https://doi.org/10.33266/2070-1004-2021-4-48-54
UDC 614.006:616.61-003.215

Reviev article

MODERN APPROACHES TO THE DIAGNOSIS OF ACUTE KIDNEY INJURY USING INNOVATIVE BIOMARKERS IN PATIENTS WITH COMBINED TRAUMA: REVIEW OF SCIENTIFIC PUBLICATIONS

M.Kh.Makhov[1], I.A.Miziev[1], A.V.Kardanov[2], L.D.Kardanova[1]

[1] Kabardino-Balkarian State University named after H.M. Berbekov, Nalchik, Russian Federation
[2] Kabardino-Balkarian Center for Disaster Medicine and Emergency Medical Aid , Nalchik, Russian Federation

Abstract. A review of scientific publications analyzing modern approaches to the diagnosis of acute kidney injury using innovative biomarkers in patients with concomitant trauma is presented. The authors of the review note that pathological processes of cellular damage, which determine the etiology and pathogenesis of acute kidney injury syndrome, require prompt and early initiation of preventive measures. Given this, the problem of early diagnosis of acute kidney injury and the scientific search for ways to optimize it remain relevant at the present time. In cases associated with the possibility of formation of acute kidney injury, as well as in situations when the renal tissue is already damaged, it is very relevant to determine markers of acute kidney injury in biological fluids.

Key words: *acute kidney injury, classification of biomarkers, diagnosis, innovative biomarkers, patients with combined trauma*

Conflict of interest. The authors declare no conflict of interest

For citation: Makhov M.Kh., Miziev I.A., Kardanova L.D., Kardanov A.V. Modern Approaches to the Diagnosis of Acute Kidney Injury Using Innovative Biomarkers in Patients with Combined Trauma: Review of Scientific Publications. *Meditsina katastrof* = Disaster Medicine. 2021;4:48-54 (In Russ.). https://doi.org/10.33266/2070-1004-2021-4-48-54

https://doi.org/10.33266/2070-1004-2021-4-48-54
УДК 614.0.06:616.61-003.215

Обзорная статья

СОВРЕМЕННЫЕ ПОДХОДЫ К ДИАГНОСТИКЕ ОСТРОГО ПОВРЕЖДЕНИЯ ПОЧЕК С ПРИМЕНЕНИЕМ ИННОВАЦИОННЫХ БИОМАРКЕРОВ У ПАЦИЕНТОВ С СОЧЕТАННОЙ ТРАВМОЙ: ОБЗОР НАУЧНЫХ ПУБЛИКАЦИЙ

М.Х.Махов[1], И.А.Мизиев[1], Л.Д.Карданова[1], А.В.Карданов[2]

[1] ФГБОУ ВО «Кабардино-Балкарский государственный университет им. Х.М.Бербекова», Нальчик, Россия
[2] ГБУЗ «Кабардино-Балкарский центр медицины катастроф и скорой медицинской помощи», Нальчик, Россия

Резюме. Представлен обзор научных публикаций, в которых анализируются современные подходы к диагностике острого повреждения почек (ОПП) с применением инновационных биомаркеров у пациентов с сочетанной травмой. Авторы обзора отмечают, что патологические процессы клеточного повреждения, определяющие этиологию и патогенез синдрома ОПП, требуют быстрого и раннего начала проведения профилактических мероприятий. Учитывая это, проблема ранней диагностики острого повреждения почек и научный поиск способов ее оптимизации остаются актуальными и в настоящее время. В случаях, связанных с возможностью формирования ОПП, а также в ситуациях, когда почечная ткань уже повреждена, очень актуально определение в биологических жидкостях таких веществ, как маркеры острого повреждения почек.

