Journal of Acute Disease

journal homepage: www.jadweb.org

Review article https://doi.org/10.12980/jad.6.2017JADWEB-2016-0069

Pediatric acute kidney injury: Appraisal of predictors and prognostic indicators

Samuel Nkachukwu Uwaezuoke*

Pediatric Nephrology Firm, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria

ARTICLE INFO

Article history:
Received 12 Sep 2016
Accepted 15 Nov 2016
Available online 8 Dec 2016

Keywords:
Acute kidney injury
Children
Predictors
Prognostic indicators

ABSTRACT

Acute kidney injury (AKI) is a major contributor to childhood morbidity and mortality worldwide. In spite of the advances in renal replacement therapy, there has been a minimal reduction in AKI-related morbidity and mortality. Identifying the prognostic indicators and the risk factors that predict disease onset and progression, and instituting appropriate measures will lead to better survival outcomes. This narrative review seeks to appraise the predictors and prognostic indicators of pediatric AKI. Several biomarkers clearly stand out as predictors and prognostic indicators of the acute disease. Some of them are urine angiotensinogen, fibroblast growth factor-23, cystacin C, neutrophil gelatinase-associated lipocalin, tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7. Combining few of these biomarkers with clinical prediction models has improved their predictive and prognostic utility for AKI. Hemodynamic parameters such as indexed systemic oxygen delivery and mean arterial blood pressure have been proved to be reliable in predicting the occurrence and progression of the disease and its outcomes. Miscellaneous predictors and prognostic indicators like AKI definition criteria, presence of co-morbidities, and health-related quality of life assessment have also been documented from evidence-based studies. An understanding and application of these indices will obviously help to reduce AKI mortality in children.

1. Introduction

Acute kidney injury (AKI) in children can be community-acquired or hospital-acquired. In both forms, it is a major contributor to pediatric morbidity and mortality worldwide[1,2]. AKI is not a single disease but rather a syndrome consisting of several clinical states. Its prognosis essentially depends on the fundamental disease, the severity and duration of renal deterioration, and the patient's pre-morbid renal status[1]. In spite of the advances in renal replacement therapy (RRT), there has been a minimal reduction in AKI-related morbidity and mortality. Identifying the prognostic indicators and the risk factors that predict disease onset and progression, and instituting appropriate measures will lead to better survival outcomes.

For instance, a group of investigators have identified a more elevated indexed systemic oxygen delivery (DO2I) and mean arterial blood pressure (MAP) as hemodynamic characteristics which are independently linked to a more reduced likelihood of stage I AKI progressing to stage III AKI[3]. A related study by other workers noted that fluid imbalance with excessive fluid administration in stage I AKI was a risk factor for progression to stage III of the acute disease[4]. Using the AKI Network (AKIN) classification, other authors reported that stages II and III AKI, severe acute pancreatitis and multiple organ failure were major prognostic indicators[5]. On the other hand, anemia was not identified as a predictor of AKI deterioration in patients hospitalized in an intensive care unit (ICU) despite the fact that it generally increases the risk of developing the disease[6]. In another retrospective study, employing the minimum value of pre-hospitalization serum creatinine as a reference parameter for renal function resulted in a better predictive ability for AKI mortality within a 60-day period[7]. Although these studies were conducted among adult patients[3-7], other researchers working on hospitalized Chinese children identified the stage of AKI, blood urea nitrogen at discharge and platelet count as independent prognostic factors for the acute disease[8]. Furthermore, urine biomarkers such

*Corresponding author: Samuel Nkachukwu Uwaezuoke, Honorary Consultant Pediatrician, Pediatric Nephrology Firm, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria.
Tel: +234 8033248108
E-mail: snuwaezuoke@yahoo.com
The journal implements double-blind peer review practiced by specially invited international editorial board members.

as tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7) have been reported as reliable predictors of poor prognoses in neonatal and childhood AKI of diverse etiology[9]. In a study, the authors identified significant independent risk factors which could predict the worsening of pediatric AKI as the use of extracorporeal membrane oxygenation, mechanical ventilation or vasopressors, intrinsic renal diseases, sepsis, and age above 1 year[10].

Expectedly, the management of AKI should be guided by the knowledge of prognostic indicators and predictors of renal deterioration which will help to reduce AKI-related morbidity and mortality. This narrative review seeks to appraise these predictors and prognostic indicators of pediatric AKI.

