A prognostic value of early urinary biomarkers NGAL and IL-18 in critically ill children: a 10-year literature review

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ABSTRACT

Introduction. Acute kidney injury (AKI) is a life-threatening syndrome caused by a sudden and rapidly progressing impairment of renal function. It is a common and complicated clinical entity among hospitalized children, occurring in 2%-4.5% of children treated in a pediatric intensive care unit. Mortality among such patients remains high (from 8% to 89%) despite improving patient care and technical possibilities. The stage of renal damage is a reversible process, and its timely detection would prevent the progression of renal damage and thus reduce pediatric mortality rates. Therefore, modern medicine necessitates the identification of novel AKI biomarkers that would correlate with renal cell damage and could be detected earlier than a rise in serum creatinine (sCr). Neutrophil gelatinase-associated lipocalin (NGAL) and interleukin 18 (IL-18) are one of such early markers of AKI.

Aim. To carry out a literature review of studies on changes in NGAL and IL-18 levels in the urine of critically ill patients and to determine a prognostic value of these biomarkers in the detection of renal injury and impact on disease outcomes.

Material and methods. This literature review includes the publications of biomedical studies assessing early biomarkers of AKI in urine (uNGAL or uIL-18) of critically ill children, published in English during the 10-year period. Search for publication was performed in the PubMed database.

Results. Analysis included 10 studies that investigated early biomarkers of AKI (NGAL or IL-18) in urine of critically ill children and compared them with sCr. Among the biomedical studies analyzed in our literature review, 9 measured the NGAL level in urine or both in urine and serum, while 2 measured IL-18 in urine. It was determined that uNGAL and uIL-18 were good early diagnostic biomarkers of AKI, which increased 48 h earlier than Cr in serum (P<0.005). The meta-analysis carried out by Haase et al. showed that uNGAL predicted the development of AKI better in critically ill children than in adults (OR, 25.4; ROC, 0.930 vs. OR, 10.6; ROC, 0.782). Three studies reported that the uNGAL level in study populations with AKI directly depended on disease severity and AKI degree (P<0.005). Four studies found that uNGAL and one study that uIL-18 are good predictive factors of mortality (P<0.005).

Conclusions. uNGAL and uIL-18 are early predictive biomarkers of AKI in critically ill children. uNGAL and uIL-18 level correlated well with disease severity and are independent predictive biomarkers of mortality.

Key words: acute kidney injury, critically ill children, biomarkers, uNGAL, uIL-18.

INTRODUCTION

Acute kidney injury (AKI) is a life-threatening clinical syndrome caused by a sudden and rapidly progressing impairment of renal function (most commonly reversible), characterized by the retention of nitrogenous waste products in blood as well as various alterations in fluid, electrolyte and acid-base homeostasis. With further worsening of AKI, cells undergo necrosis and apoptosis, and AKI develops to the stage of renal failure. However, up to date, there has been a lack of unified standardized criteria defining AKI, and few studies have investigated the prevalence of AKI and its causes in the pediatric population. (1,2) AKI is a common and complicated medical problem among hospitalized children and diagnosed in 2%-4.5% of the children, treated in pediatric intensive care units (PICUs). (3,4) According to different authors, mortality among children with AKI remains high (8% to 89%), despite improving patient care and technical possibilities. (3,5,6) Bailey et al. reported that the mortality rate among children who developed AKI and were treated in the PICUs was 11 times higher than that among children who did not develop AKI. (4) To date, there has been no specific treatment of AKI, and only renal replacement therapy is applied.

