

ANNOTATION

**to dissertation work on topic: "The predictors of acute kidney injury in newborns with congenital malformations"
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submitted for the degree of Philosophy Doctor (PhD) on the specialty 6D110100
"Medicine"**

The relevance of the research topic

Acute kidney injury (AKI) is one of the most actual and widespread problem in neonatal nephrology and resuscitation. Recently, this problem has not only medical significance, but also social significance, because late diagnostics of AKI in newborns can lead to both chronicity of the pathological process in the kidneys and further disability in that group of children.

The incidence of AKI in newborns according to different studies varies. It has been most studied in premature babies and in critically ill neonates. Thus, according to some data, the incidence of neonatal AKI is about 3.9 per 1000 live births. According to the results of one of the largest global studies AWAKEN (Assessment of Worldwide Acute Kidney Epidemiology in Neonates, 2017), the incidence of AKI in newborns in intensive care units is 30%, and one of the important risk factors for AKI is surgical operations.

According to the Bureau of National Statistics, the infant mortality rate (IMR) in Kazakhstan increased sharply in 2021, from 7.7 to 8.4 cases per 1,000 live births. Moreover, in the structure of IMR, the mortality rate from congenital malformations (CM) in Kazakhstan does not tend to decreasing, amounts to 21.6% (2021).

With this connection, the most problematic for nursing are newborns with congenital malformations, because most of them undergo surgical correction of the defect during the first 2 days of life in the form of huge abdominal and thoracic interventions. And the main cause of death among them during perioperative period still is a multiple organ failure, including AKI.

Nowadays the most known and studied form of AKI in neonates is AKI after open heart surgery, called cardiac surgery-associated AKI (CSA-AKI), with the incidence 54% (Neonatal and Pediatric Heart and Renal Outcomes Network-NEPHRON, Alten JA, 2021).

But during the reviewing of literature about AKI in newborns after general surgical operations, we identified only a few publications. According to the results of research study of Korean scientists (Yum S.K, Seo YM, 2019), the frequency of AKI was 49.1%. Chinese scientists (Yang Wu et al., 2020) have retrospectively found a frequency of 34%. And according to American scientists (Cara L. Slagle et al., 2021), the incidence of AKI after surgery was in 19% of newborns.

Despite the frequency, its early diagnostics remains a challenge in neonatal practice.

The standard for diagnosing AKI in newborns includes the determination of the level of serum creatinine, urea, and the rate of urine output. This choice is explained by the availability of these parameters in our practical health care. However, new research results confirm that serum creatinine is no so highly specific for early detection of AKI in newborns and does not fully reflect damage of kidney function. Moreover, it has been found that up to 50% of renal function can be lost already before the increase of creatinine.

In this connection, for early diagnostics of AKI, the issue of searching and studying of new modern minimally invasive biomarkers of AKI is acute, because their use allows to diagnose AKI 24-48 hours before the appearance of creatinine in the blood and prevent the irreversible processes.

Among all AKI biomarkers such one is urinary neutrophil gelatinase-associated lipocalin or urinary NGAL (neutrophil gelatinase-associated lipocalin or urinary NGAL), which is produced for the response to acute injury in the proximal tubules of the kidneys. The serum and urinary NGAL levels have similar diagnostic and prognostic value. Therefore, it is possible to use this test in urine, which is less traumatic without blood sampling in newborns.

In conclusion, taking into account the relevance, the insufficiently studied problem in the population of newborns after surgical operations, the lack of clinical presentation, the lack of widespread using of early AKI biomarkers as uNGAL is making particular interest for our practical healthcare. The results of our scientific research will help to diagnose AKI on the early stages and promptly begin therapeutic measures to prevent irreversible renal processes and mortality in this category of children.

The aim of the study. To study the features of acute kidney injury in newborns with congenital malformations based on the determination of predictors of its development.

The research objectives:

1. To study the structure of congenital malformations in the Republic of Kazakhstan and to establish the causes, frequency and stages of development of AKI in newborns
2. To determine the diagnostic and prognostic value of uNGAL levels in neonates with congenital malformations in the perioperative period
3. To identify the analysis of correlations between the main indicators of renal dysfunction and uNGAL as a possible predictor of the development of AKI in newborns with congenital malformations.
4. To determine the clinical and laboratory predictors of AKI in newborns with congenital malformations of the gastrointestinal tract and congenital heart diseases
5. To create the algorithms of early diagnostics of AKI in newborns with congenital malformations.

The scientific novelty of the research:

1. For the first time we have been established the frequency and causes of AKI in newborns with congenital malformations in the perioperative period
2. For the first time we studied the diagnostic and prognostic significance of the uNGAL biomarker as a predictor of AKI in newborns with congenital malformations
3. For the first time have been designed the algorithms of early diagnostics of AKI in newborns with congenital malformations, including the uNGAL biomarker and clinical and laboratory predictors

The practical value of the results:

1. The designed algorithms of the early diagnostics of AKI in newborns with congenital malformations will be used in neonatological practice, which will reduce the risk of development of AKI in the perioperative period
2. The uNGAL biomarker is a highly sensitive, specific and minimally invasive test for the early diagnostics of AKI in newborns, which will allow us to use it as a predictor of the development of pathological process in the kidneys.
3. The revealed prognostic value of uNGAL based on the correlation with generally accepted indicators of renal dysfunction will make it possible to determine risk groups for the formation of AKI in newborns

4. The detected clinical and laboratory predictors of AKI in combination with uNGAL can be used by practical doctors for early detection of AKI in newborns with congenital malformations

Object and subject of research.

We conducted a combined three-stage retrospective and prospective study (conclusion of the Local Ethics Commission of Kazakh National Medical University named after S.D. Asfendiyarov # 1515). The written voluntary informed agreements from children's parents was taken for participation in the study.

