Value of urinary kidney injury molecule-1 levels in predicting acute kidney injury in very low birth weight preterm infants

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Abstract

Objective: This study aimed to evaluate the significance of urinary kidney injury molecule-1 (uKIM-1) levels in predicting acute kidney injury (AKI) and mortality in very low birth weight (VLBW) preterm infants.

Methods: This prospective, observational cohort study was conducted on 39 VLBW preterm infants. Serum creatinine (SCr) and uKIM-1 levels were measured in the first 24 and 48 to 72 hours of life. The estimated glomerular filtration rate (eGFR) was calculated. Levels of uKIM-1 were measured with an enzyme-linked immunosorbent assay.

Results: Among 39 VLBW infants, 9 (23%) developed AKI. The mortality rate was 17.9% (n = 7 neonates). There was no significant difference in SCr levels, uKIM-1 levels, or the eGFR obtained in the first 24 hours in the AKI group compared with controls. However, significant differences were found in SCr and uKIM-1 levels, and the eGFR rate at 48 to 72 hours between the groups. Levels of uKIM-1 were significantly higher in non-survivors than in survivors in the first 24 and 48 to 72 hours of life.

Conclusion: The level of uKIM-1 can be used as a simple noninvasive diagnostic method for predicting AKI and mortality, especially within 48 to 72 hours of life.

Clinical trial registration: We do not have a clinical trial registration ID. In Turkey, clinical trial registration is not required for non-drug, noninvasive, clinical studies.

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Introduction

The survival of very low birth weight (VLBW) preterm infants has dramatically increased with advances in neonatal intensive care technology and improvement in treatment policies of the last four decades. Despite these advances, acute kidney injury (AKI) still causes significant morbidity and mortality in these infants. The mortality rate due to AKI is higher in preterm infants than in other age groups. Additionally, the mortality rate is higher in neonates with AKI than in those without AKI.[1] One important cause of mortality and morbidity is the inability to diagnose AKI in the early course.

Kidney injury molecule-1 (KIM-1) is an epithelial cell adhesion protein containing an immunoglobulin-binding end. KIM-1 is type 1 transmembrane protein located in the proximal tubules and has shown an increase in expression following ischemic or toxic renal injury in experimental and clinical studies.[2–7] KIM-1 mRNA and protein levels are low in the normal kidney, but they dramatically increase after post-ischemic kidney injury.[6] KIM-1 is suggested to be a useful indicator in showing AKI in humans and can be used as a sensitive biological indicator of tubular damage.[4,5,7–11]

Currently, data have not suggested any new biological parameter as an indicator of risk stratification in newborns and VLBW preterm infants with AKI. Therefore, this study aimed to investigate the value of urinary KIM-1 (uKIM-1) levels in predicting acute kidney damage in VLBW preterm infants and for stratifying a risk group for development of AKI.

Materials and methods

This study was approved by the Local Ethic Committee of Tepecik Training and Research Hospital (No: 2010/7/5) and all procedures were carried out by referring to the Declaration of Helsinki. Written informed consent was obtained from the parents of the VLBW infants before enrollment in the study.

Study population

This prospective, observational cohort study enrolled VLBW preterm infants who were admitted to our Level III neonatal intensive care unit within the first 24 hours after birth. Newborns with a major congenital anomaly, inborn errors of metabolism, antenatal urinary tract anomalies, a history of inherited kidney disease, and intrauterine growth restriction, and those who died within the first 48 hours of life were excluded.

Data collection and definitions

All clinical information, including birth weight, gestational age, sex, delivery type, antenatal steroid, neonatal morbidities, such as respiratory distress syndrome, requirement for mechanical respiratory support, intraventricular hemorrhage, retinopathy of prematurity, and bronchopulmonary dysplasia were recorded. Renal function data were collected for time points corresponding to urine collections, including urine output, serum creatinine (SCr), and blood urea nitrogen. Urine output was measured on the basis of a strict intake and output monitoring protocol per neonatal

intensive care unit standard of care (calculation of corrected diaper weight every 3 hours). Oliguria was defined as urine output <1 mL/kg/hour daily after the first day of life.