Many authors investigating AKI causes have noticed that in 50%-80% of the cases, the cause of AKI is not a renal disease, but other disease (so-called secondary AKI), and such AKI develops as a consequence of the main disease. (4,7) Thus, it is very important to identify the onset of renal damage as early as possible, apply preventive measures and adequate treatment in order to avoid the development of renal failure, reduce pediatric mortality rates, and improve outcomes. (8) Creatinine (Cr) levels start to rise only after 2 days when 50% of the renal function has been lost. It is a functional marker of glomerular filtration rate (GFR), but not a marker of damage at a cellular level. Cr is considered a late marker of AKI, closely related to patient's age, race, gender, muscle mass, medications or hydration status. (9) With recent advances in medical science, it has become evident that in the beginning, renal damage develops at the molecular level and later, at the cellular level. Substances produced by

cells (interleukins, proteins, etc.) could be early biomarkers of renal damage because later, with the progressing process, renal insufficiency develops. The stage of renal damage is a reversible process, and it is possible to prevent the progression of renal damage and thus to reduce pediatric mortality rates by its timely detection, adoption of precautionary measures, ensuring of appropriate fluid management, and avoidance of nephrotoxic factors (medications or intravenous contrast agents). (10) Therefore, modern medicine necessitates the identification of novel AKI biomarkers that would correlate with renal cell damage and could be detected earlier than a rise in serum Cr (sCr). (10,11) Novel biomarkers of AKI should help diagnose AKI early, its location and causes and would allow differentiating if the damage was caused by a renal disease or other causes. (9) Neutrophil gelatinase-associated lipocalin (NGAL) and interleukin 18 (IL-18) are one of such early markers of AKI. (12,13)

The aim of this literature review was to conduct a systematic analysis of studies on changes in urinary NGAL (uNGAL) and IL-18 (uIL-18) levels among critically ill children.

MATERIAL AND METHODS

Criteria for the inclusion of studies in the systematic review

This literature review included the publications of biomedical studies, assessing uNGAL or uIL-18 in critically ill children aged from 1 month to 21 years, published in English during the 10-year period until February 1, 2016. AKI was defined by the pediatric Risk, Injury, Failure, Loss and End Stage (pRIFLE) criteria created and validated by the Acute Dialysis Quality Initiative Group. The studies investigating NGAL or IL-18 only in plasma, examining children after cardiac surgery, or evaluating the impact of medicines on parameters were excluded. Only full-text articles were analyzed as abstracts are not sufficient for a detailed analysis. The inclusion and exclusion criteria for literature sources are shown in table 1.

Strategy of search for publications

Search for publication was performed in the PubMed database. Figure 1 depicts the key words for search and the detailed process of study identification and selection.
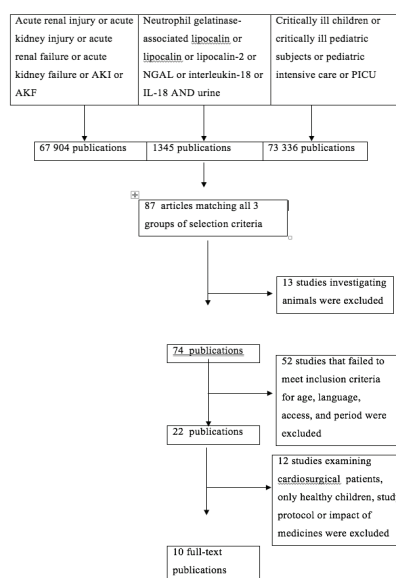
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Acute renal injury or acute      Neutrophil gelatinase-      Critically ill children or
kidney injury or acute           associated lipocalin or     critically ill pediatric
renal failure or acute           lipocalin or lipocalin-2 or subjects or pediatric
kidney failure or AKI or         NGAL or interleukin-18 or   intensive care or PICU
AKF                              IL-18 AND urine

67 904 publications    1345 publications    73 336 publications

                87  articles matching all 3
                groups of selection criteria

                                        13 studies investigating
                                        animals were excluded

74  publications
                                52 studies that failed to
                                meet inclusion criteria
                                for age, language,
                                access, and period were
22  publications                excluded

                                12 studies examining
                                cardiosurgical patients,
                                only healthy children, study
                                protocol or impact of
                                medicines were excluded

10 full-text
publications
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Figure 1. A flow chart of study search and selection for systematic review
AKI, acute kidney injury; IL-18, interleukin 18; NGAL, Neutrophil gelatinase-associated lipocalin; PICU, pediatric intensive care unit.