Ключевые слова: *диагностика, инновационные биомаркеры, классификация биомаркеров, острое повреждение почек, пациенты с сочетанной травмой*

Конфликт интересов. Авторы статьи подтверждают отсутствие конфликта интересов

Для цитирования: *Махов М.Х., Мизиев И.А., Карданова Л.Д., Карданов А.В.* Современные подходы к диагностике острого повреждения почек с применением инновационных биомаркеров у пациентов с сочетанной травмой: обзор научных публикаций // Медицина катастроф. 2021. №4. С. 48–54. https://doi.org/10.33266/2070-1004-2021-4-48-54

Contact information:
Murat Kh Makhov – Assistant at the Department of Faculty and Endoscopic Surgery of University
Address: 173, Chernyshevskiy st.,Nalchik, 360004, Kabardino-Balkar Republic, Russia
Phone: +7 (906) 484-73-89
E-mail: mahov_murat@ mail.ru

Контактная информация:
Махов Мурат Хасанович – ассистент кафедры факультетской и эндоскопической хирургии Ун-та
Адрес: Кабардино-Балкарская Республика, 360004, г.Нальчик, ул. Чернышевского,173
Тел.: +7 (906) 484-73-89
E-mail: mahov_murat@ mail.ru

In recent years, there has been a steady increase in the number of victims with injuries of various localizations, which are the leading cause of death, as well as temporary and permanent disability in persons under age of 40. A characteristic feature of modern trauma is the prevalence of multiple and combined injuries. This leads to a high and not decreasing mortality rate. Co-injury is characterized by simultaneous damage to several anatomical and function-

al areas. It is observed in 50-70% of the patients with severe mechanical injuries. In the Russian Federation, more than 35,000 people die annually as a result of combined trauma. Combined trauma is one of the three main causes of death among the population. Moreover, this cause comes first for people under age of 40. In Russia, the mortality rate from combined trauma is 59-65 cases per 100,000 people [1, 2].

Mechanical trauma causes distinct changes in the functioning of almost all organs and systems of the body. Thus, changes in renal function in trauma can increase the duration of treatment, worsen the prognosis, and lead to the development of late complications. In the pathogenesis of traumatic shock, renal dysfunction is a constant factor. Often they determine, in case of acute renal failure development, the outcome of traumatic disease [2-4]. This is especially true when the trauma is of multiple or combined nature and is accompanied by extensive soft tissue injuries. Acute renal failure is one of the most severe complications of the urinary system in patients with concomitant trauma. Unfortunately, there is still no unified approach to early diagnosis of this disease in polytrauma patients. In routine clinical practice, creatinine and urea are classic indicators of acute renal failure. However, since their levels rise in blood when more than 60% of nephrons are involved in the pathological process (on the 3rd and 4th day of oliguria), creatinine and urea do not play a significant role in the early diagnosis of acute renal failure. In particular, elevated serum creatinine levels are informative neither in terms of the exact timing of acute renal failure, nor in terms of its localization, much less in terms of the severity of glomerular or tubular damage [5-7]. The issues of correction of changes and prevention of renal dysfunction in combined trauma also remain unresolved. Thus, there is an urgent need to develop a technique for early diagnosis of renal dysfunction in patients with concomitant trauma.

Acute renal injury is a syndrome in which renal dysfunction forms and develops rapidly. It leads to significant changes in homeostasis and — sometimes — to death. Acute kidney injury is quite frequent — 181-288 cases per 100,000 population — and the number of patients with acute kidney injury tends to grow continuously [8-10].

The success of preventive measures directly depends on the timely detection of these disorders. All methods of laboratory diagnosis of acute kidney injury are based on determining the concentration and/or content of biomarkers of acute renal injury [11]. The functional capacity of kidneys is usually determined by detecting the quantity and quality of serum and urine creatinine and urea. Currently, these diagnostic methods are not sensitive enough and are not suitable for the detection of acute renal impairment [12]. For example, the concentration of serum creatinine occurs only 48-72 h after damaging effect on the kidneys, which indicates the impossibility of early diagnosis of acute renal damage [13]. At the current stage of medical science development, innovative methods with high sensitivity and reliability, capable of responding immediately to the damaging effect, are being developed. In the future, such methods will make it possible to evaluate the dynamics of the features of glomerular-tubular renal dysfunction development and to use the results in the development of methods of preventive treatment of acute kidney damage [14].