The first stage of research was carried out in order to study the structure of congenital malformations in Kazakhstan, where the data of all registered cases of congenital malformations (7904 cases) in 18 regions of Kazakhstan over 5 years (2015-2019) were retrospectively analyzed. The information was obtained from the annual Statistical Compendium "The Health of the population of the Republic of Kazakhstan and the activities of healthcare organizations" of the Republican Center for Health Development (www.rcrz.kz). The study included all malformations first identified in the neonatal period according to the World Health Organization (WHO) definition (2016), which were registered in accordance with the International Classification of Diseases of the 10th revision and fall into class XVII "Congenital anomalies (malformations), deformities and chromosomal disorders" . We took into account the number of live births with a diagnosis of "Congenital anomalies" at a period of 25 to 41 weeks of pregnancy, weighing 500 grams or more, and permanent residence in the Republic of Kazakhstan. The exclusion criteria were cases of enzymatic and immune deficiency in newborns.

The congenital malformations structure was calculated per 10,000 live births.

The second stage of the study was carried out in order to identify the incidence and causes of AKI in newborns with congenital malformations by retrospective analysis of 146 medical records of newborn patients (stationary medical history of newborns: form # 907), of which: 86 records of newborns with congenital defects of gastrointestinal tract and 60 patients with congenital heart defects (CHD). Discharge records from obstetric cards of their mothers were also analyzed in order to identify the perinatal risks factors of AKI.

The collection of retrospective data was carried out on the basis of the archive of "Scientific Center of Pediatrics and Pediatric Surgery" in two departments: Neonatology and Neonatal Surgery and Cardiac Surgery, Interventional Cardiology and Angiosurgery for 5 years (2014-2018).

Inclusion criteria to the retrospective study: all newborns with a confirmed diagnosis of congenital malformations of the gastrointestinal tract and congenital heart defects who underwent surgical operations during the neonatal period

Exclusion criteria to the retrospective study: newborns who had congenital malformations of the kidneys and urinary system.

At the third stage of our research work, we conducted a prospective study to detect the clinical and laboratory predictors of AKI using the new uNGAL biomarker in 80 patients with congenital malformations, including: 45 newborns with congenital malformations of gastrointestinal tract and 35 children with congenital heart defects (CHD).

All patients were provided the surgical correction of congenital malformations in the neonatal period under general anesthesia, plus all patients with CHD had an open heart operation with using a cardiopulmonary bypass.

The study was conducted from January 2019 to February 2021. The reference group consisted of 17 somatically healthy newborns.

Inclusion criteria of patients to a prospective study:

-positive written informed agreement from patient's parents for the conducting study

-newborns with a confirmed diagnosis of congenital malformations of the gastrointestinal tract and congenital heart defects , with gestational age 37 weeks or more (term newborns)

-correspondence of the weight of the child at birth to the gestational age;

Exclusion criteria of patients to a prospective study:

- refusal to participate in the study (lack of the written informed agreement from the patient's parents)

- newborns with a gestational age less than 37 weeks

- inconsistency of birth weight with gestational age

- newborns without confirmed diagnosis congenital malformations

- newborns with congenital malformations of kidneys and urinary system

The incidence of AKI was determined according to the modified neonatal mKDIGO (2016) classification, for neonatal patients, which includes the level of serum creatinine and hourly urine output.

Taking into account the fact that newborns were admitted from maternity hospitals 1-2 days after birth and the initial level of serum creatinine was not known, we took the normal level of creatinine in the blood of a full-term baby (gestation period more than 37 weeks) as the initial level - this is 0.6 (mg/dl) or 53 $\mu\text{mol/l}$ (Hyato G. et al., 2018).

According to the neonatal mKDIGO classification, newborns were divided into two main groups:

1. AKI(+) group - newborns who developed AKI in the pre or postoperative period.

2. AKI(-) group - newborns who did not develop AKI.

A prospective research study was conducted in the 3 clinical childrens hospitals in Almaty:

1. "Scientific Center of Pediatrics and Pediatric Surgery". In this center, patients with congenital malformations of the gastrointestinal tract and congenital heart defects were examined.

2. "Center of Perinatology and Pediatric Cardiac Surgery" of the Health Department of Almaty. On this basis patients with CHD were examined.

3. "Center for Children's Emergency Medical Care" of the Health Department of Almaty. In this center, patients with congenital malformations of the gastrointestinal tract were examined in the neonatal intensive care unit.

In order to identify the most critical periods of the perioperative period, the diagnostics of AKI of all patients was carried out in dynamics four times: once before surgery and three times after surgery (on days 1, 3, and 7 of the postoperative period).

All patients got standard research methods. **Functional methods** included: calculation of glomerular filtration rate (GFR) according to the modified Schwartz formula, assessment of water balance - percentage of excretion (%), measurement of hourly urine output (ml/kg/hour).

Laboratory general clinical methods:

A) a general blood test with the detection of the main indicators of peripheral blood: hemoglobin, hematocrit, leukocytes, platelets and ESR levels,

B) assessment of indicators of the acid-base state of the blood, with the determination of the following parameters: pH, pCO₂, glucose, Lac (lactate), cBase, CHCO₃;

C) general urinalysis (determination of the specific density of urine, pH, protein, oxalates, urates, leukocytes, erythrocytes for the presence of urinary syndrome),

D) a biochemical blood test with the determination of the concentration of creatinine, urea, total protein, potassium, sodium, chlorides, calcium, C-reactive protein,

D) biochemical analysis of urine, with the determination of creatinine, urea, total protein, potassium, sodium, chlorine, calcium in a single portion of urine.

E) Coagulogram with the establishment of the prothrombin index for children with CHD.

And **instrumental research methods**: ultrasound of the abdominal organs and kidneys, neurosonography. For children with congenital heart defects, the following were additionally performed: an electrocardiographic study (ECG) was performed on a 12-lead machine, echocardiography (ECHO CG) was performed on an expert cardiological class ultrasound machine.

