НИРКИ KIDNEYS

UDC 616.5-001.17:61-008.64 DOI: https://doi.org/10.22141/2307-1257.13.1.2024.445

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Kidney damage in burn disease. Part 2. Biochemical markers (literature review)

For citation: Počki. 2024;13(1):80-88. doi: 10.22141/2307-1257.13.1.2024.445

Abstract. *Recently discovered specific markers open up new possibilities for the diagnosis of acute kidney injury (AKI) in burn disease in order to optimize the treatment of such patients. Early diagnosis with the involvement of biomarkers prevents the sudden death of burn patients and allows predicting the course of the pathological condition. There are several characteristics that an "ideal" AKI biomarker should conform to: being non-invasive, locally specific, highly sensitive, being a stable molecule at different temperatures and pH values, having the ability to rapidly increase in response to kidney injury (quantify it), remaining at high levels during the episode and decreasing during the recovery period. There is a difference between the biomarkers that can be freely filtered in the glomerulus, so any increase in their plasma concentration (due to damage to other renal tissues) can lead to a high concentration of indicators in the urine (loss of specificity), and high-molecular-weight markers that are not freely filtered and therefore are more specific when measured in urine. Renal function in burn patients is usually determined by blood and urine tests, as biopsy can cause iatrogenic damage and is not commonly used in this cohort. After the onset of AKI, the level of biomarkers remains elevated for a certain period. None of the described indicators is monospecific for AKI; this makes estimating the time of AKI quite difficult. It has been proven that the combination of three biomarkers at two different time points in adults and the combination of two indicators at two time intervals in children allows to increase the reliability of determining AKI up to 0.78.*

Keywords: *review; burn disease; acute kidney injury; chronic kidney disease; pathogenesis; biological markers*

Severe burn injuries are associated with a high risk of acute kidney injury (AKI). When such pathological conditions coincide, the number of remote complications, the need for renal replacement therapy (RRT), the length of hospital stay, and material costs increase [1]. AKI has long been considered only a side effect of serious diseases; currently, this pathology is recognized as a serious factor of short- and long-term negative prognosis. Recently discovered specific markers open up new possibilities for the diagnosis of AKI in order to optimize the treatment of such patients [2, 3]. Early diagnosis with the involvement of biomarkers prevents the sudden death of burn patients and allows predicting the course of the pathological condition [4].

Over the past thirty years, despite the reported effectiveness of various biomarkers, their potential has not been fully realized in comparison with the insufficiently effective indicator of plasma creatinine (Crp). There are limitations to the use of indicators obtained in animal models of AKI, which are significantly different from human ones. In order to determine new biomarkers of the AKI syndrome, it is advisable to divide it into ischemic, nephrotoxic, septic, acute cardiorenal syndromes, etc. To confirm the effectiveness of the markers, it is expedient to obtain and evaluate kidney biopsy samples in human AKI populations. Research in this direction should be conducted within the framework of a general social approach, and not only by a few medical institutions. The first step to overcome severe AKI will be to find biomarkers that will have excellent performance in early diagnosis, risk assessment, response to the treatment and prediction of the course of AKI [3].

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There are several characteristics that an "ideal" AKI biomarker should meet [1, 4, 5]:

— being non-invasive, locally specific, highly sensitive;

— being a stable molecule at different temperatures and pH;

— having the ability to rapidly increase in response to kidney damage (quantify it);

— remaining at high levels for the entire episode;

— decreasing during the recovery period.

Urine is an ideal body fluid for assessing AKI biomarkers because it can be obtained non-invasively and repeatedly. However, there is a difference between biomarkers that can be freely filtered in the glomerulus; so, any increase in their plasma level (due to damaging other renal tissues) may cause high concentrations of indicators in urine (loss of specificity), and high-molecular-weight markers that are not filtered freely and therefore are more specific when measured in urine [3]. Renal function in burn patients is usually determined by blood and urine tests, as biopsy can cause iatrogenic damage and is not commonly used in this cohort [6, 7].

The volume of urine 0.8–1.0 ml/kg/h reflects adequate perfusion pressure [1, 8]. However, in oliguria it is necessary to determine whether a decrease in urine volume is a consequence of functional (prerenal) oliguria or organic (renal) insufficiency. Prolonged renal dysfunction is often observed before the development of organic damage. Under nonoliguric renal pathology, the volume of urine does not have a paramount significance for the diagnosis [8]. The rate of diuresis is a relative indicator of kidney injury, but while anuria indicates the presence of kidney injury, sufficient diuresis, on the other hand, is not a complete guarantee of safety [9]. Nevertheless, in patients with severe burn injuries, it is not easy to make a diagnosis of AKI, given that:

— clinically, the hourly urine output (UO) can be relatively normal, and due to massive fluid therapy in many cases even underestimated;

— the Crp level, despite the presence of renal injury, does not rise quickly.

Hourly UO is one of the criteria for determining AKI. UO often decreases before serum creatinine increases, making itself an urgently sensitive marker of glomerular filtration rate (GFR). However, a decrease in UO is not necessarily a sign of AKI (prerenal oligoanuria, certain variants of tubulopathies, etc.). Using the common urine chemical markers can help diagnose, evaluate, and determine the underlying cause of AKI. Therefore, in case of so-called subclinical AKI, in the absence of signs and symptoms new biomarkers are of primary importance [1, 3].