To ascertain whether a VLBW preterm infant developed AKI, SCr levels were measured in the first 24 hours of life and at 48 to 72 hours after delivery. The diagnosis of AKI was defined according to the Kidney Disease: Improving Global Outcomes workgroup AKI definition, which was modified for newborns, as previously published (Table 1).[12,13]

Urine output criteria were not taken into account for a criterion of AKI in this study because of the evidence that premature infants often have non-oliguric AKI due to immature tubular development.[14] The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula.[15]

Urinary KIM-1 measurement

Urine samples were obtained at 12 to 24 and 48 to 72 hours postnatally from all VLBW infants. Urine samples were stored in aliquots at −20°C until later assay. Levels of uKIM-1 were measured by an enzyme-linked immunosorbent assay method (USCN Life Science, Hankou, Wuhan, China). The detection range for the uKIM-1 kit was 0.156 to 10 ng/mL and the minimum detectable value was 0.042 ng/mL.

Statistical analysis

Statistical analyses were performed using IBM SPSS software (version 20.0; IBM Corp., Armonk, NY, USA). The mean value of continuous variables is expressed as mean ± standard deviation. The Mann–Whitney U-test and χ^2 test were used to determine the differences between two groups and p values <0.05 were accepted as statistically significant. To control for gestational age and birth weight as potential confounders, linear regression analyses were performed to evaluate uKIM-1 levels for predicting mortality and AKI.

Receiver operating characteristic (ROC) analysis was performed to quantify how accurately uKIM-1 levels can discriminate between patients with AKI and controls (no AKI).[16] To determine the specificity of uKIM-1 levels, the ROC curve and associated area under the curve (AUC) values were calculated. The AUC values were distributed between 0.5 and 1.0. A parameter with a value of 0.5 indicated that the parameter had no determinative value, whereas a value of 1.0 represented a highly determinative value. The Hosmer–

Table 1. Modified Kidney Disease: Improving Global Outcomes definition of acute kidney injury used in the study.

AKI stage	SCr	Urine output
0	No change in SCr levels or an increase	≥0.5 mL/kg/hour
1	Increase in SCr levels ≥26.52 μmol/L within 48 hours or an increase in SCr levels ≥133–168 μmol/L × reference SCr[a] within 7 days	<0.5 mL/kg/hour for 6–12 hours
2	Increase in SCr levels ≥177–256 μmol/L × reference SCr[a]	<0.5 mL/kg/hour for ≥12 hours
3	Increase in SCr levels ≥265 μmol/L × reference SCr[a], SCr levels ≥221 μmol/L, or receipt of dialysis	<0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours

[a]The baseline SCr level was defined as the lowest previous SCr value.
SCr, serum creatinine.

Lemeshow test was used to assess model fitting. Additionally, the sensitivity and specificity of the cutoff scores were determined.

Results

Forty-three VLBW preterm infants were enrolled in this prospective study. Of these, four were excluded from the study because three were referred to the hospital 24 hours after delivery and one died within 24 hours after admission. The mean gestational age was 28.5±2.7 weeks, the mean birth weight was 1130±338.5 g, and 24 (61.5%) newborns were boys. Sixteen newborns were delivered vaginally. Antenatal steroid was administered to 12 (30.8%) VLBW infants. AKI was present in 23% (n = 9) of patients and 30 patients had no AKI. Stage 1 AKI was detected in six (66.7%) of nine patients with acute kidney damage, whereas stage 2 AKI was found in three (33.3%) at 48 to 72 hours of life.

Table 2 shows the differences in VLBW infants' characteristics between those with AKI and controls. The mean birth weight was significantly lower in the AKI group than in the control group (p = 0.003). Similarly, the mean gestational age was significantly lower in the AKI group than in the control group (p = 0.015). There was no

significant difference in sex or the mode of delivery between the two groups. The rates of patent ductus arteriosus (PDA), perinatal asphyxia, and hypotension were significantly higher in the AKI group than in the control group (p = 0.02, p = 0.032, and p < 0.001, respectively). Boluses of normal saline were provided to 33.3% (4/12) of the hypotensive newborns. Dopamine was used in 66.7% (8/12) of the hypotensive newborns and dobutamine was used in 58.3% (7/12). The preterm hypotensive newborns received a combination of dobutamine and dopamine when hypotension was severe and refractory to one vasomotor agent. The mortality rate was significantly higher in the AKI group than in the control group (p<0.001) (Table 2). The median age of mortality was 4 days (range: 3–7 days).

There was no significant difference in SCr, uKIM-1, or eGFR values obtained in the first 24 hours between the groups (Table 3). In contrast, SCr and uKIM-1 levels were significantly higher and the eGFR was lower at 48 to 72 hours in the AKI group than in the control group (all p<0.01).