Biological substances, the levels of which in the urine and blood are of great importance for diagnosis and prognosis in the treatment of patients with renal dysfunction, were given the unified name of biomarkers of acute kidney damage. Their timely detection requires the use of unified techniques, which is possible in any medical treatment organization. Thanks to scientific developments performed at the end of the 20th-beginning of the 21st centuries, a list of possible biological markers of acute kidney damage was created, classification of these compounds was developed, and their informative role in pathological process detection was revealed, including determination of damage level (glomeruli or tubules) and etiology of biological marker synthesis [15, 16].

Biological compounds used as markers of acute kidney injury must meet certain requirements [17]. First of all, biological material should be easily accessible, and sample detection should be noninvasive and atraumatic. In addition, standardization of the used methods of laboratory diagnosis is necessary. Detectable markers must have a high tropicity to the localization of the site of nephron damage (vessels, tubules, glomeruli). Also, they should correspond to: causes of damage and time since its receipt; clinical features of the development of the pathological process; patient's need for hemodialysis; final stage of pathology (reconvalescence, lethal outcome, transition to chronic course); presence of an adequate response to the ongoing therapy [18]. At present, it has been proved that a number of markers of acute kidney injury absolutely comply with the above requirements [19, 20]. In spite of this, the problem of scientific research on the search for biomarkers of acute kidney damage is still relevant [21-23].

Scientists have developed 4 classifications of biomarkers of acute kidney damage - pathophysiological, topical, clinical and working (Table 1).

According to the pathophysiological classification, markers of acute kidney injury are divided into groups depending on their ability to determine one or another stage of the development of the pathological process in kidneys. For example, renal dysfunction can be determined by creatinine and cystatin C in blood; fat peroxidation by 4-ON-2-nonenal and 8-A2α-isoprostane; damaging effects on nephrons and interstitial tissue by IKM-1, L-FABP, NGAL; immune response by immunogram; annexin-5 is a marker of apoptosis of cell structures [26].

Topical classification divides markers into 5 groups: α1-microglobulin, β2-microglobulin, albumin, s-cystatin C — indicate glomerular nephrocyte alteration; cystatin C, NGAL (neutrophil gelatinase-associated lipocalin-2), interleukin-18 (IL-18), IKM-1 (renal damage molecule-1), α-GST (α-glutathione-S-transferase), L-FABP (protein-binding fatty acid BSA), etc. are markers of proximal tubule damage.etc.; π-GST (π-glutathione-S-transferase) together with NGAL can identify damage to the distal parts of the tubule system. In F.G.Henle loop damage, sodium hydrogen exchanger-3 acts as a marker, and OPN (osteopontin) is an indicator of collecting tubule alteration [26].

The clinical classification considers the ability to use these markers for: early diagnosis of acute kidney injury; monitoring of factors that determine the risk of pathological process; identification of characteristic features in the etiology and pathogenesis of acute kidney injury; dynamics of treatment and effectiveness of ongoing therapeutic measures, etc. [28].

Таблица 1 / Table No. 1

Классификация биомаркеров острого повреждения почек
Classification of biomarkers of acute kidney damage