Since creatinine is excreted from the body by the kidneys, its level can be recognized as a marker of their excretory function. Plasma creatinine level is related to muscle mass, and for this reason, it is usually higher in men than in women. Crp can be freely filtered in the Malpighian cells and secreted in the proximal convoluted tubules (10 % of the clearance, that is, the number of milliliters of blood plasma cleared from creatinine by the kidneys in 1 min) with a half-life of about 4 h. Age, sex, ethnicity, body weight, catabolic state, and the use of certain drugs can affect fluctuations in its blood serum concentration. In burn patients, the situation is much more complicated [1, 8]. In the patients with thermal burns whose serum creatinine level increased more than 132.6 μmol/L above the baseline in the absence of shock, the mortality was 72.7 %, much higher than in the people without renal dysfunction (16.6 %) [2, 8, 10]. Crp is a delayed and insensitive biomarker of renal function changes in intensive care unit patients. Creatinine levels can be affected by its initial concentration, fluid overload, malnutrition, and muscle exhaustion [3]. Burns cause changes in Crp, but in post-burn AKI, the result can be difficult to predict. Burns are sometimes complicated by muscle wasting, liver failure, iatrogenic hyperhydration, and sepsis, which lower Crp levels. On the contrary, its values can increase as a result of dyshydria after trauma, during fever and immobilization [6, 7, 11].

It is well known that a significant decrease in the functional state of the kidneys may not be accompanied by a corresponding increase in creatinine level, sometimes even for several days. All of the above makes us look for more accurate markers of kidney damage. The results of individual studies proved that the concentration of creatinine in blood serum and the rate of urine output cannot be universal means for assessing the risk of kidney damage in burn patients [1, 2, 12, 13] and the patients' ability to recover from severe burn disease [9].

The Crp level to a certain extent reflects GFR and is useful for assessing the prognosis in renal dysfunction, but it does not accurately reflect acute changes, since its values in the plasma increase only when the GFR decreases by 30–40 % [1, 8].

Estimated glomerular filtration rate (eGFR) is an integral indicator of the functional state of the kidneys. According to the classical definition, eGFR is determined by the clearance of a substance that is not reabsorbed in the renal tubules (inulin). Therefore, creatinine clearance always exceeds eGFR, and the use of calculation results according to the Cockroft-Gault formula can lead to hypodiagnosis of AKI [2]:

$$eGFR\ (ml/min/1.73\ m^2) = \frac{[140 - age\ (years)] \times body\ weight\ (kg)]}{[Crp\ (\mu mol/l) \times 0.8] \times \times 0.85\ (for\ women)},$$

where eGFR is the estimated GFR; Crp is blood plasma creatinine.

The advantage of the Modification of Diet in Renal Disease equation is that it was derived on the basis of a multicenter study of I125-iothalamat clearance in white and black patients with a wide range of renal pathology [2]:

$$eGFR\ (ml/min/1.73\ m^2) = 175 \times (Crp \times IDMS / 88.4) - 1.154 \times age\ (years) - 0.203 \times 0.742\ (for\ women) \times \times 1.212\ (for\ African\ Americans),$$

where IDMS = 0.95, if the isotope dilution mass spectrometry (IDMS) method is used, if not, then IDMS = 1.00.

The most reliable is the calculation of eGFR with the involvement of the urine creatinine concentration according to the formula of P. Reberg and E.M. Tareev:

$$eGFR\ (ml/min/1.73\ m^2) = \frac{\rightleftarrows Cru}{Crp} \times V,$$

where Cru is creatinine content in urine; V is the volume of urine released in one minute (minute diuresis).

Body surface area (BSA) can be calculated using D. Dubois formula:

$$BSA = 0.007184 \times [height\ (cm)]^{0.725} \times [weight\ (kg)]^{0.425}.$$

With a non-standard surface area of the patient's body (obesity, gigantism, etc.), the formula can be used to determine the GFR more accurately:

$$GFR = \frac{eGFR}{1.73} \times BSA.$$

The level of GFR < 60 ml/min/1.73 m^2 indicates a loss of 50 % of the filtration function of the kidneys. GFR values less than 60 ml/min/1.73 m^2 indicate the danger of rapid progression of both renal and related cardiovascular pathology [13]. At admission, 15.1 % of patients with thermal burns had estimated GFR < 60 ml/min/1.73 m^2. AKI occurred in 38.5 % of the patients.

The development of AKI was associated with:

— older age ($p < 0.001$);

— female gender ($p = 0.017$);

— obesity ($p = 0.055$);

— area and depth of burns, hypoxia, hypoproteinemia ($p < 0.001$);

— hypotension ($p = 0.014$);

— leukocytosis ($p = 0.010$).

Mortality was [14] 100 % with initial GFR < 60 ml/min/1.73 m^2 and early deterioration of renal function; 80 % with initial GFR < 60 ml/min/1.73 m^2 and late deterioration; 60 % with initial GFR < 60 ml/min/1.73 m^2 without deterioration of renal status.

