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NEONATAL ACUTE KIDNEY INJURY: PREDICTIVE AND DIAGNOSTIC VALUE OF URINARY PROTEIN BIOMARKERS

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Summary

Key words: term newborn, acute kidney injury, urinary concentration of total protein, urinary albumin, urinary immunoglobulin G, urinary α1-microglobulin, urinary β2-microglobulin, ROC-analyses.

Background. *The prevalence of acute kidney injury (AKI) reaches ~30% in neonates admitted to a tertiary level neonatal intensive care unit. Novel urinary biomarkers are useful for the prediction and diagnosis of AKI. The objective of this work was to determine the predictive and diagnostic value of urinary protein biomarkers for AKI in critically sick full-term newborns.*

Materials and methods. *A prospective cohort study of 150 full-term neonates was performed. Group I included 55 healthy newborns, group II – 50 critically ill newborns without AKI, group III – 45 critically ill newborns with AKI. Creatinine levels in serum (SCr), urinary concentration of total protein (UTPr), urinary albumin (UAlb), urinary immunoglobulin G (UIgG), urinary α1-microglobulin (Uα1-MG) and β2-microglobulin (Uβ2-MG) were measured on the 3rd day of life. In case the data were available, 2×2 tables were constructed to derive sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and cut-off level of urinary protein biomarkers. The area under the receiver operating characteristic (AUROC) curve was used to deduce the diagnostic accuracies of them.*

Results. *Considering AUROC values, the results of the conducted statistical analysis demonstrated that the biggest diagnostic value concerning AKI determination in critically ill term newborns was peculiar for the model with determination of UIgG level (AUROC 0.79; 95% CI 0.69-0.88, p<0.001 with cut-off level ≥ 5.1 mg/L). Similar diagnostic value was found in the models with determination of Uα1-MG (AUROC 0.73; 95% CI 0.64-0.84, p<0.05 with cut-off level ≥ 42 mg/L) and UTPr (AUROC 0.73; 95% CI 0.62-0.83, p<0.05 with cut-off level ≥ 186 mg/L). The model with determination of UAlb (AUROC 0.64; 95% CI 0.53-0.76, p<0.05 with cut-off level ≥ 23.0 mg/L) possessed the least diagnostic value. The laboratory test with determination of Uβ2-MG level demonstrated the absence of diagnostic value concerning AKI determination in term newborns (AUROC 0.56; 95% CI 0.5-0.68, p>0.05 with cut-off level ≥ 2.95 mg/L).*

Conclusions: 1. A comprehensive clinical-paraclinical examination should be performed for timely diagnostics of AKI in critically ill term newborns with determination of early markers of renal dysfunction including urinary protein

biomarkers. 2. Considering the values of AUROC the level of diagnostic value of the presented biomarkers concerning detection of AKI was determined: UIgG > Uα1-MG, UTPr > UAlb with absent diagnostic value of Uβ2-MG. 3. None of the presented diagnostic models demonstrated high discriminating ability with high values of Se and Sp at the same time concerning detection of AKI in critically ill newborns.

Introduction: The prevalence of acute kidney injury (AKI) reaches ~30% in neonates admitted to a tertiary level neonatal intensive care unit [1]. In most studies, perinatal asphyxia, sepsis, respiratory distress syndrome, dehydration, congestive heart failure and nephrotoxic drugs are the most commonly associated conditions [2, 3]. The most common form of AKI in neonates is prerenal failure due to renal hypo-perfusion or ischemia. And newborn infants are vulnerable to acute tubular necrosis or cortical necrosis [3].

Current identification of AKI relies on acute elevation of serum creatinine (SCr), but SCr-based definitions are hampered by numerous problems: most important, that SCr is a measure of function, not damage. In neonates, SCr-based AKI definitions present additional challenges because SCr levels on postnatal day 1 reflect maternal SCr, which declines over the next week or weeks depending on gestational age. In addition, acute changes in fluid status, which occur during this time period, may have an important effect on SCr values [4].

Novel urinary biomarkers are useful for the prediction of AKI. Most promising are the urine markers neutrophil gelatinase-associated lipocalin, interleukin-18, kidney injury molecule and other. Each of these has shown considerable promise diagnosing AKI earlier than serum creatinine using disease controls [5]. Improving the ability to reliably detect AKI would have important implications in the ability to care for critically ill neonates and will also improve the ability to perform clinical research [4]. But many significant questions, including how to best define, risk factors for, incidence of, early diagnosis, reference level of new markers, association with other co-morbidities, and the short-term and long-term outcomes after AKI remain unanswered [1].