Data systematization and analysis

After a detailed search for publications, a total of 10 full-text publications meeting all inclusion criteria were identified. This literature review included 10 biomedical studies, and their analysis was performed based on the set aim and objectives. The following data were extracted from the publications analyzed: general information (authors, year, and country) and characteristics of studies (design, study population, sample size, measurements, and results).

RESULTS

This literature review included 10 studies that evaluated early biomarkers of renal injury (NGAL or IL-18) in the urine of critically ill patients and compared these biomarkers between two patients' groups, i.e. those who developed and did not develop AKI. The data have been systematized and presented in table 2.

Most of the biomedical studies were carried out in North America (4 in the USA and 1 in Canada); 1, in other European counties such as Germany, Italy, United Kingdom, the Netherlands; and 1 in Turkey. A total of 9 prospective cohort studies included small sample sizes of critically ill patients treated in the PICUs. The median number of the patients investigated was 100 (min, 11; max, 308). A meta-analysis conducted by Haase et al. included 19 studies, which enrolled a considerably greater number of the investigated subjects, i.e. 2538 patients.

Among the biomedical studies analyzed in our literature review, 9 studies measured the NGAL level in urine or both in urine and serum, and 2 studies, IL-18 in urine. All the included studies analyzed only the data of critically ill patients treated in the PICUs and evaluated the changes in uNGAL or uIL-18 levels in patients and compared them between the two groups: those who developed and did not develop AKI. It was determined that uNGAL and uIL-18 were good early diagnostic biomarkers

Table 1. Inclusion and exclusion criteria for literature sources

Variable	Inclusion criteria	Exclusion criteria
Age	1 month to 21 years	Younger than 1 month and older than 21 years
Study population	Critically ill patients, humans	Patients after cardiac surgery, with diabetes mellitus, systemic connective tissue disease, or vasculitis; impact of medications; animals
Markers investigated	Urine NGAL and IL-18	Only plasma NGAL, IL-18; other parameters
Language	English	Other languages
Period	Published from January 1, 2006, to February 1, 2016	Published before 2006

IL-18, interleukin 18; NGAL, Neutrophil gelatinase-associated lipocalin.