In chronic kidney disease (CKD), GFR < 60 ml/min/1.73 m^2 is observed for more than three months [10]. An increase in the concentration of the tumor marker β_2-microglobulin in blood serum correlates with a decrease in GFR [1, 8].

AKI as defined by the Kidney Disease Improving Global Outcomes (KDIGO) is a clinical syndrome characterized by [11, 16–18]:

— an increase in serum creatinine concentration of 26.5 mmol/l within 48 h;

— or a 1.5-fold increase in serum creatinine concentration in the last 7 days;

— or UO < 0.5 ml/kg/h lasting at least 6 h.

Acute Kidney Injury Network (AKIN) guidelines rely only on Crp and not on GFR changes. The initial Crp level is not mandatory in the AKIN classification, but the method requires at least two Crp values obtained within 48 h. AKI is defined by a sudden decrease (after 48 h) in renal function with an increase in Crp of at least 26.5 μmol/L or by no less than 50 %, or a decrease in UO less than 0.5 ml/kg/h for more than 6 h. AKIN classification indicates three stages of kidney injury [19]:

— stage 1 corresponds to the risk class with an increase in Crp at least 26.5 μmol/l;

— stages 2 and 3 correspond to classes of injury and failure;

— stage 3 also considers patients who require RRT.

Loss of functions and end-stage renal disease were removed from the classification [19].

The RIFLE criteria indicate three stages of kidney injury based on serum creatinine and/or diuresis, reflecting a decrease in eGFR with subsequent duration and severity of diuresis decrease [20]. Recently, the RIFLE criteria have been adapted to the burn population to correlate early AKI, late AKI, and worst RIFLE scores with hospitalization outcomes [19, 21].

The RIFLE criteria define [1]:

— risk (R) — an increase in the serum creatinine level by 1.5–1.9 times above baseline or a decrease in GFR > 25 %, or UO less than 0.5 ml/kg/h within 6–12 h;

— injury (I) — an increase in the serum creatinine level by 2–2.9 times above baseline or a decrease in eGFR more than 50 %, or UO less than 0.5 ml/kg/h within 12 h;

— failure (F) — an increase in the serum creatinine level by 3 times or by more than 353.6 μmol/l compared to the baseline or a decrease in GFR more than 75 %, or UO less than 0.5 ml/kg/h within 24 h, or anuria lasting more than 24 h;

— loss (L) — loss of kidney function for over 4 weeks;

— end stage (E) — kidney failure for over 3 months.

Early AKI was defined as the worst RIFLE outcome within the first 48 h (17.7 %). Progressive AKI (7.3 %) developed in patients with early AKI in whom the RIFLE score either remained unchanged or subsequently worsened [21]. An increased risk of mortality was determined in burn patients as RIFLE-I (injury) and RIFLE-F (failure) [1].

Cystatin C (cyst-C) is a polypeptide with a molecular weight of 13.4 kDa, which is an inhibitor of cysteine proteases with a half-life of 90–120 min [22]. Reference values are 0.4–1.2 mg/l. It is filtered by the glomeruli, almost completely reabsorbed and catabolized (but not secreted) in the proximal tubule, and can serve as a marker of glomerular function in the absence of serum creatinine increase. Its concentration in blood plasma is affected by [2, 3, 23]:

— age, gender, height, body weight;

— smoking;

— serum level of C-reactive protein;

— steroid therapy;

— rheumatoid arthritis;

— level of triglycerides, total cholesterol and low-density lipoprotein cholesterol.

Only a small portion of cyst-C is excreted in the urine. Thus, serum cyst-C changes appear before creatinine modification, 3–6 h after the onset of renal dysfunction, with a peak at 48 h [5, 22]. The life cycle of cyst-C is only half of that of Crp (1.5–2 vs. 4 h), that is, when kidney function suffers, cyst-C level changes much earlier than Crp [24]. In the equilibrium state, there is an inverse relationship between the creatinine/cyst-C ratio and eGFR [11, 13].

Reference values of cyst-C in blood serum are:

— 0.75 mg/l in 4–19-year-olds;

— 0.74 mg/l in men and 0.65 mg/l in women aged 20–59 years;

— 0.83 mg/l for people over 60 years old.

The benefits of using cyst-C to assess GFR have not been conclusively proven. Cyst-C content in biological fluids is determined using immunoenzymatic, immunoturbodimetric, or immunonephelometric methods [2]. Measurement of cyst-C levels in blood serum reflects glomerular function, its dynamics in the entire range of eGFR, from hyperfiltration to the early stages of hypofiltration. With a normal level of creatinine, an elevated level of serum cyst-C indicates preclinical kidney disease. Measurement of the cyst-C concentration in urine reflects tubular dysfunction, which very often precedes the development of glomerular injury and microalbuminuria [25, 26]. The study of the functional cyst-C biomarker allows predicting transient forms of AKI [1, 27]. Cyst-C has a higher accuracy and sensitivity for identifying AKI after critical burns, especially in older patients [28]. Its levels may be affected by systemic inflammation, especially in burn patients who are at risk for rapid infection [1]. Cyst-C is a stronger predictor of the risk of death and cardiovascular events in the elderly than creatinine [3]. Cyst-C is a valid marker not only for diagnosing CKD, but also for predicting AKI [24, 26]. A one-time measurement of cyst-C allows to calculate GFR according to specially developed formulas, the most used of which is Hoek's formula [29]:

$$eGFR\ (ml/min/1.73\ m^2) = \frac{80.35}{cyst\text{-}C\ (mg/l)} - 4.32.$$

It has been proven that the determination of GFR in patients with CKD using the cyst-C equation is more correct if gender, race and body mass index are taken into account [11, 13].