The **objective** of this work was to determine the predictive and diagnostic value of urinary protein biomarkers for acute kidney injury (AKI) in critically sick full-term newborns.

Materials and methods. A prospective cohort study of 150 full-term neonates was performed. Group I included 55 healthy newborns, group II – 50 critically ill newborns without AKI, group III – 45 critically ill newborns with AKI.

The critically sick neonates were grouped on the basis of the neonatal Therapeutic Intervention Scoring System (nTISS) and they had maximum nTISS score 20 or higher [6]. The definition of AKI proposed by Jetton and Askenazi based on the Neonatal Acute Kidney Injury (AKIN) classification was used: increase of SCr by 0.3 mg/dl (25.6 μmol/l) or by 150-200% from the previous value and/or level of urine output less than 0.5 ml/kg/h for 6 to 12 hours [7]. The exclusion criteria of the study were birth weight ≤ 2500 g, early neonatal sepsis and major congenital anomalies of the kidneys and urinary tract.

Urine and blood samples were collected on the 3rd day and in cases of anuria/oliguria after restoration of diuresis. Creatinine levels in serum (SCr) were measured using enzymatic method. The urinary concentration of total protein (UTPr) was measured using protein dye-binding method, urinary albumin (UAlb) – immunoturbidimetric method, immunoglobulin G (UIgG), α1-microglobulin (Uα1-MG) and β2-microglobulin (Uβ2-MG) – immunonephelometric method. All the tests kits were manufactured by the laboratory Gemeinschaftslabor Cottbus (Germany).

The study was approved by the research ethics committee of Bukovinian State Medical University. Informed written consent was obtained from parents prior to enrollment of their babies into the study. All studies were conducted in compliance with the basic provisions of the Good Clinical Practice (1996), Council of Europe Convention on Human Rights and Biomedicine (1997), Helsinki Declaration of the World Medical Association on Ethical Principles for Medical Research (1964 - 2008).

Statistical analysis was performed by means of the software Statistica 7.0 (StatSoftInc., USA). The results of each group are expressed as mean (M) ± standard deviation (SD) for symmetric distributions. The normality of data distribution was tested using the Shapiro-Wilks test for sample size ≥ 30. To compare continuous variables, parametric tests (independent t test) were used. Fisher's exact test was used to compare categorical variables. The difference of the parameters was considered to be statistically significant with $p<0.05$. In case the data were available, 2×2 tables were constructed to derive sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and cut-off level of urinary protein biomarkers. The area under the receiver operating characteristic (ROC) curve was used to deduce the diagnostic accuracies of them.

Results. No statistical differences exist in the gestational age, body weight or gender signs of the three respective groups (Tab.1).

Table 1.

Neonatal epidemiological data.

	Group I (n=55)	Group II (n=50)	Group III (n=45)
Gestational age, week, M±SD	39.1±1.15	38.9±1.34	39.0±1.39
Body mass, g, M±SD	3396.1±437.43	3374.9±521.4	3459.5±494.17
Sex (boys), n (%)	32 (58.2)	28 (56.0)	28 (62.2)
Sex (girls), n (%)	23 (41.8)	22 (44.0)	17 (37.8)

The healthy newborns did not have any problems in their early neonatal period.

The critically ill neonates from group II had more serious disorders in the first week of their life. 15 (30.0%) newborns had signs of moderate asphyxia, 3 (6.0%) had severe asphyxia, 8 (16.0%) had meconium aspiration, 10 (20.0%) had moderate hypoxic-ischemic encephalopathy (HIE), and 14 (28.0%) had severe HIE. Most newborns in this group had clinical signs of multiple organ dysfunction syndrome (MODS): all of them had severe respiratory failure, 12 (24.0%) had cardiovascular failure, 9 (18.0%) had hemorrhagic syndrome, 6 (12.0%) had seizures, 5 (10.0%) had anemia, and 3 (6.05%) had necrotising enterocolitis.

In group III, 8 (17.8%) newborns had signs of moderate asphyxia, 12 (26.7%) had severe asphyxia (pII-III<0.05), 9 (20.0%) had meconium aspiration, 6 (13.3%) had moderate HIE, and 10 (22.2%) had severe HIE. MODS occurred in all critically ill full-term neonates with AKI. Severe respiratory failure was found in all 45 (100.0%) patients in group III, cardiovascular failure in 31 (68.9%; pII-III<0.05), hemorrhagic syndrome in 9 (20.0%), seizures in 9 (20.0%), and anaemia in 8 (17.8%). 8 (17.8%) neonates with AKI developed necrotising enterocolitis (pII-III<0.05). Certain association between AKI and severe asphyxia, cardiovascular failure, and necrotising enterocolitis was found.