2. Literature search strategy

Using the keywords of acute kidney injury, children, predictors and prognostic indicators, the PubMed database was searched for relevant articles published in the previous 5 years or less. The search initially yielded 539 publications. However, a preponderance of original (research) articles and systematic reviews were retrieved, with emphasis on the literature related to pediatric AKI and the topic. Only few narrative review articles were included in the present review, and some were included through cross referencing.

3. Biomarkers as predictors and prognostic indicators of AKI

The current general clinical severity scores such as Acute Physiology and Chronic Health Evaluation, Sequential Organ Failure Assessment and AKI-specific severity scores are not reliable predictors of renal recovery; hence there is paradigm shift to novel biomarkers which have increasingly been proved to be more reliable alternative tools. Evidence-based reports show that several serum and urinary biomarkers are now dependable diagnostic tools for AKI in children[11]. Interestingly, some of these biomarkers can also serve as both predictors and prognostic indicators of the acute disease[12-14].

In a pilot study in the United States[15], pre- and post-operative levels of fibroblast growth factor 23 were measured in 19 pediatric patients without chronic kidney disease (CKD) who had undergone cardiopulmonary bypass (CPB). Five of them developed AKI, while the remaining 14 who did not develop AKI were used as controls. The results showed that fibroblast growth factor 23 could function as a pre-operative prognostic indicator of the evolution of AKI post-cardiac surgery. The authors further suggested that identifying AKI-susceptible patients as a pro-active measure would help to accomplish a better management of the acute disease, as well as fluid homeostasis[15].

Elsewhere in Germany, some researchers have demonstrated the prognostic utility of two urine biomarkers in children aged 0–18 years in a prospective cohort study of 133 patients[9]. Their study findings indicated that as diagnostic biomarkers, urine TIMP-2 and IGFBP-7 could predict adverse sequelae in neonatal and pediatric AKI which was caused by heterogeneous factors. Notably, these biomarkers are triggers of G1 cell cycle arrest - a crucial process implicated in AKI. Other investigators have also corroborated the predictive value of the two biomarkers for early AKI following other major surgeries not related to the heart[16]. Apart from serving as a sensitive and specific biomarker for early prediction of AKI post-cardiac surgery in pediatric patients with congenital heart diseases[17], urine TIMP-2 and IGFBP-7 have also been proved to be a predictor of renal recovery after AKI[18], as well as unfavorable long-term outcomes in patients with the acute disease[19]. A recent review showed that these urine biomarkers have equally been validated for the detection of AKI well ahead of clinical features like azotemia and oliguria[20]. This observation is consistent with the report of a study which indicated their diagnostic utility in the detection of patients who were at increased risk of AKI on the first post-operative day following cardiac surgery[21].

Other biomarkers like cystacin C and neutrophil gelatinase-associated lipocalin (NGAL) have also been documented as both diagnostic and prognostic tools[12,13]. For instance, as a prognostic tool, urine cystacin C/urine creatinine ratio was noted to be a predictor of mortality in hospitalized AKI patients[12]. Another report also indicated that serum cystatin C was a reliable predictor of AKI, pediatric risk, injury, failure, loss, and end-stage kidney disease (pRIFLE) classification and reduced estimated glomerular filtration rate after CPB[22]. In a recent systematic review, NGAL was found to be an effective predictor of sepsis-induced AKI, RRT and AKI-related mortality[23]. Other studies show that urine NGAL can predict renal outcome and mortality in patients with cirrhosis and associated bacterial infections[24], serve as a prognostic biomarker for AKI in hospitalized cirrhotic patients with AKI-prone conditions[13], and predict the severity of contrast-induced AKI in CKD patients undergoing coronary procedures[25]. Nevertheless, in a study which compared urine biomarkers, it was observed that urine IGFBP-7 was a more reliable predictor of renal outcome (renal recovery and AKI severity) than NGAL[26]. The former is a promising novel prognostic biomarker which still requires further evaluation.