Топическая классификация / Topical classification	
1. Клубочек / Glomerulus	Альбумин, цистатин С сыворотки, альфа1-микроглобулин, бета2-микроглобулин и др. / Albumin, serum cystatin C, alpha1-microglobulin, beta2-microglobulin, etc.
2. Проксимальный каналец / Proximal tubule	NGAL, KIM-1, L-FABP, цистатин С мочи, IL-18 и др. / NGAL, KIM-1, L-FABP, urinary cystatin C, IL-18, etc.
3. Дистальный каналец / Distal tubule	GST, NGAL
4. Собирательная трубка / Collection tube	Калибиндин D28 / Calibindin D28
5. Петля Генле / Loop of Henle	Остеопонтин NHE-3 / Osteopontin NHE-3
Патофизиологическая классификация / Pathophysiological classification	
1. Биомаркеры функции почек / Biomarkers of renal function	Креатинин, цистатин С сыворотки и др. / Creatinine, serum cystatin C, etc.
2. Биомаркеры оксидативного стресса / Biomarkers of oxidative stress	8(A2a)-изопростан, 4-OH-2-ноненал и др. / 8(A2a)-isoprostane, 4-ON-2-nonenal, etc.
3. Биомаркеры структурного и клеточного повреждения: - подоцитов - тубулоинтерстиция - факторы экзосомальной транскрипции / Biomarkers of structural and cellular damage: - podocytes - tubulointerstitium - exosomal transcription factors	Подокаликсин, нефрин NGAL, KIM-1, L-FABP, АТФ-3 / Podocalyxin, NGAL nephrine, KIM-1, L-FABP, ATP-3
4. Маркеры иммунного ответа / Markers of immune response	Иммуноглобулины, хемокины, компоненты комплемента / Immunoglobulins, chemokines, complement components
5. Маркеры фиброза / Fibrosis markers	TGF-β1, CTGF, Big-H3, Collagen type IV
6. Маркеры апоптоза / Apoptosis markers	Аннексин-5, TIMP-2, IGFBP7 / Annexin-5, TIMP-2, IGFBP7
7. Маркеры задержки клеточного цикла в фазе G2 / Markers of cell cycle delay in the G2 phase	TIMP2/IGFBP
Клиническая классификация / Clinical classification	
1. Маркер в качестве фактора риска развития ОПП / Marker as a risk factor for the development of acute kidney damage	
2. Маркер, использующийся при скрининге ОПП / Marker used in acute kidney damage screening	
3. Диагностический маркер, указывающий на патогенетический вариант ОПП / Diagnostic marker indicating pathogenetic variant of acute kidney damage	
4. Биомаркер, стратифицирующий тяжесть процесса / Biomarker stratifying the severity of the process	
5. Маркер с высокой предиктивной значимостью / Marker with high predictive value	
6. Маркер, характеризующий ответ на терапию / Marker describing response to therapy	
Рабочая классификация / Working classification	
1. Белки, экспрессия которых повышается при ОПП / Proteins that are up-regulated in acute kidney damage	NGAL, L-FABP, KIM-1, IL-18
2. Функциональные маркеры / Functional markers	Цистатин С сыворотки / Serum cystatin C
3. Низкомолекулярные белки мочи / Low-molecular-weight urine proteins	Цистатин С мочи, альфа1-микроглобулин, бета2-микроглобулин / Urinary cystatin C, alpha1-microglobulin, beta2-microglobulin
4. Внутриклеточные энзимы / Intracellular enzymes	NAG, α-GST, p-GST, ГГТП, ЩФ / NAG, α-GST, p-GST, GGT, ALP

Примечание: NGAL – липокалин, ассоциированный с желатиназой нейтрофилов; KIM-1 – молекула почечного повреждения; L-FABP – печеночный протеин, связывающий жирные кислоты; GST – глутатион-S-трансфераза; NHE-3 – натрий-водородный обменник 3; TGF-β1 – фактор роста опухолей β1; CTGF – фактор роста соединительной ткани; NAG – N-ацетил-D-глюкозаминидаза; ГГТП – гамма-глутамилтранпептидаза; ЩФ – щелочная фосфатаза; TIMP-2 – ингибитор металлопептидаз-2; IGFBP7 – белок, связывающий инсулиноподобный фактор роста 7 [24, 25]

Note: NGAL – lipocalin associated with neutrophil gelatinase; KIM-1 – renal injury molecule; L-FABP – hepatic fatty acid binding protein; GST – glutathione-S-transferase; NHE-3 – sodium-hydrogen exchanger 3; TGF-β1 – tumor growth factor β1; CTGF – connective tissue growth factor; NAG – N-acetyl-D-glucosaminidase; GGT – gamma-glutamyltranspeptidase; ALP – alkaline phosphatase; TIMP-2 – metallopeptidase inhibitor-2; IGFBP7 – insulin-like growth factor 7 binding protein [24, 25]

The working classification is represented by 4 groups: Group 1 are proteins whose formation is significantly increased in acute kidney injury (L-FABP, NGAL, IL-18, IKM-1); Group 2 is a marker of renal dysfunction, serum cystatin C; Group 3 is a number of low molecular weight urinogenic proteins, such as α1-microglobulin, β2-microglobulin, cystatin C. Group 4 includes intracellular enzymes (alkaline phosphatase (ALP), lactate dehydrogenase (LDH), NAG (N-acetylglutamate), α- and π-GST, GGTP-γ-glutamyl transpeptidase [28].