The results of measurement of biochemical serum and urine markers are presented in Tab. 2. The established marker of renal dysfunction SCr was significantly higher in the groups of critically ill newborns with AKI as compared to the group of patients without AKI and healthy newborns. The critically ill newborns without AKI displayed significantly higher values of SCr as compared to the healthy neonates. The results of the study did not demonstrate critical level of SCr in group III. It was due to detection of a common group of patients with AKI exceeding the criteria of SCr level, urine output or a combination of the two.

The results of the examination of urinary protein biomarkers demonstrated that critically ill term newborns without AKI had moderate disorders of the renal tubular apparatus functioning with relatively preserved functions of glomerular barrier. It was evidenced by statistically much higher rates of urinary excretion of UAlb and Uα1-MG with relatively stable rates of UIgG and Uβ2-MG in infants of the II group as compared to the infants from the I group. AKI formation in term children is accompanied by total disorders in the functioning of glomerular and tubular renal apparatus. It was evidenced by statistically much higher rates of UTPr, UAlb, UIgG, Uα1-MG in children of the III group as compared to the children from the II and I groups of the study.

The glomerular basement membrane, vascular endothelium of the capillaries and podocytes are components of the glomerular filtration barrier which prevents leakage of protein. In a healthy neonatal kidney, the proximal tubule function is often not mature enough to prevent leak of smaller proteins and therefore it is normal to see increased urinary protein in a neonates' urine when compared to adult urine. The amount of physiologically normal protein excreted in the urine can be inversely correlated with gestational age [8].

Table 2.

Neonatal biochemical data.

	Group I (n=55)	Group II (n=50)	Group III (n=45)
SCr, μmol/l, M±SD	41.6±8.49	54.1±11.78*	68.7±15.56*#
UTPr, mg/l, M±SD	165.4±64.75	142.5±35.09*	185.5±62.15#
UAlb, mg/l, M±SD	10.5±3.27	17.6±5.38*	21.3±8.63*#
UIgG, mg/l, M±SD	4.3±1.19	4.38±0.74	5.73±1.52*#
Uα1-MG, mg/l, M±SD	24.2±9.87	32.8±8.41*	42.7±14.74*#
Uβ2-MG, mg/l, M±SD	2.38±1.11	2.66±0.94	2.41±1.07

* − significant difference from group I, p<0.05; # − significant difference between groups II and III, p<0.05.

ROC analysis was conducted with calculation of appropriate operational characteristics to determine prognostic and diagnostic value of the presented urinary protein biomarkers concerning neonatal AKI (Tab. 3).

Table 3.

Results of ROC analysis of urinary protein biomarkers for neonatal AKI

		UTPr	UAlb	UIgG	Uα1-MG	Uβ2-MG
Cut-off level, mg/l		186	23.0	5.1	42.0	2.95
AUROC	M	0.73	0.64	0.79	0.73	0.56
	95% CI	0.62-0.83	0.53-0.76	0.69-0.88	0.64-0.84	0.5-0.68
p (AUC)		0.002	0.041	<0.001	0.001	0.23
Se,%	M	48.9	46.7	71.1	62.2	71.1
	95% CI	33.7-64.2	31.7-62.1	55.7-83.6	46.5-76.2	55.7-83.6
Sp, %	M	90.0	82.0	82.0	86.0	41.8
	95% CI	78.2-96.7	68.6-91.4	68.6-91.4	73.3-94.2	28.7-55.9
PPV, %	M	81.5	70.0	78.1	80.0	50.0
	95% CI	64.5-91.4	54.5-82.0	65.7-86.9	65.9-89.2	42.8-57.2
NPV, %	M	66.2	63.1	75.9	71.7	63.9
	95% CI	59.2-72.5	55.8-69.8	66.2-83.6	65.9-89.2	50.4-75.5
PLR	M	4.89	2.59	3.95	4.44	1.22
	95% CI	2.02-11.8	1.33-5.06	2.12-7.35	2.16-9.17	0.91-1.64
NLR	M	0.57	0.65	0.35	0.44	0.69
	95% CI	0.42-0.77	0.48-0.88	0.22-0.57	0.30-0.65	0.40-1.20

Discussion. The amount of urinary excreted proteins, especially those of low molecular weight proteinuria, is a result of glomerular filtration of proteins and their reabsorption in the proximal tubules [9]. Acute tubular necrosis is a common cause for AKI especially in the neonatal intensive care unit and as a consequence, proteinuria can be seen in the setting of this [8].