Special research methods. The detection of uNGAL level in the urine by method of immunochemiluminescence.

Along with the generally accepted methods for assessing kidney function and general laboratory examination, all examined patients underwent a specific examination for the purpose of early diagnostics of AKI with the determination of a sensitive, minimally invasive urinary biomarker of AKI - uNGAL by a quantitative microparticle chemiluminescence immunoassay (CMIA) method using flexible assay protocols called Chemiflex, using the ARCHITECT Urine NGAL tests (Abbott Diagnostics, Abbott Park, USA) on the ARCHITECT i2000SR analyzer (Abbott, USA), was carried out in the express laboratory in the Scientific Center of Pediatrics and Pediatric Surgery.

The urine sampling for uNGAL was performed in a single portion. The range of expected values for the uNGAL test (Abbott, USA) was determined to be 40-131.7 ng/mL or less. Values above 131.7 ng/mL were considered predictive of the development of AKI.

An analysis of maternal risk factors was also carried out (aggravated pregnancy, previous diseases, the presence of chronic pathology).

Anamnestic data were also analyzed for each patient: Apgar scores at birth at 1 and 5 minutes, gestational age, birth weight, age at the time of admission to the hospital, assessment of the patient's clinical status (determination of the severity of the general condition according to the international scale NTISS - Neonatal Therapeutic Intervention Scoring System), blood pressure indicators, hyperhydration states, duration of surgery, volume of blood loss, duration of artificial lung ventilation in the postoperative period, duration of stay in the NICU, duration of hospitalization. In children with CHD, the level of central venous pressure (CVP) and saturation, the duration of peritoneal dialysis (PD), the duration of aortic clamping, and the duration of cardiopulmonary bypass (EC) were additionally studied.

The anesthesiological support for newborns with congenital malformations was carried out in accordance with accepted modern standards using general anesthesia and mechanical ventilation.

Statistical analysis.

Statistical analysis was performed using SPSS software (version 22.0, IBM SPSS Inc., Chicago, Illinois, USA). Statistical analysis of the congenital malformation structure was performed using univariate (uncorrected) and multivariate (corrected) analyses.

The study variables were quantitative and continuous. Student's T-test was used to test the hypothesis about the difference between the means for the two groups (main and control). The generally accepted methods of variation statistics were used with the calculation of average values (M), the error of the mean for absolute and relative values (m), and the indicator of the significance of differences when comparing between groups (p). The obtained values of the odds ratio (OR) and 95% confidence interval (CI) were compared with one. The relative risk indicator indicates the presence of a direct relationship between the factors and the likelihood of developing AKI. The significance level of this relationship corresponds to $p < 0.05$, since 95% CI does not include a unit.

The general characteristics of newborn patients were established using descriptive statistics. Categorical data were presented as frequencies (percentages) and quantitative variables as medians (IQR interquartile interval, first and third quartiles). For comparison of continuous quantitative variables, the Mann-Whitney test, T-test, and Chi-square were used to compare categorical data. The resulting variables with significant significance were processed using a single-factor analysis and then with a multivariate analysis, which was carried out using a logistic regression model. A p value less than 0.05 was considered statistically significant.

The direction and closeness of the correlation between two quantitative indicators were assessed using the Pearson correlation coefficient (with a normal distribution of the compared indicators). Subsequently, the closeness of the connection was assessed on the Chaddock scale.

For determination the quality of the model, an ROC-curve was constructed, where the AUC indicator (area under the ROC-curve) is considered, which, taking into account the confidence

interval, should be above 0.5. For the determination of the cut-off point or threshold values (cut-off point), the Youden coefficient was used, obtained on the basis of indicators of specificity and sensitivity. The resulting observation point at which it takes the maximum value is the cutoff point. The calculation of the coefficient is carried out according to the formula: Sensitivity + Specificity -

For establishing the prognostic significance of the uNGAL marker, we used the Predictive value method. In order to establish the positive and negative predictive value of the uNGAL test, a statistical analysis was performed using a medical statistical online formula calculator (MedCalc Software Ltd. Diagnostic test evaluation calculator. https://www.medcalc.org/calc/diagnostic_test.php (Version 20.118 ; accessed November 22, 2022).

The basic statements for the defense:

1. In the structure of congenital malformations in the Republic of Kazakhstan, the birth rate of neonates with congenital heart defects (CHD) and congenital malformations of the gastrointestinal tract is high in comparison with the other types of malformations, so they form the main risk group of developing of the dangerous pathological conditions in the perioperative period.
2. The high incidence of AKI (58%) in newborns with CHD and congenital malformations of the gastrointestinal tract, predominantly of prerenal etiology (66%; 86%) justify the necessity of finding the new approaches for the improving of the diagnostics of AKI
3. The uNGAL biomarker is a promising diagnostic test for the early diagnosis of neonatal AKI in comparison with the gold standard -serum creatinine. The highest sensitivity (average 80%) and specificity (average 90%) of uNGAL in the preoperative period allows to predict the formation of AKI in newborns with congenital malformations and to choose further tactics for managing the patient on time.
4. A correlation was found between the generally accepted indicators of renal dysfunction and uNGAL, which proves the prognostic value of the biomarker in the diagnostics of AKI.
5. The uNGAL biomarker in combination with the identified clinical and laboratory predictors can be used for the predictive diagnostics of AKI in neonates with congenital malformations

The research results.

The incidence of congenital malformations in the Republic of Kazakhstan during the study period was 0.4% per 10,000 live births. In the structure of congenital malformations among newborns in Kazakhstan, congenital heart defects and congenital malformations of the gastrointestinal tract are more common, among which there is a high risk of developing AKI.

There is a high prevalence of congenital malformations of the circulatory organs, unlike other types of congenital malformations, equal to an average of 5 years - 15 per 10,000 births, but still remaining high compared to the countries of the Organization for Economic Development and Cooperation (OECD). Thus, according to the data of the European congenital malformations registry EUROCAT, the incidence of congenital heart defects in Italy is 2 times lower and amounts to 7.05 cases per 10,000 births, in Spain 7.44 cases, in Poland 10.1 per 10,000 births (2019).