Overall, the mortality rate was 17.9% (7 neonates) in the VLBW infants. The mean birth weight was 860 ± 198 g in non-survivors and 1189 ± 335 g in survivors (p = 0.01). Although the mean gestational

Table 2. Clinical characteristics of very low birth weight infants with and without AKI.

Variable	AKI group (n = 9)	Control group (n = 30)	p
Birth weight (g)*	858.8±166	1211.6±335	**0.003**
Gestational age (weeks)*	26.7±1.5	29.1±2.8	**0.015**
Male sex, n (%)	5 (55.6)	19 (63.3)	0.67
Cesarean delivery, n (%)	4 (44.4)	19 (63.3)	0.31
Maternal preeclampsia, n (%)	4 (44.4)	5 (16.7)	0.17
Respiratory distress syndrome, n (%)	9 (100)	27 (90)	0.32
Perinatal asphyxia, n (%)	5 (55.6)	5 (16.6)	**0.032**
Patent ductus arteriosus, n (%)	7 (77.7)	9 (30)	**0.02**
Hypotension, n (%)	8 (88.8)	4 (13.3)	**<0.001**
Mortality, n (%)	6 (66)	1 (3.3)	**<0.001**

*Data are mean ± standard deviation.

AKI, acute kidney injury.

Table 3. Comparison of serum creatinine levels, the eGFR, and uKIM-1 levels in very low birth weight infants with AKI.

	AKI group (n=9)		Control group (n=30)		
	Mean ± SD	Median (25%, 75%)	Mean ± SD	Median (25%, 75%)	p
Creatinine (μmol/L) (0–24 hours)	73.3 ± 17.6	70.7 (53.0, 97.2)	69.8 ± 17.6	70.7 (61.8, 79.5)	0.94
Creatinine (μmol/L) (48–72 hours)	123.7 ± 17.6	141.4 (114.9, 141.4)	88.4 ± 17.6	88.4 (79.5, 97.2)	0.001
uKIM-1 (pg/mL) (0–24 hours)	969 ± 888	654 (272, 1478)	653 ± 618	420 (253, 773)	0.27
uKIM-1 (pg/mL) (48–72 hours)	1125 ± 574	1020 (824, 1388)	549.8 ± 454	341 (264, 734)	0.005
eGFR (mL/minute/1.73 m^2) (0–24 hours)	11.6 ± 2.3	11.9 (9.4, 13.7)	12.6 ± 2.7	12.5 (10.2, 14.8)	0.32
eGFR (mL/minute/1.73 m^2) (48–72 hours)	7.8 ± 1.8	7.2 (6.8, 9.6)	12.1 ± 2.5	11.6 (10.6, 14.8)	0.001

eGFR, estimated glomerular filtration rate; uKIM-1, urinary kidney injury molecule-1; AKI, acute kidney injury; SD, standard deviation.

age appeared to be lower in non-survivors, there was no significant difference between the groups (p = 0.17). The frequency of AKI was significantly higher in patients who died than in those who survived (six versus one patient, p<0.001). However, there were no significant differences in sex, type of delivery, and frequency of antenatal steroid administration between survivors and non-survivors.

There was no significant difference in SCr levels or eGFR values in the first 24 hours between the survivors and non-survivors. However, SCr levels were significantly higher and the eGFR was lower in non-survivors than in survivors at 48 to 72 hours postnatally (both p < 0.01). Levels of uKIM-1 were significantly higher in survivors than in non-survivors in the first 24 hours of life and at 48 to 72 hours (p = 0.04 and p = 0.01, respectively) (Table 4).

Figure 1 shows the ROC curve of uKIM-1 levels in the first 24 hours of life and at 48 to 72 hours. In determining AKI, the AUC value of uKIM-1 levels at 0 to 24 hours was 0.62 and it was 0.81 for 48 to 72 hours. To predict mortality, the AUC value of uKIM-1 levels at 0 to 24 hours was 0.44 and it was 0.92 at 48 to 72 hours (Figure 2). The positive predictive values of uKIM-1 levels for AKI and mortality were low, whereas the negative predictive values were high (Table 5).

To control for gestational age and birth weight as potential confounders, multiple logistic regression analysis was performed to evaluate uKIM-1 levels for predicting AKI and mortality. We found that uKIM-1 levels at 48 to 72 hours postnatally were an independent factor for predicting the presence of AKI and a higher mortality rate (p = 0.03, estimation coefficient: 2.2 and = p = 0.01, estimation coefficient: 2.5, respectively).