When making the diagnosis of AKI in critically ill children born in physiological term of gestation, the model with UTPr detection demonstrated good discriminating ability with cut-off level ≥ 186 mg/L (AUROC 0.73; 95% CI 0.62-0.83, p<0.05), high Sp (90.0%; 95% CI 78.2%-96.7%) and low Se (48.9%, 95% CI 33.7%-64.2%). It is indicative of the fact that examination of critically ill newborns will not find AKI signs in 90.0% of cases in children with negative test result, but the diagnosis will be confirmed more than in 50.0% of cases with positive laboratory test. PPV, determining the probability of the disease available in a patient in case of a positive result of the test at the present moment, constituted 81.5% (95% CI 64.5%-91.4%); NPV, determining the probability of absence of the disease in case of a negative result of the test at the present moment was 66.2% (95% CI 59.2%-72.5%). Probability of a positive result in a newborn with AKI is approximately 5 times as high compared to a negative result in a child without AKI, which is evidenced by PLR 4.89 (95% CI 2.02-11.8).

Albumin is a 66 kDa, 585-amino acid, negatively charged globular protein found in plasma of mammals. It is produced and excreted by the liver and is the most abundant protein in plasma. Serum albumin is multifunctional as it buffers pH; provides oncotic pressure; and is a carrier protein for a wide range of molecules, including amino acids, fatty acids, inorganic ions, medications, and metabolites. Preventing or reducing urinary albumin excretion thus makes the kidney a key player in "protecting" the organism from excessive loss of albumin and its ligands. Albumin loss in urine has long been used as a marker of kidney injury, whether it originates from glomerular dysfunction, defective total protein reabsorption, or a combination [10].

When making the diagnosis of AKI in critically ill term newborns the model with UAlb determination demonstrated an average diagnostic value with cut-off level ≥ 23.0 mg/L (AUROC 0.64; 95% CI 0.53-0.76, p<0.05). And this model was characterized by high Sp (82.0%; 95% CI 68.6%-91.4%) and low Se (46.7%; 95% CI 31.7%-62.1%) with insufficiently high PPV (70.0%; 95% CI 54.5%-82.0%) and NPV (63.1%; 95% CI 55.8%-69.8%) results. Probability of a positive result in newborns with AKI is approximately 2.6 times as much compared to the probability of a negative result in children without AKI for the presented laboratory test, which is evidenced by PLR 2.59 (95% CI 1.33-5.06).

Immunoglobulin G is a protein with high molecular weight (150 kDa) which is produced by active lymphocytes, circulate in plasma as a component of the immune system. It does not penetrate through intact glomerular membrane, and it's not detected under physiological conditions in the urine of healthy individuals [11].

When making the diagnosis of severe renal dysfunction in term newborns the model with UIgG determination demonstrated good discriminating ability with cut-off level ≥ 5.1 mg/L (AUROC 0.79; 95% CI 0.69-0.88, p<0.001), high Sp (82.0%; 95% CI 68.6%-91.4%) and moderate Se (71.0%; 95% CI 55.7%-83.6%), as well as moderate PPV (78.1%; 95%

CI 65.7%-86.9%) and NPV (75.9%; 95% CI 66.2%-83.5%). Probability of a positive result in newborns with AKI is practically 4 times as high compared to a negative result in children without AKI for the given diagnostic pattern, which is evidenced by PLR 3.95 (95% CI 2.12-7.35).

α1-microglobulin is a glycosylated protein of molecular weight estimated to be between 26 kDa and 33 kDa according to the type of measurement containing 167 amino acids. α1-MG is synthesized in the liver, that is half of protein circulated is bound to immunoglobulin A complex. The free forms are filtrated by glomeruli and undergo reabsorption by proximal tubular cells [12].

When making the diagnosis of AKI in term newborns with clinical signs of severe perinatal pathology the diagnostic model with determination of Uα1-MG level demonstrated good discriminating ability with cut-off level ≥ 42 mg/L, which is evidenced by AUROC 0.73 (95% CI 0.64-0.84, p<0.05). High Sp (86.0%; 95% CI 73.3%-94.2%) with insufficiently high Se (62.2%; 95% CI 46.5%-76.2%) are determined for this laboratory test. PPV, determining the probability of the disease available in a patient in case of a positive result of the test at the present moment, constituted 80.0% (95% CI 65.9%-89.2%); NPV, determining the absence of the disease in case of a negative result of the test at the present moment was 71.7% (95% CI 65.9%-89.2%). Probability of a positive result in critically ill newborns with AKI is approximately 4.5 times as high compared to the probability of a negative result in children without AKI, which is evidenced by PLR 4.44 (95% CI 2.16-9.17).