In a pioneer study that demonstrated the usefulness of urine angiotensinogen as a prognostic biomarker of AKI after cardiac surgery, elevated urine angiotensinogen/creatinine ratio was found to be associated with unfavorable sequelae in patients with

AKI[27]. The investigators specifically noted that the prognostic and predictive power of urine angiotensinogen/creatinine ratio was high in stage I AKI patients among whom it predicted progression to stage III AKI or mortality[27]. In addition, the combination of urine angiotensinogen and renin was able to predict progression to stage III AKI in patients with stage I AKI following cardiac surgery[28]. In a related study, the authors reported that incorporating some novel biomarkers, such as plasma NGAL, matrix metalloproteinase-8, and neutrophil elastase-2, into renal angina index improved their discriminative ability for severe AKI in critically ill pediatric patients[29]. Other researchers observed that combining biomarkers (such as urine NGAL and TIMP-2 and IGFBP-7) with clinical prediction models (such as kinetic estimated glomerular filtration rate) enhanced the differentiation and re-categorization of patients who will get better from AKI or become worse with significant unfavorable renal outcomes[30].

A recently published study which was conducted in the United States among children with AKI after CPB for congenital heart disease showed that some of the novel biomarkers (interleukin 18 and liver-type fatty acid-binding protein) may hold prospects for the prediction of long-term renal sequelae after the acute disease[31]. These urine biomarkers remarkably remain raised seven years after an episode of CPB-AKI and may thus constitute a more sensitive indicator of chronic kidney injury.

One systematic review has highlighted the usefulness of pre-AKI renal function and post-AKI renal function (determined by the traditional biomarker - serum creatinine) in predicting long-term mortality and renal outcome[32]. The authors advocated that future AKI studies should consider these parameters as additional factors which can potentially modify disease prognosis, even though the long-term prognosis of AKI varies depending on etiology and clinical scenario.

4. Hemodynamic and acid-base parameters as predictors and prognostic indicators of AKI

The risk factors for AKI severity and renal deterioration can reliably predict disease outcomes. Attention is gradually being focused on the role of hemodynamic parameters such as MAP and renal oxygen delivery in risk stratification, disease progression and improvement of patient outcome[33]. However, while some researchers have noted that higher MAP and systemic oxygen delivery were renoprotective in early AKI and precluded disease progression[33], others have reported that high MAP did not reduce the risk of post-operative AKI during normothermic CPB, or change the duration of hospitalization and mortality rate[34]. In one study, critically ill patients with early AKI and DO2I > 450 mL/min/m^2 within the first 12 h of diagnosing the early stage of the disease had a significantly lower susceptibility of progressing to late disease in comparison to patients with DO2I < 450 mL/min/m^2[3].

Interestingly, the findings of another study showed that hyperthermic CPB was an independent predictor of AKI, as avoiding arterial outlet hyperthermia may help to reduce AKI risk[35]. Furthermore, few evidence-based studies indicated that the avoidance of hypotension in stage I AKI, by for instance maintaining MAP at less than 70–75 mmHg, may reduce the incidence of stage III AKI[36,37]. Some investigators recorded haemodynamic characteristics (DO2I, cardiac index, central venous pressure, MAP), hemoglobin, oxygen saturation, fluid balance and urinary output on the day of diagnosing stage I AKI with subsequent daily documentations until progression to stage III AKI or return to baseline renal function, and observed that an elevated MAP by 5 mmHg between early AKI and late AKI was independently associated with a reduced mortality risk[38]. Conversely, an increase in cumulative fluid balance by > 1 L was noted to be independently associated with a high mortality risk, underscoring the need for therapeutic plan of action to focus on maintaining adequate MAP and avoiding fluid imbalance in order to reduce mortality in critically ill patients with early AKI[38].

Other studies showed that cumulative fluid balance not only influenced AKI outcomes[39,40], but was also associated with increased likelihood of AKI deterioration over 12–72 h after onset of the acute disease[4]. Specifically, fluid overload is recognized as a key prognostic determinant in patients with AKI; one study suggested that a greater degree of fluid overload predicts a lower possibility of renal recovery that is characterized by non-dependence on RRT[40]. In clinically unstable patients with stage I AKI, a positive fluid imbalance induced by excessive fluid administration is associated with an increased risk of AKI progression and mortality[41]. Furthermore, urine output was noted to be a sensitive and early marker for AKI, and was associated with adverse outcomes in ICU patients as AKI diagnosis occurred earlier in oliguric than in non-oliguric patients[42]. For instance, oliguria of more than 12 h and oliguria of 3 or more episodes predicted a high mortality rate.

In another recent study, some investigators reported that metabolic acidosis (evidenced by low bicarbonate of less than 22 mmol/L) was a potential predictor of mortality in AKI cases which were generated by electronic alerts[43]. In addition, the patients who were reviewed a day or more after AKI alert by the Critical Care and Outreach Team, when compared with their counterparts reviewed within 24 h of the alert, were observed to have a 2.4 times rise in mortality and seven times more probability to require acute dialysis[43].