Neutrophil gelatinase-associated lipocalin (NGAL), or renal troponin, is a protein with a molecular weight of 25 kDa. It is a component of lipocalin, which is produced by immune cells, renal epithelium and hepatocytes under stress conditions. NGAL is freely filtered from the blood plasma through the Malpighian glomeruli and further is largely reabsorbed in the proximal tubule and break up. The renal source of NGAL is found in the distal nephron, while the proximal convoluted tubule is responsible for its reabsorption [1, 26, 30]. Excretion of plasma NGAL in the urine occurs only when the proximal convoluted tubule is damaged, which limits the reabsorption of lipocalin. When the renal endothelium is damaged, during the first hours, NGAL in increased amounts enters the lumen of the renal tubules and is excreted in the urine (the concentration of NGAL in the urine increases 25–1000 times) [31]. Quantitative determination of NGAL is carried out by the method of immunoenzyme analysis, and its level in the blood correlates with the duration and severity of AKI. Usually, blood content is low, 40–100 ng/ml, due to free filtration and a short half-life (about 10 min). An increase in the serum level of NGAL greater than 170 ng/ml is an indicator of the development of manifest cardiorenal syndrome with a sensitivity of 100 % and a specificity of 86.7 %. The content of NGAL in blood serum above 258 ng/ml in the combination with an APACHE II score over 13 points is the most powerful predictor of postoperative AKI in combustiology. Determination of the urinary NGAL level reflects tubular dysfunction, its increase with a normal level of Crp indicates subclinical AKI [2, 25, 30]. Urinary NGAL has high accuracy and sensitivity in diagnosing early AKI approximately 24–48 h before serum creatinine increases, as well as the ability to predict the need for RRT and identify prerenal azotemia. Whole blood NGAL is an independent predictor of AKI in the first four hours after severe burn compared with changes in serum creatinine or UO, which showed no significant variation and had no prognostic value in patients who developed AKI within the first week after burn. NGAL is used as an early marker of AKI and as a predictor of AKI outcome in burn patients, and at the same time helps predict morbidity and mortality in these patients, that is, plasma NGAL is recognized as a valid predictor of severe burn injury. High levels of NGAL in plasma and urine are prognostic markers of early burn AKI and mortality in patients who develop burn shock, but it is not recognized as a useful indicator of late AKI [3, 23, 24, 27].

An increase in the urinary NGAL on the first day is the main marker of AKI development; NGAL urinary concentration increases within 3 h after an injury, with a peak in 6 h [1, 32, 33]. Urinary NGAL shows good results in predicting the occurrence of kidney damage starting from the fourth week of burn disease [1, 22, 24].

In a cohort of patients with critical burns, despite the fact that cyst-C level increased in the first 12 h after burn injury and was independently associated with the occurrence of AKI, it did not show superiority over NGAL [1]. In patients with massive burns, plasma and urinary NGAL levels increased rapidly during early AKI, followed by serum cyst-C and creatinine. Elevated NGAL in plasma and urine within 48 h in the early postburn period has been associated with early mortality from AKI and burn shock [26, 27]. Serum NGAL increases within 7 days before the development of burn-induced AKI, significantly correlating with burn surface area, AKI and mortality [1]. NGAL is also a reflection of the inflammatory state in burn patients. Therefore, it should not be used as a single marker to predict AKI in this population. The level of NGAL can increase in conditions of sepsis and CKD [1, 3].

Kidney injury molecule-1 (KIM-1) is a transmembrane protein with immunoglobulin and mucin segments with a molecular weight of 38.7 kDa. It is not detected in normal kidney tissues, but is expressed at a very high level on the surface of epithelial cells of the proximal tubules after their ischemic or toxic damage; can be localized in the proliferating undifferentiated epithelial cells of the proximal tubule 48 h after the alteration, while an increase in the serum concentration of KIM-1 precedes an elevation in the levels of urea and creatinine [25]. It is determined by immunoenzymatic analysis. In case of normal kidney function, it is usually not detected in plasma. The concentration in the urine of healthy people is less than 1 ng/ml. However, after ischemic kidney damage, its level can be increased to 3–7 ng/ml. With ischemia, the level of KIM-1 in the plasma begins to increase after 6 h and remains elevated for 48 h after its termination. An elevation of the KIM-1 level in urine is associated with an increased risk of AKI. A correlation between the KIM-1 level and the APACHE II score, in-hospital mortality and the need for RRT was determined. High

levels of KIM-1 were associated with worse survival after kidney transplantation. Renal dysfunction most closely correlated with KIM-1 and to a lesser extent with NGAL and interleukin-18 (IL-18) [2]. Elevated KIM-1 levels are associated with a more than 12-fold increased risk of AKI [3]. In patients with severe burn injuries, urinary KIM-1 is high that is detected earlier compared to serum creatinine. It also demonstrates the ability and sensitivity to predict the development of AKI after hospitalization, correlating with the burn area and the presence of rhabdomyolysis. In addition, KIM-1 and IL-18 can be used to predict the development of AKI in the post-burn period. Further research in this area is needed to show the utility of KIM-1 in patients with severe burns. It is a marker of both renal injury and repair, which begins to increase 6 h after injury, with a peak value at approximately 48 h [1]. KIM-1 can be increased in conditions of chronic proteinuria and inflammatory diseases [3].

