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ДИССЕРТАЦИОННЫМИ СОВЕТАМИ ФАКУЛЬТЕТОВ МЕДИЦИНЫ, СТОМАТОЛОГИИ, ОБЩЕСТВЕННОГО ЗДРАВООХРАНЕНИЯ И ФАРМАЦИИ ТБИЛИССКОГО ГОСУДАРСТВЕННОГО МЕДИЦИНСКОГО УНИВЕРСИТЕТА ЖУРНАЛ ВКЛЮЧЕН В СПИСОК НАУЧНЫХ ИЗДАНИЙ, РЕКОМЕНДУЕМЫХ ДЛЯ ПУБЛИКАЦИИ ФРАГМЕНТОВ ДИССЕРТАЦИОННЫХ ТРУДОВ

РЕЗЮМЕ ОПУБЛИКОВАННЫХ СТАТЕЙ ПЕЧАТАЮТСЯ В "ГРУЗИНСКОМ РЕФЕРАТИВНОМ ЖУРНАЛЕ" ТЕХИНФОРМА

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NEONATAL ACUTE KIDNEY INJURY: DIAGNOSTIC AND PREDICTIVE VALUE OF SERUM CYSTATIN C

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SUMMARY

Background. Neonatal acute kidney injury (AKI) is common, partially due to incomplete renal maturation and due to frequent exposure to risk factors for AKI such as perinatal asphyxia, extracorporeal-membrane-oxygenation, cardiac surgery, sepsis, prematurity and nephrotoxicity. The **objective** of the work was to determine diagnostic and predictive value of serum cystatin C (SCysC) in case of AKI in full-term newborns with severe perinatal pathology. **Methods.** A prospective cohort study was performed. 67 full-term neonates with severe perinatal pathology were enrolled in the study including 31 newborns with AKI (group I) and 36 newborns without AKI (group II). The control group included 42 healthy full-term neonates (group III). SCysC level was measured by immune-nephelometric methods. **Results.** In the newborns of the group I SCysC was 1.75±0.02 mg/L, in the group II – 1,56±0.02 mg/L, in the group III – 1,54±0.03 mg/L, $\delta_{I-II}<0,05$, $p_{I-III}<0,05$. A cut-off level of SCysC which is indicative of the formation of AKI in full-term newborns with severe perinatal pathology was detected to be higher than 1,59 mg/L, AUC 0.83 (95% CI 0.74; 0.83, $p<0.001$). For AKI sensitivity and specificity of SCysC were 88.9% (95% CI 75.9%; 96.3%) and 64.0% (95% CI 49.2%; 77.1%) respectively, with negative predictive value 86.5% (95% CI 73.2%; 93.8%). **Conclusions.** Considering a high predictive and diagnostic value the authors recommend to measure SCysC level for identification of AKI in full-term neonates with severe perinatal pathology into the practical work of neonatal intensive care units.

Introduction: Neonatal acute kidney injury (AKI) is common, partially due to incomplete renal maturation and also due to frequent exposure to risk factors for AKI such as perinatal asphyxia, extracorporeal-membrane-oxygenation, cardiac surgery, sepsis, prematurity and nephrotoxicity. The current method by which AKI is diagnosed is sub-optimal and not universally accepted which impairs an accurate estimation of true incidence of neonatal AKI. Serum cystatin C (SCysC), urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 and interleukin-18 are promising neonatal AKI biomarkers, however, the diagnosis of AKI remains serum creatinine/urine output-based in many studies [6,10].

Cystatin C (CysC) is a non-glycosylated, low molecular weight, cation protein that is regularly synthesized by most nucleated cells. Due to its low molecular weight and positive charge at physiological

pH, it is freely filtered by the glomerulus and then reabsorbed and catabolized by proximal tubular cells [3]. CysC is also a more accurate marker for estimation of glomerular filtration rate (GFR) in paediatric patients with AKI. Elevation of CysC occurs before elevation of serum creatinine; therefore, CysC can be used as a preferable marker for early detection of AKI, as well as in future AKI outcome studies and clinical trials [1-3]. However, similar to creatinine, an extensive CysC range in neonates is only partially explained by renal (patho) physiology. Its applicability in neonatal medicine can be further improved by the use of assay specific reference values, adapted to neonatal renal physiology (e.g. weight, age) and should be compared to a gold standard such as inulin clearance [9].