β2-microglobulin is a single-chain, low molecular weight (11,8 kDA) polypeptide and has similar structure to the CH3 domain of the immunoglobulin molecule. β2-MG forms the invariant light chain portion of major histocompatibility complex class I molecules, which can be found on the membrane of all nucleated cells. β2-MG serves as a useful biomarker to evaluate both glomerular and tubular function [13].

When making the diagnosis AKI in critically ill term newborns the test with Uβ2-MG determination was not diagnostically valuable, which was evidenced by the absence of statistically important AUROC level constituting 0.56 (95% CI 0.5-0.68, p>0.05) with cut-off level of the index ≥ 2.95 mg/L.

Therefore, considering AUROC values, the results of the conducted statistical analysis demonstrated that the biggest diagnostic value concerning AKI determination in critically ill term newborns was peculiar for the model with determination of UIgG level (AUROC 0.79; 95% CI 0.69-0.88, p<0.001 with cut-off level ≥ 5.1 mg/L). Similar diagnostic value was found in the models with determination of Uα1-MG (AUROC 0.73; 95% CI 0.64-0.84, p<0.05 with cut-off level ≥ 42 mg/L) and UTPr (AUROC 0.73; 95% CI 0.62-0.83, p<0.05 with cut-off level ≥ 186 mg/L). The model with determination of UAlb (AUROC 0.64; 95% CI 0.53-0.76, p<0.05 with cut-off level ≥ 23.0 mg/L) possessed the least diagnostic value. The laboratory test with determination of Uβ2-MG level demonstrated the absence of diagnostic value concerning AKI determination in term newborns.

Conclusions. 1. A comprehensive clinical-paraclinical examination should be performed for timely diagnostics of AKI in critically ill term newborns with determination of early markers of renal dysfunction including urinary protein biomarkers (UTPr, UAlb, UIgG, Uα1-MG, Uβ2-MG). 2. Considering the values of AUROC the level of diagnostic value of the presented biomarkers concerning detection of AKI was determined: UIgG > Uα1-MG, UTPr > UAlb with absent diagnostic value of Uβ2-MG. 3. None of the presented diagnostic models demonstrated high discriminating ability with high values of Se and Sp at the same time concerning detection of AKI in critically ill newborns.

The perspectives for further studies are directed to the development of a comprehensive prognostic-diagnostic mathematic model concerning determination of AKI in term newborns including the most important risk factors, clinical signs, laboratory and instrumental methods of examination, investigation of their value and introducing into the practical work of medical establishments.

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CAZ CLINIC

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SINDROMUL TESTICULUI FEMINIZANT

(Sindromul insensibilității la androgeni / sindromul Goldberg-Maxwell-Morris, sindromul Morris)

USMF „Nicolae Testemițanu”, Catedra Obstetrică și Ginecologie FECMF

(Șef catedră – prof.univ., dr. hab. med. Olga Cernețchi)

Summary

Keywords: Androgen Insensitivity Syndrome. Androgen receptor, management, gonadal tumor, hormone replacement therapy, gonadectomy.

The goal *In this article is discussed a clinical case of disorder of sex development (DSD) such us: Testicular feminization in the context of contemporary literature.*

Patient and Methods: *A 15-year-old patient is admitted at Gynecology for primary amenorrhea. The clinical examination shows a female phenotype: the breasts are normally developed, but there few hair in the groins and axillary areas, the urinary meatus is normally inserted, and the vulva is unpigmented. The gynecological exam reveals that the hymen is present, the vagina short, while the uterus is absent. The karyotype was mapped in order to differentiate the androgen insensitivity syndrome from other genetic abnormalities. The testes were removed in order to avoid the malignant risk. We performed gonadectomy.*

Results: *Surgically, the patient had a simple evolution. Mentally, the patient kept thinking she was a woman, so the decision of telling her the truth was left to the parents.*

Conclusions: *Testicular feminization is a rare disease that must be diagnosed and treated through close work between gynecologists, endocrinologists, geneticians, urologists, and psychiatrists. Bilateral gonadectomy is the best procedure to avoid their malignant transformation.*