Given the documented role of hemodynamic parameters in predicting the occurrence of AKI and its outcome, it is not

surprising that the use of mechanical ventilation and vasopressors was part of the independent risk factors for disease progression, as reported in the previously mentioned study[10].

5. Other miscellaneous predictors and prognostic indicators of AKI

A recent review has revealed the usefulness of several health-related quality of life (HRQOL) tools in the assessment and management of children with CKD[44]. As a clinical measure, HRQOL assessment aims to improve quality of life outcomes in pediatric patients with CKD. Similarly, this tool has been applied to children with AKI for prognostication. HRQOL measured by Health Utilities Index Mark 3 was an independent predictor of death among survivors of AKI after modifying for clinical risk parameters[45]. Poor ambulation and other HRQOL variables were also linked with increased risk of mortality. Thus, HRQOL may arm clinicians with additional data to help identify patients at high risk of mortality following AKI that required RRT.

Several co-morbid states have also been identified as predictors of recurrent AKI. Apart from a more prolonged AKI duration, some authors have reported these predictors as congestive cardiac failure (primary diagnosis), fulminant hepatic failure, malignancy with or without chemotherapy, acute coronary syndrome, or volume depletion[46].

In one prospective study which aimed to investigate the relationship between the occurrence of AKI according to pRIFLE criteria and unfavorable outcomes in children after cardiac surgery in a tertiary health facility in Brazil, the investigators followed up the subjects during their admission in the pediatric ICU (PICU) or up to the time of mortality. The exposure variable was occurrence of AKI according to pRIFLE criteria which grouped AKI into three categories: R (risk), I (injury), and F (failure). The evaluated outcomes were mortality, duration of mechanical ventilation, and duration of PICU admission. The occurrence of AKI according to pRIFLE criteria was linked to unfavorable outcomes after cardiac surgery[47]. Other workers who assessed the applicability of pRIFLE as a prognostic tool in the ICU reported that the incidence of AKI was not only significant but positively correlated with mortality and the duration of admission in the ICU and outside the intensive care setting[48]. The pRIFLE classification therefore facilitated the definition of AKI, making it a notable predictor of disease prognosis[48]. Nevertheless, the predictive value of RIFLE urine output criteria for the evolution of contrast-induced AKI predicated upon creatinine levels was low, thus limiting its utilization for measuring the effects of treatment interventions on the onset and progression of AKI[49].

One observational study in a children's hospital has indicated that when pRIFLE was used with other definition criteria such as AKIN and Kidney Disease: Improving Global Outcomes, AKI was associated with higher mortality and longer duration of stay within and outside the ICU[50]. The three definition criteria however resulted in disparities in the incidence and staging of the acute disease. The findings of other similar studies appear to be in line with this observation. For instance, the pRIFLE was the most sensitive classification in detecting AKI, especially in infancy, as well as in the early identification of the acute disease in low-risk patients. The AKIN definition was more specific and detected mostly high-risk patients across all age groups. The performance of Kidney Disease: Improving Global Outcomes classification stayed between pRIFLE and AKIN. All the three classifications showed AKI deterioration which was related to mortality[51]. The AKIN classification however correlated better with mortality than the RIFLE criteria did[52].

In a retrospective study conducted in a PICU, stage I AKI when evaluated with pRIFLE criteria could predict prolonged ICU admission, need for prolonged mechanical ventilation, as well as mortality[53]. Another study which evaluated the performance of pRIFLE score for AKI diagnosis and prognosis among infants with congenital heart diseases after cardiac surgery, revealed that the method was seamlessly applied to these patients. The pRIFLE classification showed that AKI incidence was not only high but was also associated with poorer outcomes[54].

6. Conclusions

The role of biomarkers as predictors and prognostic indicators of AKI is now well established despite the differences in sensitivity and specificity. While their employment as novel diagnostics is presently the norm; there is need for more discovery of prognostic biomarkers which can predict disease severity early enough. Combining some of the biomarkers with clinical prediction models has improved their predictive and prognostic utility for AKI. Hemodynamic parameters have equally been proved to be reliable in predicting the occurrence and progression of the acute disease and its outcomes. Miscellaneous predictors and prognostic indicators such as AKI definition criteria, presence of co-morbidities, and HRQOL assessment have also been documented from evidence-based studies. An understanding and application of these indices will obviously help to reduce AKI mortality in children.