The **objective** of the work was to determine diagnostic and predictive value of SCysC in case of AKI in full-term newborns with severe perinatal pathology.

METHODS. A case-control study from January 2014 to March 2015 was performed. 67 full-term neonates with severe perinatal pathology were enrolled in the study including 31 newborns with AKI (group I) and 36 newborns without AKI (group II). The control group included 42 healthy full-term neonates (group III).

Critically sick neonates were grouped on the basis of the neonatal Therapeutic Intervention Scoring System (nTISS) [7]. All 67 newborns from groups I and II had clinical symptoms of severe disorders in their first postnatal week, and had maximum nTISS score 20 or higher. The babies from the control group III had nTISS score zero.

The definition of AKI suggested by Jetton and Askenazi based on the Neonatal Acute Kidney Injury classification was used: 1) increase of SCr by 0.3 mg/dl (25.6 μmol/L or by 150-200% from the previous value and/or 2) level of urine output less 0.5 ml/kg/h for 6 to 12 hours [9]. Serum creatinine (SCr) level was measured by photometric methods with picric acid, SCysC level was measured by immune-nephelometric methods. Classically glomerular filtration rate (GFR) was calculated on the basis of G.Schwartz's formula: GFR (ml/min/1.73 m^2) = k · d (cm) / SCr (μmol/L) · 0,0113, where k = 0,45 for term neonates [8]. The alternative method of calculation of GFR was based on A.Grubb's formula: GFR (ml/min/1.73 m^2) = 84,69 x cystatin $C^{-1,680}$ x 1,384 [4]. The analyses were conducted on the basis of the laboratory Gemeinschaftslabor Cottbus (Germany).

The data obtained were statistically processed by means of the program Statistica 7.0 (StatSoftInc., USA). The results of each group are expressed as mean (M) and standard error (m) for symmetric distribution. The normality of data distribution was tested using 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 compiled 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 SCysC. The area under the receiver operating characteristic (ROC) curve was used to deduce the diagnostic accuracies of SCysC.

Ethical approval was obtained from the research ethics committee of the Higher State Educational Establishment of Ukraine "Bukovinian State Medical University". Informed written consent was obtained from parents prior to enrollment of their babies into the study.

Results. Demographic, antenatal/intranatal, and clinical characteristics of critically sick infants with AKI and without AKI, and healthy newborns are presented in **Tab. 1.**

Table 1. Neonatal clinical data

Parameters	Group I (n=31)	Group II (n=36)	Group III (n=42)
Neonatal epidemiological data			
Gestational term, week, M±m	39.1±1.47	38.9±1.15	39.1±1.94
Weight, g, M±m	3384.1±33.1	3343.1±13.5	3410.0±33.5
Body length, cm, M±m	53.1±2.69	53.2±2.17	53.4±2.25
Sex (boys), n (%)	20 (64.5)	24 (68.6)	26 (61.9)
Antenatal/Intranatal data			
First pregnancy, n (%)	16 (51.6)	19 (52.8)	19 (45.2)
First delivery, n (%)	21 (67.7)	22 (61.1)	22 (52.4)
Age of mother > 35 years, n (%)	9 (29.0)*#	4 (11.1)*	2 (4.8)
Sever preeclampsia, n (%)	3 (9.6)*#	0 (0)	0 (0)
Emergency caesarean section, n (%)	10 (32.3)*	10 (27.8)*	3 (7.1)
Meconium in amniotic fluid, n (%)	16 (51.6)*	16 (44.4)*	0 (0)
Fetal distress during labor, n (%)	8 (25.8)*	6 (16.7)*	0 (0)
Vacuum extraction, n (%)	3 (9.7)*	5 (13.9)*	0 (0)
Umbilical cord entanglement, n (%)	6 (19.4)*	4 (11.1)	3 (7.1)
Neonatal clinical data			
Moderate asphyxia, n (%)	9 (29.0)*	15 (41.7)*	0 (0)
Sever asphyxia, n (%)	7 (22.6)*#	2 (5.6)	0 (0)
Meconium aspiration syndrome, n (%)	9 (29.0)*	10 (27.8)*	0 (0)
Moderate HIE, n (%)	5 (16.1)*	10 (27.8)*	0 (0)
Severe HIE, n (%)	25 (80.6)*	26 (72.2)*	0 (0)
Seizures, n (%)	11 (35.4)*	8 (22.2)*	0 (0)
Severe respiratory failure, n (%)	31 (100.0)*	36 (100.0)*	0 (0)
Cardiovascular failure, n (%)	20 (62.5)*#	10 (27.8)*	0 (0)
Hemorrhagic syndrome, n (%)	9 (29.0)*	7 (19.4)*	0 (0)
Anemia, n (%)	3 (9.6)*	2 (5.6)	0 (0)
Milk intolerance, n (%)	24 (77.4)*#	13 (36.1)*	0 (0)
Necrotizing enterocolitis, n (%)	5 (16.1)*#	2 (5.6)	0 (0)
Neonatal jaundice, n (%)	10 (32.3)*	8 (22.2)*	0 (0)
Hypoglycemia, n (%)	5 (16.1)*	6 (16.7)*	0 (0)
Morpho-functional immaturity, n (%)	6 (19.3)*	7 (19.4)*	0 (0)