Table 2. Analysis of biomedical studies

Author	Year, country	Study design	Sample size	Biomarkers investigated	Outcome
Zappitelli et al. (14)	2007, USA	Prospective cohort study	140 patients aged 1 month to 21 years, treated in the PICU	uNGAL, sCr	uNGAL is an early diagnostic marker of AKI development, which increased 48 h earlier than sCr (P<0.05)
Washburn et al. (15)	2008, USA	Prospective cohort study	137 patients aged 1 month to 21 years, treated in the PICU	uIL-18, sCr	In patients with AKI, uIL-18 concentration rose earlier than that of sCr (OR=3.5, P<0.05)
Haase et al. (16)	2009, Germany	Meta-analysis of 19 studies from 8 countries	2538 children and adults	sNGAL, uNGAL, sCr	uNGAL level had a better predictive value for AKI in children than adults (OR=25.4, 95% CI 8.9-72.2 vs. OR=10.6, 95% CI 4.8-23.4)
Di Nardo et al. (17)	2013, Italy	Prospective cohort study	11 patients treated in the PICU and 10 healthy children	sNGAL, uNGAL, sCysC, uCysC, sCr	uNGAL, sCysC, and uCysC were significant predictors of AKI. sNGAL increased in case of sepsis, but did not discriminate patients with AKI from those without AKI
Polat et al. (18)	2013, Turkey	Prospective cohort study	32 patients aged 1 month to 18 years, treated in a PICU, and 20 healthy children	sNGAL, uNGAL, sCysC, sCr	uNGAL and sNGAL increase in case of AKI and help discriminate intrinsic from prerenal AKI (P<0.001 and P=0.002)
Wai et al. (19)	2013, USA	Prospective cohort study	39 patients aged 1 week to 21 years, treated in the PICU, and 21 healthy children	uNGAL, uFGF-2, uEGF, sCr, uCr	uNGAL was a more sensitive biomarker to detect AKI in critically ill patients than uFGF-2 (P<0.001). ROC analysis combining all three biomarkers showed a sensitivity of 89% and a specificity of 89%
Yavuz et al. (20)	2014, Turkey	Prospective cohort study	22 patients aged 1 month to 21 years, treated in the PICU	sNGAL, uNGAL, sCr, CRP	sNGAL and uNGAL are reliable early indicators of AKI. sNGAL can be used as an indicator of inflammation
McCaffrey et al. (10)	2015, UK	Prospective cohort study	49 patients aged 16 days to 15 years, treated in the PICU	sNGAL, uNGAL, uKIM 1, sCr, sCysC	sNGAL and uNGAL are early and better predictors of AKI than sCr. sNGAL increased in case of sepsis, but was not associated with AKI development
Lagos-Arevalo et al. (21)	2015, Canada	Prospective cohort study	160 patients aged 1 month to 18 years, treated in the PICU	uNGAL, uIL-18, uKIM-1, sCysC, uCysC, sCr	sCr cannot be replaced by uCysC to define AKI. uNGAL and uIL-18 were more sensitive for predicting AKI than uCysC (AUC 0.78 and 0.62)
Zwiers et al. (22)	2015, the Netherlands	Prospective cohort study	100 patients aged 1 day to 1 year, treated in the PICU	uNGAL, uKIM 1, sCr	uNGAL and KIM -1 levels at 6-12 h and 12-24 h after admission to the PICU, respectively, were significantly higher in patients who developed AKI (P<0.001). The uNGAL level increased 48 h earlier than the sCr level in 84% of the patients. With a cut-off value of >126 ng/mL, uNGAL had a sensitivity of 84% and a specificity of 86%

AKI, acute kidney injury; Cr, creatinine; CRP, C-reactive protein; CysC, cystatin C; EGF, epithelial growth factor; FGF-2, fibroblast growth factor 2; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; NGAL, Neutrophil gelatinase-associated lipocalin, PICU, pediatric intensive care unit; s, serum; u, urine.

Table 3. Studies investigating associations between AKI markers and disease severity

Author	Year, country	Sample size	Biomarkers investigated	Outcome
Zappitelli et al. (14)	2007, USA	140	uNGAL, sCr	uNGAL level depended on the severity of AKI ($P\leq0.05$)
Zwiers et al. (22)	2015, The Netherlands	100	uNGAL, uKIM 1, sCr	uNGAL and KIM-1 levels depended on the severity of AKI ($P\leq0.018$)
McCaffrey et al. (10)	2015, UK	49	pNGAL, uNGAL, uKIM 1, sCr, sCystC	pNGAL ($P=0.027$), uNGAL ($P=0.0079$), and sCystC ($P=0.0001$) levels were higher with progressing AKI

AKI, acute kidney injury; Cr, creatinine; CysC, cystatin C; KIM-1, kidney injury molecule 1; NGAL, Neutrophil gelatinase-associated lipocalin, p, plasma; s, serum; u, urine.