The structure of congenital malformations of the gastrointestinal tract in the Republic of Kazakhstan for 5 years (2015 - 2019) with a downward trend, but still remains high: 2015 - 5.3 per 10,000 births, 2016 - 4.1; 2017 - 4.3; 2018 - 3.7; 2019 - 3.1 per 10,000 births.

According to the results of a retrospective study, the incidence of AKI in newborns with congenital malformations in the perioperative period was 58%. According to our data, among the prerenal causes of AKI, prerenal etiology dominated and amounted to 86% in newborns with congenital heart defects, and 66% in newborns with congenital defects of gastrointestinal tract. Renal causes accounted for 14% and 34%, respectively.

In the structure of prerenal causes in newborns with congenital malformations of the gastrointestinal tract, the following were identified: dehydration (hypovolemia) - 51.6%, asphyxia -

24.2%, sepsis - 12.1%, disseminated intravascular coagulation (DIC) syndrome - 12.1%. The causes of the renal etiology were similar to those in patients with congenital malformations of the gastrointestinal tract: acute tubulointerstitial nephritis (ATIN), which was detected in 10 (58.9%) cases, and acute tubulonecrosis (ATN) in 7 (41.1%) children, confirmed by pathomorphological examination.

In the structure of prerenal causes in newborns with congenital heart defects (CHD), DIC was more common - 43.3%, hypoxemia in the postoperative period, including asphyxia at birth in 33.3% of cases, sepsis 20% and a decrease in circulating blood volume (hypovolemia) in the form of dehydration in 3.4%. The reasons for the renal nature of AKI in patients with CHD were: ATN in 60% (3) and ATIN in 40% (2), also confirmed pathomorphologically.

Analysis of the distribution of the incidence of AKI by stages according to the neonatal mKDIGO classification in patients with congenital malformations most often developed stage first of AKI: stage 1 - 47.5% and 50%, stage 2 - 31.5% and 25%, stage 3 - 21% and 25 % respectively.

The first group for studying of AKI was patients with congenital malformations of the gastrointestinal tract.

The patients in both groups had normal birth weight as in the AKI group (+) 3100 g. (IQR 2880-3218, $p=0.115$) and in the AKI(-) group 3210 (IQR 3093-3613), were full-term: median in the group with AKI - 38 weeks (37-39, $p=0.404$), and in the group without AKI - 39 weeks (37.7-39.2).

The age of newborns with congenital malformations of the gastrointestinal tract at the time of admission to the hospital was 2 days of life in both groups ($p=0.944$).

In the structure of congenital malformations of the gastrointestinal tract of the group with AKI, atresia of the esophagus with a lower tracheoesophageal fistula was most often observed, while in the AKI(-) group, children with anorectal malformations predominated.

The analysis of maternal factors of patients with congenital malformations of the gastrointestinal tract of the AKI (+) group showed that the main significant factors of them were: proteinuria during pregnancy, edema - 10 (52.6%, OR-3.7 (95% CI 1-13.3 ; $p=0.041$), maternal history of fetal loss syndrome - 9 (47.3%, OR-3.8 (95% CI 1-14.3; $p=0.044$) and severe preeclampsia -7 (36.8% ,OR - 4.0 (95% CI - 1-17.0; $p=0.044$). Among the factors of extragenital pathology showed that mothers of children with AKI more often had anemia in 15 (78.9%) cases ($p<0.05$); infections of the genitourinary system (UTI) of pregnant women in 12 (63.1%) cases ($p<0.05$) and chronic arterial hypertension in 9 (47.3%) cases, $p<0.05$.

The analysis of the results of risk factors for the development of AKI in newborns with malformations of the gastrointestinal tract showed that in the group with AKI (+) there were significantly lower Apgar scores at 1 minute, a median of 6 points (IQR 5-7, $p=0.001$), an average the duration of the surgical intervention was longer (120 minutes (IQR 60-180, $p=0.043$), the hospitalization in the ICU was longer (Me-16 days (IQR 11-33, $p=0.046$), the duration of hospitalization was longer (Me-27 days; IQR17 - 31, $p=0.231$).

The mortality rate was 31.5% in the group of infants with AKI, and 15.4% in the group of children without AKI.

Children of the AKI(+) group were initially admitted in a more serious condition, with the 2nd category of severity 11.8421 ± 4.1 ($p<0.05$), in comparison with the group of patients without AKI (1st category 8.5385 ± 2.3). In the dynamics, there is a deterioration in the general condition of patients in the AKI(+) group, i.e. on the 1st and 3rd days after the operation, the general condition of the children worsened to the 3rd category of severity (1 day - 24.6316 ± 3.1 and 3 days - 23.9474 ± 5.8 ; $p<0.05$), in comparison with the AKI(-) group (1 day - 20.8462 ± 2.82 , 3 days - 15.8462 ± 5.3) and gradually the risk decreased by the 7th day.

The analysis of these indicators of hourly urine output in patients with congenital malformations of the gastrointestinal tract in both groups before surgery were within the normal range, more than 1.5 ml/kg/hour. However, on the 1st day after surgery, newborns with AKI(+) showed a significant decrease in urine output to 1.2 ml/kg/hour compared to patients in the AKI(-) group - 1.8

ml/kg/hour. On the 3rd and 7th days after the operation, hourly urine output reached an average of 2.5 ml/kg/h and 2.7 ml/kg/h, respectively, which confirms the non-oliguric type of AKI in newborns. GFR did not reveal significant differences.

A comparative analysis of the parameters of the general blood test did not reveal statistically significant differences, but in the biochemical analysis of blood in neonates with congenital malformations of the gastrointestinal tract, there was a difference in the levels of creatinine and urea: the creatinine level significantly increased on 3 day (97.6 $\mu\text{mol/l}$, $p = 0.001$) and 7 day (104.4 $\mu\text{mol/l}$, $p=0.003$) after surgery in patients in the AKI(+) group.