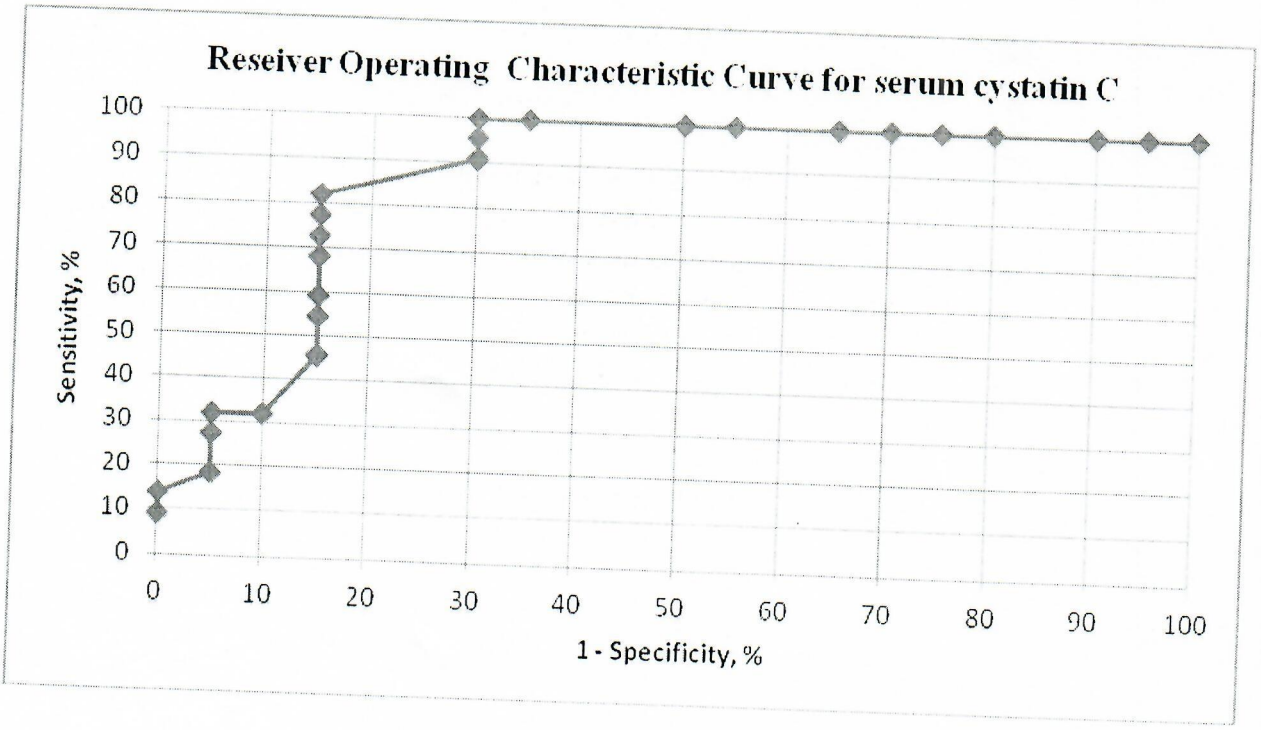
The results of measurement of biochemical serum and urine markers are presented in **Tab. 2.**

Table 2. Neonatal renal data.