A burn injury, which leads to AKI, as a preliminary undergoes the earliest stage of increased risk or acute renal stress that can actually be detected before kidney damage occurs [3]. Over the past decade, a number of new biomarkers of damage have been evaluated for their ability to detect "subclinical" AKI before renal function begins to decline. Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), which are expressed and secreted in tubular cells, are markers of cell cycle arrest, and play an important role during the early phase serving as such markers at the early stage of cellular stress. The first one has a molecular weight of 24 kDa, and the second one of 29 kDa [3, 34]. TIMP-2 and IGFBP7 are considered biomarkers of the pre-alterative phase because they are filtered by the glomeruli. These biomarkers can predict the development of moderate to severe AKI in high-risk patients within 12 h. In addition, there is evidence that TIMP-2 and IGFBP7 may better predict the development of moderate and severe stages of AKI. A meta-analysis on the same issue demonstrated that these urinary biomarkers are particularly useful in ruling out the diagnosis of AKI. They also predict the need for RRT [34]. The combined urinary biomarker [TIMP-2] × [IGFBP7] is already FDA approved and commercially available in the US. But it should not be used in outpatient practice, it does not benefit patients with KDIGO stage 2 or 3 of AKI. The level of [TIMP-2] × [IGFBP7] may be increased in diabetes [3]. Most researchers have concluded that NGAL (tubular biomarker) is predictive for early detection of AKI. The combination of stress biomarkers and tubular NGAL may serve as the best tool for predicting moderate and severe stages of AKI [1]. Research on the benefit of urinary TIMP-2 and IGFBP7 in burn patients is limited. A recent report showed that these markers are superior in the early prediction and diagnosis of AKI in high-risk patients. The utility of NGAL in combination with IGFBP7 is the second best choice, with NGAL as a single biomarker being less predictive [1].

IL-18 is a 22-kDa proinflammatory cytokine that mediates ischemic renal injury, which increases after renal reperfusion. Patients with AKI had significantly higher mean urinary IL-18 concentrations than those with other diseases (prerenal azotemia, urinary tract infection, CKD, and nephrotic syndrome). Mean urinary IL-18 concentrations measured in the first 24 h after kidney transplantation were higher in patients who received a cadaveric kidney than in patients who received a kidney from a living donor. However, urinary IL-18 levels measured one day before AKI were average. An increase in the content of IL-18 in the hypoxia zone and its elevated urinary levels were determined in the ischemic variant of AKI. A significant increase in the serum level of IL-18 was found in all patients with acute tubular necrosis. In kidney recipients, in cases of delayed transplant rejection, an increase in IL-18 content in urine was noted, compared to patients with acute rejection. An increase in the IL-18 level was also associated with a longer intensive care unit and total hospital stay, with high risks of RRT and death [2, 3, 23, 24]. The level of IL-18 increases within 24–48 h before the development of AKI (especially ischemia-reperfusion injury), on average about 2 days before the changes in serum creatinine or urea nitrogen. Urinary IL-18 level increases during the first 6 h after kidney injury, with a peak at 12–18 h, and has a high sensitivity and specificity (more than 90 %) for the diagnosis of AKI. It should be emphasized that several studies have concluded that IL-18 may be a useful biomarker for the detection of subacute tubular necrosis rather than prerenal AKI, but since it can also be elevated in patients with sepsis, interpretation of this increase should be done with caution. Compared to NGAL levels, IL-18 shows a slower rise [1] and has a low to moderate ability to predict AKI, RRT, or 90-day mortality in this large cohort of critically ill patients. Thus, it should be used with caution in critically ill patients for diagnostic or prognostic purposes [35].

As a rule, after kidney injury, IL-18 causes additional kidney damage during the inflammatory phase. NGAL, due to its antiapoptotic properties, limits this dangerous reaction, and TIMP-2 and IGFBP7 limit kidney injury even more. KIM-1 and TIMP-2 appear to support renal tissue repair and remodeling, with NGAL stimulating tubular cell proliferation. In addition, it has been documented that the combined assessment of several biomarkers provides opportunities to better predict the development and evolution of AKI [1].

Liver-type fatty acid-binding protein (L-FABP) is a 14-kDa protein localized primarily in the proximal tubule. An increase in the level of L-FABP in urine is observed 1 h after ischemia onset. A meta-analysis revealed an estimated sensitivity of urinary L-FABP level for the diagnosis of AKI, which was 74.5 %, and specificity of 77.6 %. Although urinary L-FABP may be a promising biomarker for early detection of AKI, prediction of dialysis requirement and in-hospital mortality, it is suggested that the potential value of L-FABP needs to be confirmed in larger studies and in a wider range of clinical observations [2, 3]. Elevation of L-FABP may be associated with anemia in non-diabetic patients [3].