Discussion

This study aimed to investigate the significance of uKIM-1 levels in predicting development of AKI and mortality in VLBW preterm infants as a stratified risk group. We found that uKIM-1 levels that were measured between 48 and 72 hours of life

Table 4. Comparison of serum creatinine levels, the eGFR, and uKIM-1 levels in survivors and non-survivors.

	Non-survivors (n=7)		Survivors (n=32)		
	Mean ± SD	Median (25%, 75%)	Mean ± SD	Median (25%, 75%)	p
Creatinine (μmol/L) (0–24 hours)	68.0 ± 8.8	70.7 (53.0, 79.5)	70.7 ± 0.17.6	70.7 (61.8, 79.5)	0.64
Creatinine (μmol/L) (48–72 hours)	132.6 ± 17.6	141.4 (114.9, 141.4)	88.4 ± 17.6	88.4 (79.5, 97.2)	0.001
uKIM-1 (pg/mL) (0–24 hours)	1189 ± 921.6	912 (540, 1708)	624.5 ± 600.4	391 (253, 719)	0.04
uKIM-1 (pg/mL) (48–72 hours)	1264.2 ± 729.8	1020 (739, 2025)	555.5 ± 395	359 (269, 867)	0.01
eGFR (mL/minute/1.73 m^2) (0–24 hours)	12.2 ± 2.2	12.7 (9.9, 14.5)	12.4 ± 2.7	12.1 (10, 14.7)	0.85
eGFR (mL/minute/1.73 m^2) (48–72 hours)	7.6 ± 1.4	7.2 (6.4, 9.0)	11.9 ± 2.6	11.4 (10.5, 14.6)	0.003

eGFR, estimated glomerular filtration rate; uKIM-1, urinary kidney injury molecule-1; SD, standard deviation.
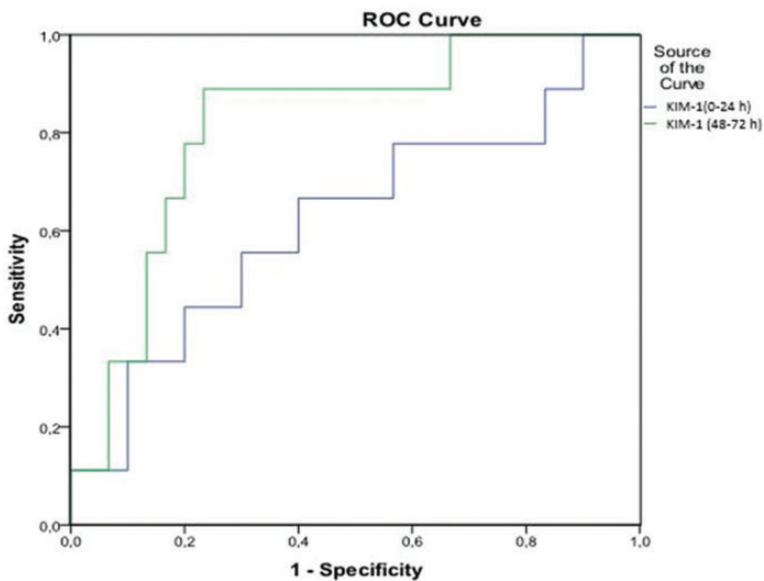
Figure 1. Urinary KIM-1 levels for predicting acute kidney injury.
KIM-1, kidney injury molecule-1.