Conflict of interest statement

The author reports no conflict of interest.

References

[1] Singbartl K, Kellum KA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. *Kidney Int* 2012; **81**(9): 819-25.

[2] Jha V, Parameswaran S. Community-acquired acute kidney injury in

tropical countries. *Nat Rev Nephrol* 2013; **9**: 278-90.

[3] Raimundo M, Crichton S, Syed Y, Martin JR, Beale R, Treacher D, et al. Low systemic oxygen delivery and bp and risk of progression of early AKI. *Clin J Am Soc Nephrol* 2015; **10**(8): 1340-9.

[4] Raimundo M, Crichton S, Martin JR, Syed Y, Varrier M, Wyncoll D, et al. Increased fluid administration after early acute kidney injury is associated with less renal recovery. *Shock* 2015; **44**(5): 431-7.

[5] Zhou J, Yang L, Zhang K, Liu Y, Fu P. Risk factors for the prognosis of acute kidney injury under the Acute Kidney Injury Network definition: a retrospective, multicenter study in critically ill patients. *Nephrology* (*Carlton*) 2012; **17**(4): 330-7.

[6] Powell-Tuck J, Crichton S, Raimundo M, Camporota L, Wyncoll D, Ostermann M. Anaemia is not a risk factor for progression of acute kidney injury: a retrospective analysis. *Crit Care* 2016; **20**: 52.

[7] Thongprayoon C, Cheungpasitporn W, Kittanamongkolchai W, Srivali N, Ungprasert P, Kashani K. Optimum methodology for estimating baseline serum creatinine for the acute kidney injury classification. *Nephrology* (*Carlton*) 2015; **20**(12): 881-6.

[8] Zhou YM, Yin XL, Huang ZB, He YH, Qiu LR, Zhou JH. Risk factors and prognostic factors of acute kidney injury in children: a retrospective study between 2003 and 2013. *J Huazhong Univ Sci Technolog Med Sci* 2015; **35**(6): 785-92.

[9] Westhoff JH, Tönshoff B, Waldherr S, Pöschl J, Teufel U, Westhoff TH, et al. Urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) • insulin-like growth factor-binding protein 7 (IGFBP7) predicts adverse outcome in pediatric acute kidney injury. *PLoS One* 2015; **10**(11): e0143628.

[10] Chang JW, Jeng MJ, Yang LY, Chen TJ, Chiang SC, Soong WJ, et al. The epidemiology and prognostic factors of mortality in critically ill children with acute kidney injury in Taiwan. *Kidney Int* 2015; **87**(3): 632-9.

[11] Uwaezuoke SN. Acute kidney injury in children: enhancing diagnosis with novel biomarkers. *J Acute Dis* 2016; **5**(4): 267-70.

[12] Park MY, Choi SJ, Kim JK, Hwang SD, LeeYW. Urinary cystatin C levels as a diagnostic and prognostic biomarker in patients with acute kidney injury. *Nephrology* (*Carlton*) 2013; **18**(4): 256-62.

[13] Treeprasertsuk S, Wongkarnjana A, Jaruvongvanich V, Sallapant S, Tiranathanagul K, Komolmit P, et al. Urine neutrophil gelatinase-associated lipocalin: a diagnostic and prognostic marker for acute kidney injury (AKI) in hospitalized cirrhotic patients with AKI-prone conditions. *BMC Gastroenterol* 2015; **15**: 140.

[14] Ronco C, Legrand M, Goldstein SL, Hur M, Tran N, Howell EC, et al. Neutrophil gelatinase-associated lipocalin: ready for routine clinical use? An international perspective. *Blood Purif* 2014; **37**(4): 271-85.

[15] Ali FN, Hassinger A, Price H, Langman CB. Preoperative plasma FGF23 levels predict acute kidney injury in children: results of a pilot study. *Pediatr Nephrol* 2013; **28**(6): 959-62.

[16] Gocze I, Koch M, Renner P, Zeman F, Graf BM, Dahlke MH, et al. Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. *PLoS One* 2015; **10**(3): e0120863.

[17] Meersch M, Schmidt C, Van Aken H, Rossaint J, Görlich D, Stege D, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury after pediatric cardiac surgery. *PLoS One* 2014; **9**(10): e110865.