The urea indicators in this group also increased in dynamics on 3 day -10.9 $\mu\text{mol/l}$ ($p=0.001$) and on the 7th day - 13.6 $\mu\text{mol/l}$ ($p=0.001$) compared with the AKI(-) group .

Analyzing the data of the results of acid-base state analysis in both groups, we found that children in the group with AKI even before surgery had signs of metabolic acidosis, the pH was 7.327 ± 0.018 ($p=0.01$) compared with the 2nd group, where the pH was normal 7.388 ± 0.01 . And also in the group with AKI on the 1st and 3rd days after the operation, lactatemia above 3 mmol/l was observed.

AKI manifested itself in the form of urinary syndrome as a proteinuria. According to the results of our study, proteinuria as a predictor of AKI manifested itself in varying degrees of severity at all stages of observation. Proteinuria 0.5 g/l was statistically significant in the AKI(+) group on day 1 after surgery in 12 (63.1%) children and on day 3 after surgery in 10 (52.6%) children with AKI. On the 7th day, proteinuria up to 1 g/l was observed in 5 (26.3%) children with AKI, the difference was significant, which could probably indicate a chronic process.

The results of a biochemical analysis of urine similarly revealed proteinuria: before the operation in the AKI(+) group, the protein was determined at the level of 1062 mg/l, on the 1st day after the operation, the protein was at the level of 884.6 mg/l ($p=0.048$).

An analysis of the diagnostic levels of the new AKI biomarker uNGAL in patients with congenital malformations showed that in the AKI(+) group, high levels of the uNGAL marker were noted already at the preoperative stage. Thus, the uNGAL index before surgery was 4.5 times higher than the index of the reference group, 3.3 times higher than the index of patients in the AKI(-) group and amounted to 184.4 ng / ml ($p<0.001$), against 40.7 ng / ml in the reference group and 56.5 ng/ml in the AKI(-) group. The highest peak of uNGAL increase in urine in newborns with AKI was observed as early as 24 hours after surgery with an increase of 2.6 times, amounting to 493.9 ng / ml, ($p < 0.001$), relative to the AKI (-) group of 60.7 ng / ml. On the 3rd and 7th days after surgery, uNGAL in the AKI(+) group began to decrease (435.4 ng/ml and 389.8 ng/ml, respectively), but was still quite high compared to the AKI(-) group (68.3 ng/ml and 34.8 ng/ml, respectively). A comparative analysis of the levels of uNGAL and serum creatinine showed that in the group of children with AKI, the peak of the increase in creatinine began to appear only by the 3rd day, while uNGAL began to decrease already by the 3rd day, which can be taken into account when assessing the prognosis of AKI in newborns: up to operation, the average value of serum creatinine was 76.4316 $\mu\text{mol/l}$ (group AKI(-) - 57.95 $\mu\text{mol/l}$, $p=0.001$); on the 1st day after the operation in the AKI(+) group - 90.6421 $\mu\text{mol/l}$ (the AKI(-) group - 54.2808 $\mu\text{mol/l}$, $p=0.001$), on the 3rd day after the operation - 97.6316 $\mu\text{mol/l}$ (48.7923 $\mu\text{mol/l}$, respectively, $p=0.001$) and on day 7, creatinine in the AKI(+) group reached a peak of 104.4 $\mu\text{mol/l}$ ($p=0.001$).

According to ROC-analysis, the highest prognostic sensitivity was registered on the 1st (89.5%) and 7th (94.7%) days after surgery. The specificity of the early marker of AKI uNGAL in urine was significantly determined on the 1st (96.2%) and 3rd (100%) days of the postoperative period. Analyzing the sensitivity of creatinine before surgery, it was revealed that it was lower compared to the uNGAL marker and amounted to 65% versus 68.4%, and the specificity was 89% versus 91.7%. On the 1st day after the operation, the sensitivity of serum creatinine was also lower - 66.7%, while in uNGAL it was 89.5%. On the 3rd day after the operation, the sensitivity of creatinine was 70%,

and uNGAL - 73.7%. And on the 7th day, the sensitivity of creatinine was lower (57.1%) compared to the uNGAL marker (94.7%). Creatinine specificity was also lower to the uNGAL marker.

We also identified the threshold values of urinary uNGAL at which the development of AKI was predicted: before surgery - 168 ng/ml, on day 1 after surgery - 200.5 ng/ml, on day 3 - 227 ng/ml and on day 7 day - 191.7 ng / ml. In the period before the operation, the positive predictive value of the uNGAL test in children with congenital malformations of the gastrointestinal tract was 38.46% and was less than on the 1st day after the operation - 50%. On the 3rd day after the operation, the prognostic value of uNGAL increased to 64.29% and on the 7th day was 63.64%.

As a result of the analysis of correlations between serum creatinine and uNGAL, a weak direct relationship was found (according to the Chaddock scale) in the period before surgery ($r_{xy} = 0.501$; $p = 0.001$) and a moderate direct relationship after surgery on day 1 ($r_{xy} = 0.600$; $p = 0.001$), 3rd ($r_{xy} = 0.582$; $p = 0.001$) and 7 days ($r_{xy} = 0.584$; $p = 0.001$). Between urea and uNGAL, a direct weak relationship was found before surgery, on the 1st day after surgery. On the 3rd and 7th days after the operation, a moderate direct relationship was found. There was no relationship between GFR and uNGAL, indicating that GFR is not significant in the early diagnosis of AKI in newborns with gastrointestinal tract.