were an easy, reliable and non-invasive method for predicting AKI in VLBW newborns. We believe that this finding will be helpful for reviewing pharmacological treatments and other intensive care support applied to newborns with a high risk of AKI. However, further studies are required on this issue.
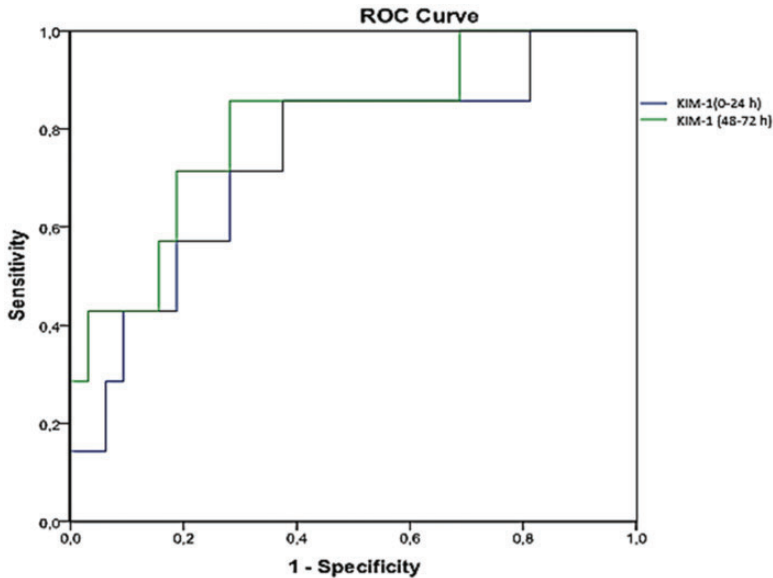
Figure 2. Urinary KIM-1 levels for predicting mortality.
KIM-1, kidney injury molecule-1.

Table 5. Levels of uKIM-1 for predicting AKI and mortality.

	uKIM-1 (0–24 hours)		uKIM-1 (48–72 hours)	
	AKI	Mortality	AKI	Mortality
Sensitivity	66%	85 %	88%	85%
Specificity	56%	59%	63%	59%
PPV	31%	31%	42%	31%
NPV	85%	95%	95%	95%
AUC	0.62	0.44	0.81	0.92

uKIM-1, urinary kidney injury molecule-1; AKI, acute kidney injury; PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve.

The diagnosis of AKI is based on SCr levels and urine output. Because newborns often have non-oliguric renal insufficiency, urinary output is not a sensitive indicator for AKI. The SCr level reflects the maternal SCr level in the first few days after birth.[17] Therefore, SCr levels are also not a reliable test, especially for newborns, for the diagnosis of AKI.[18] Therefore, there is an urgent requirement to predict AKI in the neonatal period. Currently, there is no proven ideal marker for predicting AKI in preterm infants.[19,20]

KIM-1 is a transmembrane protein, which is increased following ischemic or nephrotoxic AKI. Measurement of uKIM-1 levels is a useful test for diagnosing AKI in adulthood.[3,21,22] A clinical study that evaluated urine biomarkers in AKI showed that uKIM-1 levels were significantly higher in patients than in the control group, and were not affected by urinary tract

infection.[11] In another study, a high KIM-1 level was suggested as a reliable marker for diagnosis of AKI.[23] KIM-1 is recommended as an ideal indicator for diagnosing kidney injury because KIM-1 expression is absent in the normal kidney.[8] In our study, which only included patients with AKI in the neonatal period, we found that uKIM-1 levels were significantly higher in the AKI group than in the control group at 48 to 72 hours. However, despite, the finding that uKIM-1 levels were higher in the first 24 hours of life in the AKI group than in the control group, this was not significant.

Askenazi et al.[24] found that uKIM-1 levels did not show any significant difference between neonates with AKI and the control group, but its significance increased together with other biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL). In our study, determination of uKIM-1 levels in predicting AKI was evaluated with the ROC curve. We found that uKIM-1 levels were a good predictor of AKI when it was measured between 48 to 72 hours. In a study of 20 pediatric patients who underwent cardiopulmonary bypass surgery, uKIM-1 levels were significantly higher in patients who developed AKI in the postoperative period compared with the control group.[11] Additionally, the AUC value calculated by the ROC curve for determining acute kidney damage at 12 hours postoperatively was 0.83. Askenazi et al.[24] reported that the AUC value of uKIM-1 levels for predicting AKI was 0.63. However, they collected urine samples from patients in the first 4 days of life and urine sampling in their patients was not standard. These factors may explain why uKIM-1 levels and AUC values were different in their study from those in our study.

Perinatal asphyxia is one of the most common causes of AKI in newborns.[18] In a multicenter study of 113 infants with neonatal encephalopathy with ≥34 weeks' gestation, the incidence of AKI was 41.8%.[25] Additionally, in this previous study, the duration of hospital stay in those with AKI was found to be significantly longer than those without AKI. In a previous study of term newborns with perinatal asphyxia, NGAL levels were significantly higher in umbilical cord blood in the first 24 hours of life and in serum at 24 hours after birth in asphyxiated newborns who developed AKI compared with those without AKI.[26] Additionally, the AUC of the ROC of NGAL for predicting AKI at 24 hours after birth was 0.93. In our study, five (55.6%) of nine newborns with acute kidney damage had perinatal asphyxia. When patients with AKI and the control group were compared in terms of perinatal and clinical risk factors, we found that the rate of perinatal asphyxia was significantly higher in patients with AKI than in controls.