[18] Meersch M, Schmidt C, Van Aken H, Martens S, Rossaint J, Singbartl K, et al. Urinary TIMP-2 and IGFBP-7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. *PLoS One* 2014; **9**(3): e93460.

[19] Koyner JL, Shaw AD, Chawla LS, Hoste EA, Bihorac A, Kashani K, et al. Tissue inhibitor metalloproteinase-2 (TIMP-2)·IGF-binding protein-7 (IGFBP-7) levels are associated with adverse long-term outcomes in patients with AKI. *J Am Soc Nephrol* 2015; **26**: 1747-54.

[20] Kellum JA, Chawla LS. Cell-cycle arrest and acute kidney injury: the light and the dark sides. *Nephrol Dial Transplant* 2016; **31**(1): 16-22.

[21] Wetz AJ, Richardt EM, Wand S, Kunze N, Schotola H, Quintel M, et al. Quantification of urinary TIMP-2 and IGFBP-7: an adequate diagnostic test to predict acute kidney injury after cardiac surgery? *Crit Care* 2015; **19**(1): 3.

[22] Hassinger AB, Backer CL, Lane JC, Haymond S, Wang D, Wald EL. Predictive power of serum cystatin C to detect acute kidney injury and pediatric-modified RIFLE class in children undergoing cardiac surgery. *Pediatr Crit Care Med* 2012; **13**(4): 435-40.

[23] Zhang A, Cai Y, Wang PF, Qu JN, Luo ZC, Chen XD, et al. Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: a systematic review and meta-analysis. *Crit Care* 2016; **20**: 41.

[24] Barreto R, Elia C, Solà E, Moreira R, Ariza X, Rodríguez E, et al. Urinary neutrophil gelatinase-associated lipocalin predicts kidney outcome and death in patients with cirrhosis and bacterial infections. *J Hepatol* 2014; **61**(1): 35-42.

[25] Tasanarong A, Hutayanon P, Piyayotai D. Urinary neutrophil gelatinase-associated lipocalin predicts the severity of contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures. *BMC Nephrol* 2013; **14**: 270.

[26] Aregger F, Uehlinger DE, Witowski J, Brunisholz RA, Hunziker P, Frey FJ, et al. Identification of IGFBP-7 by urinary proteomics as a novel prognostic marker in early acute kidney injury. *Kidney Int* 2014; **85**(4): 909-19.

[27] Alge JL, Karakala N, Neely BA, Janech MG, Tumlin JA, Chawla LS, et al. Urinary angiotensinogen and risk of severe AKI. *Clin J Am Soc Nephrol* 2013; **8**(2): 184-93.

[28] Alge JL, Karakala N, Neely BA, Janech MG, Tumlin JA, Chawla LS, et al. Association of elevated urinary concentration of renin-angiotensin system components and severe AKI. *Clin J Am Soc*

Nephrol 2013; **8**(12): 2043-52.

[29] 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.

[30] Dewitte A, Joannès-Boyau O, Sidobre C, Fleureau C, Bats ML, Derache P, et al. Kinetic eGFR and novel AKI biomarkers to predict renal recovery. *Clin J Am Soc Nephrol* 2015; **10**(11): 1900-10.

[31] Cooper DS, Claes D, Goldstein SL, Bennett MR, Ma Q, Devarajan P, et al. Follow-up renal assessment of injury long-term after acute kidney injury (FRAIL-AKI). *Clin J Am Soc Nephrol* 2016; **11**(1): 21-9.

[32] Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. *BMJ Open* 2015; **4**: e006497.

[33] Koyner JL. The golden hours of AKI: is oxygen delivery the key? *Clin J Am Soc Nephrol* 2015; **10**(8): 1311-3.

[34] Azau A, Markowicz P, Corbeau JJ, Cottineau C, Moreau X, Baufreton C, et al. Increasing mean arterial pressure during cardiac surgery does not reduce the rate of postoperative acute kidney injury. *Perfusion* 2014; **29**(6): 496-504.

[35] Newland RF, Tully PJ, Baker RA. Hyperthermic perfusion during cardiopulmonary bypass and postoperative temperature are independent predictors of acute kidney injury following cardiac surgery. *Perfusion* 2013; **28**(3): 223-31.

[36] Poukkanen M, Wilkman E, Vaara ST, Pettilä V, Kaukonen KM, Korhonen AM, et al. Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study. *Crit Care* 2013; **17**: R295.

[37] Redfors B, Bragadottir G, Sellgren J, Swärd K, Ricksten SE. Effects of norepinephrine on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. *Intensive Care Med* 2011; **37**: 60-7.