Parameters	Group I (n=31)	Group II (n=36)	Group III (n=42)
SCr, μmol/L, M±m	68.7±2.31*#	54.1±1.67*	41.6±1.14
GFR/SCr, ml/min/1.73m², M±m	30.3±1.78*#	39.8±1.56*	52.8±1.91
SUr, mmol/L, M±m	6.76±0.32*#	3.76±0.17*	2.78±0.08
UCr, μmol/L, M±m	1311.6±66.5*#	2006.8±103.98*	3459.7±157.39
UUr, mmol/L, M±m	42.9±1.38*#	34.9±0.79*	48.4±2.62
SCysC, mg/L, M±m	1.75±0.02*#	1.56±0.02	1.54±0.03
GFR/CysC, ml/min/1.73m², M±m	46.3±0.89*#	56.1±1.11	58.7±1.92

Note: * - significant difference from group III, $p<0.05$; # - significant difference between groups I and II, $p<0.05$. SCr: serum creatinine; GFR/SCr: glomerular filtration rate for serum creatinine; SUr: serum urea; UCr: urine creatinine; UUr: urine urea; SCysC: serum cystatin C; GFR/SCysC: glomerular filtration rate for serum cystatin C.

A cut-off level of SCysC which is indicative of the formation of AKI in full-term newborns with severe perinatal pathology was detected to be higher than 1,59 mg/L, AUC 0.83 (95% CI 0.74; 0.83, $p<0.001$). For AKI, Se and Sp of SCysC with a cut-point value of 1.59 were 88.9% (95% CI 75.9%; 96.3%) and 64.0% (95% CI 49.2%; 77.1%) respectively, PPV value of 68.9% (95% CI 60.2%; 76.5%), and NPV value of 86.5% (95% CI 73.2%; 93.8%), PLR value of 2.47 (95% CI 1.68; 3.62), and NLR value of 0.17 (95% CI 0.07; 0.41). The result of ROC analysis is demonstrated on **Fig. 1.**



DISCUSSION. As compared to the previous studies in neonatal groups, our study included common group of sick neonates with interpretation of AKI biomarkers in the context of the clinical status. Our data demonstrated that AKI in critically ill full-term neonates is characterized by high levels of SCysC with high level of Se and NPV.

The previous studies demonstrated that SCysC should be considered as an early biomarker of AKI, improving the risk prediction for complicated outcome in paediatric cardiac surgery. Post-surgery SCysC values were found to be early diagnostic markers of AKI showing the best area under the ROC curve value at 12 h (0.746, CI 95% 0.674–0.818) [2]. N.Abdelaal et al. [1] showed that SCysC is an early marker for AKI in neonates with respiratory distress syndrome. ROC curves area under the curve was 0.97 for predicting the development of AKI within 72 h (P = 0.001). With the best cut-off value of ≥1.28 mg/L, the Se and Sp of SCysC for detecting AKI within 72 h were 100 and 83.3%, respectively [1].

In addition, S.Tomotaki et al. showed that cord blood CysC levels were significantly higher in the non-survivor group with congenital abnormalities of the kidney and urinary tract than in the survivor group. These results suggested that cord blood CysC levels may be a good marker of the severity of renal dysfunction at birth [11]. A.Kasamatsu et al. demonstrated that it may be possible to use SCysC levels at birth to predict urine volume during the first 24 h of life. A significant negative correlation was seen between neonatal SCysC levels and urine volume (r = -0.47, $p < 0.0001$) [5].

However, our study is limited by certain factors: 1) It was a single-center study; 2) with a small patient cohort suffering from AKI. The diagnostic and prognostic values of other serum and urinary markers of renal dysfunction should be studied and a common mathematical model for prognosis and diagnosis of AKI in newborns formulated.

Conclusions. Considering a high predictive and diagnostic value the authors recommend to measure SCysC level for identification of AKI in full-term neonates with severe perinatal pathology into the practical work of neonatal intensive care units.

Conflict of Interests. The Authors declare that there are no conflict of interests.

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