Table 4. Studies investigating associations between AKI markers and outcome

Author	Year, country	Sample size	Markers investigated	Outcome
Zwiers et al. (22)	2015, the Netherlands	100	uNGAL, uKIM 1, sCr	The uNGAL level in non-survivors was significantly higher than in survivors (P≤0.009)
Wai et al. (19)	2013, USA	39	uNGAL, uFGF-2, uEGF, uCr	Non-survivors had a greater uNGAL level than survivors (P=0.006). uNGAL with a cut-off value of 6,808 ng/mg had a sensitivity of 80% and specificity of 78.6%
Polat et al. (18)	2013, Turkey	32	sNGAL, uNGAL, sCystC, sCr	uNGAL level was significantly higher in patients who died than that in those who survived (568±387 vs. 352±366 ng/mL, P=0.004)
Haase et al. (16)	2009, Germany	2538	sNGAL, uNGAL, sCr	Non-survivors had a higher uNGAL level than survivors. uNGAL with a cut-off value of 212 ng/mL (121.8-506.7) had a sensitivity of 65% and a specificity of 82.6%
Washburn et al. (15)	2008, USA	137	uIL-18, sCr	uIL-18 was associated with mortality (OR=1.29, P<0.05)
Zappitelli et al. (14)	2007, USA	140	uNGAL, sCr	There was no significant difference in the uNGAL concentration between survivors and non-survivors (P>0.05)

AKI, acute kidney injury; Cr, creatinine; CRP, C-reactive protein; CysC, cystatin C; EGF, epithelial growth factor; FGF-2, fibroblast growth factor 2; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; NGAL, Neutrophil gelatinase-associated lipocalin, s, serum; u, urine.

of AKI, which increased 48 h earlier than Cr in serum (P<0.005). Among the studies analyzed, 3 studies examined newborns as well and 1 study, critically ill adults. The meta-analysis carried out by Haase et al. showed that uNGAL predicted the development of AKI better in critically ill children than adults (OR, 25.4; ROC, 0.930 vs. OR, 10.6; ROC, 0.782). (16) Three studies investigated uNGAL and sNGAL levels in healthy children as well, and all of them showed that NGAL levels differed depending on a child's age. (17-19) Among the publications analyzed, 3 studies showed associations between the uNGAL level and disease severity. (10,14,22) Studies have noted that the uNGAL level in study populations with AKI directly depends on disease severity and AKI degree (P<0.005) (table 3). Among the publications analyzed, no study investigated the relationship between uIL-18 and disease severity.

There were 6 studies that investigated the associations of uNGAL or uIL-18 with patient mortality. Only 1 study analyzed uIL-18. Table 4 summarizes the studies where the relationship between early AKI biomarkers and mortality was evaluated. Five studies analyzed the changes in uNGAL levels depending on patient survival. Of them, 4 studies showed that uNGAL is a good prognostic marker of mortality. Zappitelli et al. did not report a statistically significant association between uNGAL and mortality. (14)

DISCUSSION

Human NGAL is expressed by neutrophils, macrophages, and epithelial cells of various tissues such as the uterus, prostate, salivary glands, lung, trachea, esophagus, colon, and kidney. (12) When these cells or organs are damaged, NGAL is released into systemic circulation (so-called systemic pool). Presence of renal failure and reduced GFR lead to a rapidly increasing NGAL concentration in systemic circulation. Therefore, the NGAL level in plasma can increase due to injury to both the kidneys and the parenchymal organs synthe-

sizing NGAL.

Data on changes in the sNGAL level among critically ill children are contradictory. Di Nardo et al. examined children with severe sepsis and did not find any significant difference in the sNGAL level comparing septic children with and without AKI. (17) In 2015, the study by McCaffrey et al. analyzed 49 patients treated in the PICUs, with 12 of them having sepsis. The authors reported that the pNGAL level was increased in septic patients, but its increase did not have any significant relationship with the development of AKI (P=0.71). (10) An increase in the urinary NGAL level directly correlated with renal tubular injury. (6) As NGAL is secreted into the urine in case of ischemic and nephrotoxic injury to distal and collecting renal tubules and its reabsorption is altered in case of injury to proximal tubules, the NGAL level in the urine increases (the so-called renal pool). Therefore, in order to determine renal injury, scientists recommend investigating early AKI biomarkers excreted with urine because they are more