[38] Raimundo M, Crichton S, Syed Y, Martin J, Lemmich Smith J, Bennett D, et al. Reduced blood pressure and fluid accumulation in critically ill patients with early AKI are associated with increased mortality. *Nephrol Dial Transplant* 2012; **27**(Suppl 2): ii358.

[39] Teixeira C, Garzotto F, Piccinni P, Brienza N, Iannuzzi M, Gramaticopolo S, et al. Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. *Crit Care* 2013; **17**: R14.

[40] Heung M, Wolfgram DF, Kommareddi M, Hu Y, Song PX, Ojo AO. Fluid overload at initiation of renal replacement therapy is associated with lack of renal recovery in patients with acute kidney injury. *Nephrol Dial Transplant* 2012; **27**: 956-61.

[41] Raimundo MR, Crichton S, Syed Y, Martin J, Ostermann M. Fluid accumulation increases the risk of AKI progression and death in critically ill patients with early AKI. *Crit Care* 2014; **18**(Suppl 1): S134-5.

[42] Macedo E, Malhotra R, Bouchard J, Wynn SK, Mehta RL. Oliguria is an early predictor of higher mortality in critically ill patients. *Kidney Int* 2011; **80**(7): 760-7.

[43] Prendecki M, Blacker E, Sadeghi-Alavijeh O, Edwards R, Montgomery H, Gillis S, et al. Improving outcomes in patients with acute kidney injury: the impact of hospital based automated AKI alerts. *Postgrad Med J* 2016; **92**(1083): 9-13.

[44] Uwaezuoke SN, Muoneke VU. Role of health-related quality of life assessment in children with chronic kidney disease. *Curr Pediatr Res* 2015; **19**(1&2): 45-50.

[45] Joyce VR, Smith MW, Johansen KL, Unruh ML, Siroka AM, O'Conno TZr, et al. Health-related quality of life as a predictor of mortality among survivors of AKI. *Clin J Am Soc Nephrol* 2012; **7**(7): 1063-70.

[46] Siew ED, Parr SK, Abdel-Kader K, Eden SK, Peterson JF, Bansal N, et al. Predictors of recurrent AKI. *J Am Soc Nephrol* 2016; **27**(4): 1190-200.

[47] dos Santos El Halal MG, Carvalho PR. Acute kidney injury according to pediatric RIFLE criteria is associated with negative outcomes after heart surgery in children. *Pediatr Nephrol* 2013; **28**(8): 1307-14.

[48] Bresolin N, Bianchini AP, Haas CA. Pediatric acute kidney injury assessed by pRIFLE as a prognostic factor in the intensive care unit. *Pediatr Nephrol* 2013; **28**(3): 485-92.

[49] Hocine A, Defrance P, Lalmand J, Delcour C, Biston P, Piagnerelli M. Predictive value of the RIFLE urine output criteria on contrast-induced nephropathy in critically ill patients. *BMC Nephrol* 2016; **17**: 36.

[50] Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol* 2015; **10**(4): 554-61.

[51] Lex DJ, Tóth R, Cserép Z, Alexander SI, Breuer T, Sápi E, et al. A comparison of the systems for the identification of postoperative acute kidney injury in pediatric cardiac patients. *Ann Thorac Surg* 2014; **97**(1): 202-10.

[52] Bastin AJ, Ostermann M, Slack AJ, Diller GP, Finney SJ, Evans TW. Acute kidney injury after cardiac surgery according to Risk/Injury/Failure/Loss/End-stage, Acute Kidney Injury Network, and Kidney Disease: Improving Global Outcomes classifications. *J Crit Care* 2013; **28**(4): 389-96.

[53] Gil-Ruiz Gil-Esparza MA, Alcaraz Romero AJ, Romero Otero A, Gil Villanueva N, Sanavia Morán E, Rodríguez Sánchez de la Blanca A, et al. Prognostic relevance of early AKI according to pRIFLE criteria in children undergoing cardiac surgery. *Pediatr Nephrol* 2014; **29**(7): 1265-72.

[54] Ricci Z, Di Nardo M, Iacoella C, Netto R, Picca S, Cogo P. Pediatric RIFLE for acute kidney injury diagnosis and prognosis for children undergoing cardiac surgery: a single-center prospective observational study. *Pediatr Cardiol* 2013; **34**(6): 1404-8.