PDA is a common complication of preterm infants. A shunt across a PDA can cause an unfavorable distribution of cardiac output and may lead to poor renal perfusion.[27] This could cause AKI or renal dysfunction due to ischemia. Additionally, non-steroidal anti-inflammatory drugs, which are the standard pharmacological treatment of PDA, can cause renal damage with a reduction in renal perfusion and urine output. A recent study showed that moderate-to-large PDA in preterm infants < 28 weeks of gestational age was strongly associated with any stage of AKI.[28] Additionally, developing any stage of AKI was 5.3 times greater in preterm infants with moderate-large PDA.[28] However, in another report, PDA was not an independent risk factor for development of AKI in preterm infants.[29] In our study, we found that PDA was a significant risk factor in VLBW infants with AKI compared with controls.

Renal blood flow may also be directly impaired in states of hypotension and this

condition can cause pre-renal AKI.[30] Inotropic support used in treating hypotension may also cause AKI owing to renal vasoconstriction. Lower systolic blood pressure and inotropic support were independent risk factors for developing AKI in preterm infants in a previous study.[29] Another study showed that developing any stage of AKI was 3.67 times greater in preterm infants with hypotension.[28] In the present study, we found that the rate of hypotension was significantly higher in patients with AKI than in controls.

Despite an increase in diagnosis and treatment modalities in AKI, the mortality rate in newborns remains high, ranging from 10% to 61%.[31] Csaicsich et al.[32] reported a 69% mortality rate in VLBW preterm infants with AKI. Askenazi et al.[33] showed that developing AKI increased the rate of mortality in VLBW infants by approximately four times and every 1 mg/dL increase in SCr levels increased mortality by 1.94 times in this group. The mortality rate in our study was 17.9%. Six of the nine VLBW infants with AKI died in contrast to only one without AKI. In concordance with other published studies,[19,34,35] we found that the mortality rate in VLBW infants with AKI was significantly higher than that in controls. Because only one patient was lost in the control group in our study, we were not able to evaluate the effect of uKIM-1 levels on mortality in this study. Further studies involving more patients are required to determine this effect.

AKI is a clinical picture that independently affects mortality in VLBW preterm infants.[3,5] The secondary objective of our study was to evaluate the predictive value of uKIM-1 levels for mortality. Askenazi et al.[20] reported that the diagnostic value of uKIM-1 levels in determining the mortality rate was statistically significant and powerful. In our study, we also found that uKIM-1 levels were a reliable indicator in predicting mortality in VLBW preterm infants.

The levels of biomarkers for detecting AKI are inversely related to gestational age and birthweight owing to glomerular and tubular immaturity in premature newborns.[36] A recent study showed that there is a complex relationship between early renal biomarkers and perinatal characteristics in VLBW healthy preterm infants during the first few days of life.[37] In particular, gestational age, the presence of PDA, and antenatal maternal hypertension were significantly associated with levels of SCr, NGAL, and cystatin C after birth.[37]

In our study, regression analysis showed that uKIM-1 levels at 48 to 72 hours postnatally were an independent factor in predicting AKI. Additionally, repetitive measurement uKIM-1 levels at 48 to 72 hours of life was also a significant predictor of AKI, regardless of gestational age and birth weight. In a study on 30 VLBW infants, uKIM-1 levels were an independent effective factor in predicting AKI and mortality, which is consistent with our results.[8]

One limitation of our study is that we examined the association between uKIM-1 levels and occurrence of AKI in non-survivors in a small number of patients. Furthermore, because of the high occurrence of AKI in the non-survivor group, the association that we found between uKIM-1 levels and high mortality remains a speculation and needs to be validated in further studies.

AKI is an important clinical problem with increasing mortality in VLBW preterm infants. We believe that uKIM-1 levels that are measured between 48 and 72 hours of life can be used as a highly sensitive and easy to apply non-invasive method for predicting development of AKI and mortality. However, further research with a larger number of newborns is required to investigate the significance of uKIM-1 levels in predicting kidney damage due to different etiological causes.

Authors' contributions

Declaration of conflicting interest

Funding

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