specific to renal injury. (11,14,16-18,20) The first prospective study investigating NGAL in children who underwent cardiac surgery was carried out in 2005. (9) Plasma NGAL was measured in 71 patients for 5 days. The study showed that even within 2 h after surgery the NGAL level in plasma and urine was increased by 10 and 100 times respectively in patients who subsequently developed renal injury 2-3 days later. The NGAL level after 2 h in urine better correlated with disease outcome and treatment duration than the NGAL level in plasma. The patient population after cardiac surgery or with contrast-induced nephropathy represents a more homogenous group with a known onset and mechanism of renal injury. Therefore, the results obtained in this patients' group should not be compared with those recorded in the critically ill population treated in the PICUs, where neither onset, nor mechanism of renal injury is known exactly. The mechanism of AKI development among critically ill children varies a lot, and after cardiac surgery, the mechanism of ischemic renal injury prevails. (9) Scientists have started to examine children with other diseases, who are at risk of developing AKI. Du et al. evaluated five urinary biomarkers of AKI in 252 patients who arrived to an emergency center. It was shown that uNGAL, uKIM-1, and beta-2 microglobulin had good or very good accuracy (AUC >0.7 to 0.8) to predict patients who developed AKI when Cr levels still were within a reference range. However, the authors did not investigate AKI progression in hospitalized patients, 823), therefore , the evaluation of these biomarkers should in the future be available for patients at risk of developing AKI, treated in pediatric emergency centers and PICUs. Bailey et al. examined 985 patients hospitalized to the PICUs and reported that mortality was 11 times higher in patients who developed AKI than those who did not develop AKI. (4) Therefore, the evaluation of early urinary biomarkers of AKI should become a routine test as the estimation of troponin in case of myocardial infarction. This would allow reducing pediatric mortality and improving disease outcomes. Our literature review has extensively discussed statistically significant data providing evidence that uNGAL is a good predictive biomarker of AKI, associated with disease severity and outcomes.

A study by Cangemi et al. compared uNGAL levels between healthy newborns and children. This study showed that the uNGAL concentration in 25 neonates was significantly greater than that in children (neonates: mean 44.2 ng/mL, median 30.3 ng/mL, range 5.2-137.4 ng/mL; children: mean 10.2 ng/mL, median 4.6 ng/mL, range 0.2-146.7 ng/mL; P<0.0001). (24) The study evaluating the NGAL, IL-18 levels in urine of healthy children were published in 2015. Median values were: uNGAL (6,6ng/ml; IQR 2,8-17), uIL-18 (21,6pg/ml; IQR 13,6-32,9). The study showed reported that the uNGAL and uIL-18 levels differ, depending on a child's age. (25) However, the comparison of PICU-treated children who developed or did not develop AKI with healthy children showed that critically ill children had a significantly greater uNGAL level than their healthy peers (P<0.005). (17-19)

Analysis of inflammatory markers has shown that the IL-18 level increases considerably in the urine of critically ill patients. Scientists have started to assess relationships between IL-18 and AKI severity as well as disease outcome. (13,15) Washburn et al. reported that the urinary IL-18 level increased most in those critically ill children who had more severe AKI. An increase in IL-18 after 24 and 48 h from the disease onset correlated well with early development of AKI and occurred earlier than a significant rise in sCr (P=0.008). It is not only an early biomarker of AKI, but also an independent factor for mortality. The authors found a considerably greater urinary IL-18 level in children with sepsis. (15)

To date, efficient treatment strategies for AKI do not exist even though the relationship between AKI severity and mortality is obvious. (3,5,8,22) Therefore, there is a need for early AKI biomarkers that would help determine AKI etiology, duration, and severity and would allow to predict disease outcomes. Early diagnosis of AKI would allow applying preventive measures that would protect patients from the development of AKI. Therefore, many nephrologists-scientists now give priority to this area of research.

CONCLUSIONS

Urinary NGAL and IL-18 are early predictive biomarkers of acute kidney injury in critically ill children.
An increased NGAL level in the urine correlates well with disease severity.
Urinary NGAL and IL-18 are early independent predictive biomarkers of mortality in critically ill children.

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