MicroRNAs (mRNAs) are endogenous single-stranded non-coding mRNAs of approximately 19–23 nucleotides. Several mRNAs have been investigated for their potential as novel biomarkers for the early detection or prediction of AKI. Given the complex pathophysiology and dynamic nature of AKI, a mRNA panel may be more appropriate as a predictor than a single mRNA. Further validation studies are needed to assess the clinical utility of such a panel [3].

Wnt/β-catenin signaling is relatively suppressed in the adult kidney, although it plays an important role in kidney development. Over the past few years, studies have shown that Wnt/β-catenin signaling may play a key role in promoting tubular repair and regeneration after AKI. The Dickkopf protein family (DKK1–4) is expressed in the developing kidney but is turned off in adulthood. The DKK3 protein (Dickkopf Wnt signaling pathway inhibitor 3) is induced by stress, is secreted exclusively by the epithelium of the proximal tubules, inhibits the activation of the Wnt/β-catenin pathway. So, its concentration in urine can serve as a biomarker of the stress phase before kidney damage, but it is not effective for the diagnosis of late stages of AKI. Further multicenter studies are needed to assess the clinical utility of such AKI markers [3].

Hemojuvelin (HJV) is a glycophosphatidylinositol-linked membrane protein highly expressed in liver and skeletal muscle. The molecular weight of HJV is 42 kDa for the soluble form, so HJV may be filtered by the Malpighian glomeruli and reabsorbed by the renal tubules. Increased iron content in the kidneys and urine is observed in animal models and in burn patients with AKI, and increased iron load can cause damage to renal tubular cells. Elevated expression of the hemojuvelin-hepcidin-ferroportin pathway is an internal response to conditions of iron overload in AKI. Thus, urinary HJV may be an early biomarker of AKI in response to disturbances in iron homeostasis, which explains the temporal relationship between urinary HJV and its prognostic ability [3].

Osteopontin (OPN) is an extracellular matrix protein that participates in the inflammatory response, binds integrin, modulates the activation, migration and differentiation of leukocytes, as well as the secretion of cytokines in both acute and chronic inflammation. Circulating levels of OPN are not only elevated in burn sepsis, but they also increase progressively throughout the systemic inflammatory response syndrome, sepsis, and septic shock; they are associated with a higher mortality rate in both animal models and patients with sepsis. OPN plasma concentration is an independent predictor of sepsis and is positively correlated with plasma creatinine. However, this association does not explain the development of AKI, as no difference in OPN concentration was found between patients with and without AKI. Therefore, further studies are needed to clarify the role of OPN in septic AKI [3].

Among all marker variables, blood urea nitrogen (BUN) was independently associated with the development of AKI. A direct correlation between BUN and burn AKI has been found [1, 4, 8].

Lactate dehydrogenase (LDH) is an intracellular cytoplasmic enzyme that catalyzes the conversion of pyruvate to lactate via the glycolytic pathway. LDH increases in the extracellular environment when cells are lysed or their integrity is disrupted. LDH over 380 U/l is the leading risk factor for AKI [36]. Early elevation of LDH after hospitalization is an independent risk factor for early AKI in patients with severe burns, increasing by 45.2 % for each 100 U/l increase in LDH. It also serves as an indicator of mortality risk [37].

Under significant thermal damage, up to 50 % of circulating erythrocytes are destroyed within the first 48 h. An increase in the concentration of free hemoglobin in blood serum of more than 1 g/l indicates hemolysis. With burns of 21–50 % of the body surface, hemoglobinuria occurs in 33 % of victims already on the first day. Absorbed by the tubular epithelium, free hemoglobin decomposes into globin and heme; the latter can cause tubule damage through the formation of oxygen free radicals via iron ions. These proteins can be etiological factors in the development of hemoglobinuria and hemoglobinuric nephrosis on the first or second day after a burn injury [8].

The feature of burns is a significant systemic tissue destruction [36]. Rhabdomyolysis is a key feature for the development and progression of AKI caused by burns [38]. Rapid release of myoglobin due to rhabdomyolysis causes the development of myoglobinuric nephrosis resulting from tubular obstruction due to the formation of myoglobin casts and direct nephrotoxicity. Normally, the blood contains from 7 to 85 ng/ml of myoglobin. Myoglobin has a half-life of 3 h only. The renal threshold of serum myoglobin is 150–170 μg/l [39, 40]. When its content in blood serum exceeds 250 ng/ml, macromyoglobinuria develops with urine acquiring a dark brown color ("tea color" or "cola color") later, and anuria develops rather quickly [41]. It has been proven that free myoglobin has a significant prognostic value for AKI with pronounced sensitivity and specificity [42].

Platelet distribution width (PDW) after hospitalization is an early independent biomarker of the risk of severe AKI and the need for RRT in large burns; the risk of AKI increases by 30.9 % for every 1 % increase in PDW. There is a higher predictive value of PDW in combination with BUN for the development of AKI. If PDW exceeds 17.7 %, burn patients always have a higher risk of AKI with a greater degree of severity. Due to the low cost and wide availability, it can be predicted that PDW may be an indicator of AKI development in burn patients [15].