Determined particular value in our study was the determination of clinical and laboratory predictors of early diagnosis of AKI at each perioperative period in newborns with gastrointestinal tract malformations: before surgery: the presence of one or more maternal risk factors (anemia, chronic pyelonephritis, chronic arterial hypertension); early proteinuria in urine analysis less than 0.5 g/l; uNGAL level > 168 ng/ml before surgery; on the 1st day after the operation: blood lactate 3 or more, decrease in PCR below 1.2 ml/kg/h; proteinuria in OAM less than 0.5 g/l; proteinuria in the biochemical analysis of urine > 884 mg / L; uNGAL level > 200.5 ng/ml; on the 3rd day after surgery: proteinuria in OAM less than 0.5 g/l; blood lactate 3 or more; uNGAL level > 227 ng/mL; on the 7th day after the operation: proteinuria in urine analysis from 1 to 3 g/l; uNGAL level > 200.5 ng/ml.

The next group of congenital malformations for studying AKI was patients with congenital heart defects. The age of newborns with congenital heart defects at the time of admission to the hospital was 1.5 days of life in the group with AKI, and 2 days of life in the group without AKI ($p = 0.565$).

In the nosological structure of patients with congenital heart defects in children with AKI (+) group was the most common - coarctation of the aorta (5-31.2%, $p = 0.042$), while in the group without AKI, transposition of the great vessels was more common (10-52.6%, $p = 0.039$).

The obstetric anamnesis of mothers of children with congenital heart defects was burdened equally in both groups. The main significant risk factors were identified: fetal loss syndrome, which was more common in mothers (7-43.7%, $p = 0.025$) of the AKI(+) group; caesarean section in 6 (37.5%) mothers (ATI+, $p = 0.044$). Among the extragenital pathology in the anamnesis of mothers of children with AKI, anemia occurred in 8 (50%) cases ($p = 0.030$); chronic pyelonephritis in 7 (43.7%, $p = 0.025$) cases; Acute respiratory viral infection (ARVI) in the 1st trimester (6 - 37.5%, $p < 0.05$).

The main risk factors for AKI in newborns with congenital heart defects were statistically significantly higher: the duration of surgery - 240 minutes ($p = 0.05$), the duration of the use of pulmonary bypass - 146 minutes ($p = 0.008$) and aortic clamping - 92.5 minutes ($p = 0.024$), duration in the ICU - 24.5 days ($p = 0.024$), receiving mechanical ventilation - 10 days ($p = 0.05$), performing of peritoneal dialysis - 37.5% (6) ($p = 0.05$).

Analysis of the assessment of the severity of the general condition of newborns according to the NTISS scale of children with congenital heart defects showed that on the 1st and 3rd days after the operation, the general condition worsened to a high 4th category of severity (35.9 ± 2.8 and 34.3 ± 5.3 , respectively, $p = 0.001$). On day 7 after surgery, the risk of mortality remained high with category 4 in the AKI group and amounted to 30.6 ± 8.3 ($p = 0.001$).

On the 1st day after surgery, newborns with AKI(+) showed a significant decrease the urine output to 1.1 ml/kg/h, so this should be considered a risk factor for AKI in newborns with congenital

heart disease. GFR according to the Schwartz formula was significantly lower on days 3 day (21.4 ml/min/1.73 m²) and 7 day (31.4 ml/min/1.73 m²) after surgery.

The main clinical symptoms of AKI in newborns with both congenital malformations were edematous syndrome and abnormal weight gain.

The saturation in both groups was below 90% in the period before surgery, indicating the presence of critical heart defect, with an increase on the 1st, 3rd day after surgery.

A comparative analysis of blood biochemical parameters in the group with AKI showed that the creatinine level significantly increased only on the 3rd (89.4 µmol/l, p=0.001) and 7th days after surgery (95.3 µmol/l, p=0.001). The urea levels as well as creatinine in the AKI (+) group, were also statistically significantly higher closer to the 3rd (11.6 µmol/l, p=0.04) and 7th days (11.3 µmol/l) after surgery (p=0.023), compared with the AKI(-) group.

The study of acid-base state analysis in both groups revealed that children with AKI had signs of metabolic acidosis on the 1st day after open heart surgery, pH was 7.3180 (p=0.01) compared with the second group, where the pH was normal 7.4328, which indicated the severity of the surgical intervention and could further affect the formation of AKI. The level of lactate in the acid-base state analysis was significantly high on the 1st and 3rd days after surgery in newborns with AKI.

One of the most important identified clinical and laboratory predictors of AKI was early proteinuria in the general analysis of urine and biochemical analysis of urine. It was observed on the 3rd day after the operation in 10 (62.5%) children, with an increase on the 7th day after the operation in 14 (87.5%), the difference was significant. The proteinuria up to 0.5 g/l was statistically significant on 3rd day after surgery in 9 (56.2%) children versus 4 (21%) and on day 7 after surgery in 12 (75%) children with AKI against 5 (26.3%).

In the biochemical analysis of urine on the 1st day 591.3 mg/l (p=0.002), on the 3rd day 467.7 mg/l (p=0.030), on the 7th day after surgery 467.7 mg/l (p=0.001), compared with patients without AKI.

The diagnostic levels of the uNGAL biomarker showed that already at the preoperative stage in AKI(+) newborns, the mean uNGAL value was 173.5 ng/ml (p<0.001), while in the AKI(-) group it was 30.1 ng/ml. In children in the reference group, this figure was 40.7 ng/ml.

In the first 24 hours after surgery, there was an increase in urine uNGAL in children with AKI on average - 320.7 ng/ml (p<0.001), compared with patients without AKI - 31.8 ng/ml. On the 3rd day after the operation, the average level of uNGAL slightly decreased in the group with AKI to 263.6 ng/ml (without AKI - 31.8 ng/ml) and on the 7th day increased again to 418.6 ng/ml, which is almost 1.5 times more than the marker values on the 3rd day, the difference was statistically significant (p<0.001).

