.9)	0.97 (0.89-0.99)
Positive likelihood ratio	0.30	REM	<0.001 (87.3)	28.45 (7.28-111.27)
Negative likelihood ratio	0.30	REM	0.01 (57.2)	0.18 (0.14-0.24)
Diagnostic odds ratio	0.30	REM	<0.001 (99.8)	158.50 (43.34-579.66)

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