Functional azotemia can occur against the background of prerenal oligoanuria (PRO) as a result of inappropriate fluid resuscitation with dehydration and hypovolemia, or at a late stage of the pathological process. In septic shock, the creatinine synthesis may be reduced or have false negative values in case of fluid overload [1].

Free water clearance (CH_2O) is a useful parameter for early diagnosis of renal failure. The calculation is carried out according to the formula:

$$CH_2O = UO - UO \times \frac{\textit{urine osmolarity}}{\textit{plasma osmolarity}}.$$

The reference value of CH_2O is [+15] ml/h, which drops to almost zero before renal failure develops [1, 8].

Traditional urinary biomarkers such as low- and high-molecular-weight proteins (α_1-microglobulin, β_2-microglobulin, retinol-binding proteins, etc.), tubular brush-border antigens (Na^+/H^+ exchange isoform-3), urinary enzymes (α-glutathione-S-transferase, γ-glutamyl transpeptidase, N-acetyl-β-D-glucosaminidase, etc.), Tamm-Horsfall protein were not included in the diagnostic algorithm for AKI due to the lack of standardized tests and the specificity of urine markers [3].

Proteinuria is an indicator of the risk of developing kidney injury and the severity of burn disease [9], and it is a fairly common clinical finding in patients with severe burns and AKI associated with septic shock [6, 8]. Sepsis, burn area above 30 % of the body surface, and old age are the main independent risk factors for proteinuria whose duration and nature directly correlate with the severity of the burn and septic process [6]. Glomerular dysfunction is associated with increased renal excretion of high-molecular-weight proteins, and tubular dysfunction is associated with increased secretion of low-molecular-weight proteins (less than 60 kDa) due to impaired tubular reabsorption and/or degradation of these proteins (selective proteinuria). In some patients with burns, transient damage to the glomeruli may be accompanied by albuminuria immediately after the burn, with a subsequent increase in the excretion of high-molecular-weight proteins (non-selective proteinuria) up to 5 days after the burn. However, a direct correlation between proteinuria and the development of renal dysfunction was not found [8]. The severity of proteinuria positively correlated with the peak creatinine at continuous RRT. Plasma from patients with severe burn sepsis is able to induce apoptosis of podocytes and renal tubular cells, thereby increasing their permeability to albumin. Urinary albumin was detected in significant amounts after burn injury, then decreased markedly during the first year, disappeared after 2–4 years, and was not detected during the follow-up endpoint [3, 6, 7].

Epithelial cells of renal tubules have a high proliferative capacity, so damaged tubules can repair themselves, but the loss of podocytes is usually permanent. Therefore, the disappearance of proteinuria in burn patients does not necessarily mean that the kidney has fully recovered [7]. Categories of persistent albuminuria (KDIGO, 2023) are: A1 < 30 mg/g; A2 = 30–300 mg/g; A3 > 300 mg/g [11]. According to the National Institute for Health and Care Excellence classification (2019) [43], the urine albumin-to-creatinine ratio is used and three its categories are defined [6, 7, 11, 18]: A1 < 3, A2 = 3–30, A3 > 30.

The other values used for AKI assessment are:

1. FENa (fractional excretion of sodium):

$$FENa = \frac{NaU \times Crp}{NaP \times Cru} \times 100\ \%,$$

where NaU is Na concentration in urine; NaP is Na concentration in blood serum (PRO < 1.0 %; AKI > 2.0 %).

2. FEurea (fractional excretion of urea):

$$FEurea = \frac{UUN \times Crp}{BUN \times Cru} \times 100\ \%,$$

where UUN is urine urea nitrogen (PRO < 20–30; AKI > 40–70 %).

3. Plasma urea/creatinine concentration index (normal > 40; AKI < 20).

4. Reduction of concentration indices (concentration in urine/concentration in plasma) of:

— creatinine (PRO > 40; AKI < 20);

— urea (PRO > 20; AKI < 20);

— sodium (PRO < 20; AKI > 40) [15–17];

— osmolarity (PRO > 1.8; AKI < 1.1);

— medium mass molecules (PRO > 1.6; AKI < 1.2).

A decrease in the effective circulating blood volume stimulates the release of antidiuretic hormone, which leads to increased distal reabsorption of water and urea. Therefore, a low FEurea (< 35 %) is more sensitive and specific than FENa for differentiating between prerenal and renal causes of AKI, especially when diuretics are used. FEurea and FENa have a low diagnostic sensitivity for differentiating azotemia associated with renal vasoconstriction and intact tubular function from AKI with tubular dysfunction [3].

Routine test strips and microscopic examinations of urine often help determine the cause of AKI:

— when the glomeruli are affected, protein and erythrocyte cylinders are found in the urine sediment; in case of tubulopathy, cellular detritus and tubular cylinders;

— acute tubulointerstitial nephritis is characterized by the presence of polymorphonuclear leukocytes, eosinophils;

— acute tubular obstruction is accompanied by abundant crystalluria, the presence of hemoglobin or myoglobin casts.