During the comparing of the mean levels of uNGAL and serum creatinine, we found that in the AKI(+) group, the uNGAL values were elevated starting from the preoperative period, while the serum creatinine level began to increase significantly only by 3 (89.4 µmol/l) and the 7th day after the operation (95.3 µmol/l).

The comparative ROC analysis in the AKI group showed that in the AKI(+) group, the sensitivity of creatinine before surgery was 66%, and the specificity was 76.8%, which compared with the uNGAL marker (93.3% and 90%, respectively) was much lower. On the 1st postoperative day, creatinine sensitivity was also lower (87%), while in uNGAL it was 92.9%. On the 3rd day after the operation, the sensitivity of creatinine was 75%, in uNGAL it was 87.5%. On the 7th postoperative day, the patients' creatinine sensitivity was again lower than that of uNGAL (77% versus 80%). The specificity of creatinine was also lower at all stages of observation in comparison with the uNGAL marker.

We identified the cutoff values of uNGAL at which the development of AKI was predicted: before surgery - 152.8 ng/ml, on day 1 after surgery - 284.2 ng/ml, on day 3 - 193.4 ng/ml and on the 7th day - 268.7 ng/ml.

During the period before surgery, the positive predictive value of the uNGAL test was 80%. The prognostic value of uNGAL on day 1 of the postoperative period was 66.67%. On the 3rd postoperative day, the predictive value of uNGAL was 60%, and on the 7th day, the positive predictive value became the highest and was determined at the level of 77.78%.

As a result of the analysis of correlations between serum creatinine and uNGAL, a moderate direct relationship ($r_{xy} = 0.649$; $p = 0.001$) was found (Chaddock scale) on the 1st day after surgery; on the 3rd day moderate direct relationship ($r_{xy} = 0.644$; $p = 0.001$); on the 7th day, a moderate direct relationship ($r_{xy} = 0.789$; $p = 0.001$).

In the study of the correlation between urea and uNGAL, a weak feedback between uNGAL and urea ($r_{xy} = -0.253$; $p = 0.143$) was determined at all stages of observation.

The correlation between GFR and uNGAL showed no relationship, indicating that GFR is not significant in the early diagnosis of AKI in newborns with congenital heart disease, as well as in newborns with congenital malformations.

The main clinical and laboratory predictors of AKI in newborns with congenital heart defects in the perioperative period are as follows: before surgery, the presence of one or more maternal risk factors (anemia, chronic pyelonephritis; ARVI in the 1st trimester; fetal loss syndrome, caesarean section; uNGAL level > 152.8 ng/ml, lactate 3 or more on the 1st day after surgery, early proteinuria in urine analysis less than 0.5 g/l, decrease urine output to 1.1 ml/kg/h, proteinuria in the biochemical analysis of urine > 591 mg/L; uNGAL level > 284.2 ng/ml; on the 3rd day after surgery - increase in blood Lactate > 2.5 ; proteinuria in TAM < 0.5 g/l; proteinuria in biochemical analysis of urine > 467 mg/L; uNGAL level > 193.4 ng/ml; on the 7th day after the operation - proteinuria in TAM < 0.5 g/l; proteinuria in the biochemical analysis of urine > 622 mg/L; uNGAL level > 268.7 ng/ml.

The above results of our scientific research work became the basis for the creation of algorithms of the early diagnostics of AKI in newborns with congenital malformations of gastrointestinal tract and congenital heart defects (2 algorithms), including available valuable clinical and laboratory predictors, as well as cutoff levels of the uNGAL biomarker. The algorithms will be useful for practical healthcare doctors in order to timely for identifying high-risk patients for AKI, the reducing the development of AKI and, consequently, increase the survival rate of newborns with congenital malformations after surgical interventions.

The conclusions.

1. In the structure of congenital malformations of newborns in Kazakhstan, congenital heart defects and congenital malformations of the gastrointestinal tract are more common, among them there is a high risk of development of AKI. The established incidence of AKI in newborns with congenital malformations of the gastrointestinal tract and congenital heart defects was 58%. According to neonatal mKDIGO, stage 1 AKI was the most common. In newborns with congenital malformations of the gastrointestinal tract and congenital heart defects: stage 1 - 47.5% and 50%, stage 2 - 31.5% and 25%, stage 3 - 21% and 25%, respectively.
2. In 80% of etiology of AKI in neonates with congenital malformations it was due to prerenal causes (congenital malformations of the gastrointestinal tract: dehydration - 51.6%; in neonates with congenital heart defects: disseminated intravascular coagulation syndrome - 43.3%), in 12% of renal causes: acute tubulointerstitial nephritis in 58.9% and acute tubulonecrosis at 41.1%.
3. The biomarker uNGAL showed itself as a predictor of AKI with more high sensitivity and specificity compared with serum creatinine. On average, in newborns with congenital malformations of gastrointestinal tract, the sensitivity of uNGAL was 81.6% (64.7% - serum creatinine), and the specificity was 94.1% (91% - serum creatinine). In children with congenital heart defects, the sensitivity was 88.4% (76% - serum creatinine) and the specificity was 87.3% (76% of serum creatinine). The predominant role of the new biomarker uNGAL is also confirmed with a revealed result of the established correlation with the generally accepted indicators of renal dysfunction.

4. The dynamics of diagnostic levels of uNGAL in the perioperative period in newborns with congenital malformations and AKI compared with the reference group showed its prognostic significance for the detection of AKI. The uNGAL rate in newborns with AKI (mean - 178.7 ng/ml) already in the preoperative period was 4 times higher than the data of the reference group (40.7 ng/ml), and the increasing of serum creatinine levels were noted only after 3 days after surgery.
5. The identified cut off values of uNGAL and clinical and laboratory predictors can be included in to the algorithms of early diagnostics of AKI in newborns with congenital malformations.