Although granular or epithelial casts in the urine are quantitatively increased in acute tubular necrosis, they lack sufficient sensitivity, specificity, and prognostic value for routine clinical use [3].

After the onset of AKI, the level of biomarkers remains elevated for a certain period. None of the described indicators is monospecific for AKI; this makes evaluation of the time of AKI course quite difficult [3, 44]. It has been proven that the combination of three biomarkers at two different time points in adults and the combination of two indicators at two time intervals in children can increase the specificity of AKI detection up to 0.78 [3].

NGAL, TIMP-2, IGFBP7, KIM-1, HJV, OPN, a decrease in initial GFR and hypoalbuminemia are recognized as risk factors [1, 3, 6].

Early diagnosis of kidney failure is very important [8]; recently, cyst-C and NGAL levels in blood plasma and urine have been proposed as early biomarkers of AKI, as their levels may increase 24–48 h before Crp elevation [27, 45, 46].

Biomarkers such as IL-18, NGAL, L-FABP, KIM-1 are used to evaluate glomerular and tubular functions, persistent proteinuria, and urinary tubule enzymes, in addition to determination of UO, BUN, and Crp [1, 3, 8].

The combination of Crp, NGAL and KIM-1 predicts the need for RRT and the risk of mortality within 7 days of the onset of acute renal failure.

NGAL and cyst-C emphasize the risk of developing severe forms of AKI.

Crp and NGAL make it possible to predict mortality, length of hospital stay, and the need for intensive care with RRT [1].

Urinary NGAL and L-FABP provide a 6-month prognosis for the kidney recipient [3].

The osmolality of urine and serum, as well as the concentration of electrolytes, are useful for the differential diagnosis of PRO and AKI [8]. An important sign of late AKI was the lowest 24-hour glucose level not exceeding 4.2 mmol/L; in this group, 68.8 % of patients experienced late AKI [21]. Conventional biomarkers, including white blood cell count, lactate

level, total bilirubin, and prothrombin time, have been serially evaluated to predict AKI progression and mortality (p = 0.01) [4, 36]. The degree of hyperkalemia severity depends on the area and depth of damage to tissue arrays [39, 40].

The reasons for the long road to the validation of candidates for new AKI biomarkers are as follows [3]:

— candidates for new biomarkers have been identified and studied in animal models of AKI, but they are not homologous to human AKI conditions;

— large multicenter prospective studies take a lot of time, require long-term expensive standardization, clinical and methodological resources.

The use of biomarkers without proper stratification of clinical risk can lead to their vain use. Despite their utility, there are not many healthcare facilities where biomarkers can be easily and quickly measured on site, and cost-effectiveness must be considered. For these reasons, most biomarkers have not yet been included in the panel of classical laboratory parameters used in clinical settings [3, 44].

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Received 19.11.2023
Revised 27.12.2023
Accepted 05.01.2024

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Conflict of interest. The authors declare that there is no conflict of interest and no financial interest in the preparation of this article.

Authors' contributions. *O.V. Kravets* — conceptualization, methodology, review and editing; *V.V. Yekhalov* — conceptualization, methodology, original draft; *V.V. Gorbuntsov* — review and editing, translation; *D.A. Krishtafor* — review and editing.

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Пошкодження нирок при опіковій хворобі. Частина 2. Біохімічні маркери (огляд літератури)

Резюме. Нещодавно виявлені специфічні маркери відкривають нові можливості для діагностики гострого пошкодження нирок (ГПН) при опіковій хворобі з метою оптимізації лікування таких хворих. Рання діагностика із залученням біомаркерів запобігає раптовій смерті опікових пацієнтів і дозволяє прогнозувати перебіг патологічного стану. Існує кілька характеристик, яким повинен відповідати «ідеальний» біомаркер ГПН: бути неінвазивним, локально специфічним, високочутливим, бути стабільною молекулою при різних температурах і pH, мати здатність швидко підвищуватися у відповідь на ураження нирок (кількісно його відображати), залишатися на високих рівнях протягом усього епізоду та знижуватися в період відновлення. Існує різниця між біомаркерами, що можуть вільно фільтруватися в клубочках, тому будь-яке збільшення їх концентрації в плазмі (внаслідок пошкодження інших ниркових тканин) може призвести до високої концентрації індикаторів у сечі (втрачається специфічність), і високомолекулярними маркерами, які не фільтруються вільно і тому є більш специфічними при вимірюванні в сечі. Функцію нирок у пацієнтів з опіками, як правило, визначають за показниками крові та сечі, оскільки біопсія може спричинити ятрогенне пошкодження та зазвичай у цій когорті не використовується. Після виникнення ГПН рівень біомаркерів залишається підвищеним протягом певного часу. Жоден з описаних індикаторів не є моноспецифічним для ГПН. Це робить оцінку часу перебігу ГПН досить складною. Доведено, що комбінації трьох біомаркерів у двох різних часових точках у дорослих та поєднання двох індикаторів у двох часових проміжках у дітей здатні збільшити достовірність визначення ГПН до 0,78.

Ключові слова: огляд; опікова хвороба; гостре пошкодження нирок; хронічна хвороба нирок; патогенез; біологічні маркери