The practical recommendations:

1. The high prevalence of congenital malformations of the circulatory system and gastrointestinal tract in comparison with other malformations requires the improvement of prenatal diagnostic methods and the work of prenatal consultations.
2. For the purpose of early detection of AKI and timely assessment of the severity of the condition of a newborn with congenital malformations, it is recommended to use and implement the classification neonatal modified KDIGO criteria (2016) into neonatological practice.
3. The uNGAL biomarker as a predictor of AKI in newborns, is the most highly sensitive and specific test compared to standard diagnostic tests, and therefore it is recommended to include it in clinical protocols and use it in practice service.
4. The ability to determine the uNGAL biomarker in urine gives the advantage of this method as a minimally invasive, safe and minimizes the risk of trauma to the newborn.
5. The designed algorithms for the early diagnostics of AKI for newborns with congenital malformations of the gastrointestinal tract and congenital heart defects will be useful for practical health care doctors to correctly assess the risk of development or formation of AKI in the perioperative period, taking into account new approaches to diagnosis and prognosis.

The approbation of the results of the dissertation. The results of the research according to the topic of the dissertation were reported and discussed at 14 conferences of the republican and international levels:

- The International Conference of Clinical Neonatology, June 9-11, 2019, Venice, Italy. Poster report;
- The International Scientific and Practical Conference "Young Researcher: Challenges and Prospects for the Development of Modern Pediatrics and Pediatric Surgery", March 1, 2019, Almaty, Kazakhstan;
- III Forum of young scientists "Burabay Forum" with the support of the Foundation of the First President of the Republic of Kazakhstan, August 6-9, 2019, Nur-Sultan, Kazakhstan;
- III Scientific and Practical Conference of Young Scientists, National Scientific Cardiac Surgery Center, September 16, 2019, Nur-Sultan, Kazakhstan;
- 3rd Congress of joint European Neonatal Societies-jENS 2019, September 17-21, 2019 Maastricht, Netherlands, Poster presentation;
- II International Congress "Continuing Medical Education in the Republic of Kazakhstan. Emergency medicine: education, science and clinical practice", October 24-25, 2019, Almaty, Kazakhstan;
- Scientific and practical conference with international participation "Integration of pediatric science, education and practice", December 6, 2019, Almaty, Kazakhstan;
- International Scientific and Practical Conference "Young Researcher: Challenges and Prospects for the Development of Modern Pediatrics and Pediatric Surgery", March 3, 2020, Almaty, Kazakhstan;
- IX Congress of Pediatricians of Kazakhstan "Achievements and Prospects for the Development of Pediatrics and Pediatric Surgery", April 21-23, 2021, Almaty, Kazakhstan;
- IV International Scientific and Educational Forum "Ana Men Bala", May 20-21, 2021, Almaty, Kazakhstan;

- Scientific and practical conference with international participation "Innovative technologies in the service of perinatology and pediatric cardiac surgery", November 19, 2021, Almaty, Kazakhstan;
- International Scientific and Practical Conference "Young Researcher: Challenges and Prospects for the Development of Modern Pediatrics and Pediatric Surgery", April 22, 2022, Almaty, Kazakhstan;
- International scientific and practical conference "Pediatrics of Kazakhstan: yesterday, today and tomorrow", October 6-7, 2022, Almaty, Kazakhstan;
- Th Republican scientific and practical conference with international participation "Topical issues and innovative technologies in anesthesiology, resuscitation and intensive care", October 13-14, 2022, Almaty, Kazakhstan.
- VI Congress of the "Kazakh Society of Anesthesiologists and Resuscitators", March 31-April 1, 2023, Almaty, Kazakhstan

The publications on the topic of dissertation. Based on the results of the study, 14 scientific papers were published and accepted for publication, of which 1 article was published in a journal indexed by Scopus and Thomson Reuters databases and has a percentile above 25% at the time of publication-33%; 4 articles were published in publications recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, 9 publications in the materials of international and local conferences.

The implementation. We have 4 acts of implementation, 2 copyright certificates have been received. The use of an early minimally invasive AKI biomarker uNGAL was introduced into the work of 4 pediatric resuscitation centers in Almaty. In 2 intensive care units of the neonatal profile: neonatal ICU of the Scientific Center of Pediatrics and Pediatric Surgery and ICU of the Center for Children's Emergency Medical Care in Almaty and in 2 intensive care units of the cardiosurgical profile: the cardiac intensive care units of the Center for Perinatology and Pediatric Cardiac Surgery in Almaty and the ICU Scientific Center of Pediatrics and pediatric surgery.

The results of the study on early diagnostics of AKI in newborns with congenital malformations are included in the educational program for the training of neonatologists for residents of the course "Neonatology" of the Kazakh-Russian Medical University.

The author's certificates: 1. "The algorithm for the early diagnostics of AKI in newborns with congenital malformations of the gastrointestinal tract" (No. 32253 dated February 3, 2023),
2. "The algorithm for the early diagnostics of AKI in newborns with congenital heart defects" (No. 32254 of February 3, 2023).

Author's certificates: 1. "The algorithm for the early diagnostics of AKI in newborns with congenital malformations of the gastrointestinal tract" (No. 32253 dated February 3, 2023),
2. " The algorithm for the early diagnostics of AKI in newborns with CHD" (No. 32254 of February 3, 2023).

The personal contribution of PhD candidate is in the formation the choice, justification of the direction of research; creating a study design; organizing and conducting all its stages; collection, processing and analysis of data; design, presentation and discussion of the results of the dissertation. The author personally collected the laboratory material of each patient at all stages of observation, the volume of special research methods was also carried out with the personal participation of the dissertation student. A set of archive data for 5 years was independently carried out, its analysis and statistical analysis were carried out. The formulation of conclusions, practical recommendations was carried out, the development of two algorithms belongs to the author.

The structure and volume of the dissertation. The dissertation is presented on 158 pages, consists of an introduction, a review of the literature, materials and research methods, sections of the results of their own research, conclusions and practical recommendations, and two applications. The work is illustrated with 62 tables and 61 figures. The bibliographic list contains 130 literature sources.