In recent years, in acute kidney injury, it became possible to detect parenchymal damage 24-48 h before the appearance of clinical signs of disease. In acute kidney damage, the effect of ischemic, toxic and other causes on kidneys initially provokes molecular transformations that turn into damage of cellular structures. The latter begin to form specific markers, and only then the pathognomonic symptomatology of renal pathology appears.

For the purpose of preventive diagnosis of ischemic acute tubular necrosis it is appropriate to detect the number of granular cylinders, tubular enzymes (α-glutathione-S-transferase, leucinaminopeptidase, alkaline phosphotase, N-acetyl-β-D-glucosaminidase (NAG), γ-glutamyl transpeptidase), cells of tubular epithelium in the urine. Currently, for the early detection of acute kidney damage the most promising are biological markers associated with renal parenchyma damage, cell proliferation, apoptosis, differentiation, immune disorders, formation of chemokines and cytokines, but not with a decrease in glomerular filtration rate. The study of biomarker excretion processes is used to investigate preventive diagnosis and other clinical problems of acute renal failure, which cannot be solved using conventional functional tests. The latter include: early differentiation of prerenal, renal, postrenal acute renal failure; study of its causes (renal toxins, sepsis, ischemia, acute inflammation of renal parenchyma in nephropathy and

urinary tract infections, ischemia-reperfusion syndrome); completion of terminal uremia as a prognosis of possible fatal outcome; reaction to the ongoing therapy. Of great importance are markers associated with the early stage of acute kidney injury.

Among the markers of acute kidney injury, the detection of which is increasingly used, we should mention lipocalin associated with neutrophil gelatinase (NGAL), a protein with a molecular weight of 25 kDa, initially detected in neutrophils and subsequently — in a small volume — in the tubular epithelium. Due to ischemia and toxic effects on the kidneys, its excretion in tubule cells increases significantly, its excretion in the urine also increases, indicating in one to two days an increase in serum creatinine blood levels. Increased amount of NGAL in serum and urine is detected 2-6 hours after cardiac surgical treatment and reflects the initial stage of postoperative acute kidney injury.

The sensitivity and specificity of this study are over 90%. As a predictor of renal transplant ischemia-reperfusion syndrome, an increased number of NGAL indicates delayed functional capacity and the need of the recipient for urgent hemodialysis.

The first clinical studies on this issue were performed in pediatric practice in patients after cardiac surgical interventions. The role of this marker as a sensitive predictor of the development of acute kidney damage after surgical intervention with the use of a heart-lung machine as well as after coronarography was proved. In clinical practice, in the diagnosis of acute kidney injury, a number of limitations of NGAL use should be considered. There is evidence that serum NGAL levels can increase in chronic kidney disease, arterial hypertension, infections, anemia, hypoxia, and malignant neoplasms. In addition, there is experimental and clinical data showing the dependence of NGAL excretion with urine on the level of proteinuria. The latter fact is particularly important in the diagnosis of acute kidney damage in patients with nephrotic syndrome, who are known to be initially predisposed to prerenal acute kidney damage. Examination of 79 patients with primary glomerular pathology revealed that proteinuria above 3.5 g/day significantly increased urinary NGAL excretion. Table 2 presents data on the diagnostic significance of serum and urinary NGAL determination in the diagnosis of acute kidney injury.

Dynamic monitoring of urinary NGAL level is informative: when building a prognosis of the severity of acute kidney damage due to post-diarrheal hemolytic-uremic syndrome in childhood; in patients of intensive care units; in X-ray-contrastinduced nephropathies. An increase in blood serum α1-microglobulin, which also belongs to the lipocalin group, is specific in the early diagnosis of acute tubular necrosis (specificity — 81%, sensitivity — 88%) and in the diagnosis of the need for acute hemodialysis (Table 3).

Cystatin C is a cysteine protease inhibitor formed in a significant number of cells containing the nucleus and is filtered by the glomeruli. Because serum cystatin C concentration is unrelated to age, muscle mass volume, and gender identity, it is a significantly better determinant of the functional state of renal filtration capacity compared with creatinine. The increase of serum cystatin C outstrips the increase of creatinine level in blood for 24-48 hours, it is considered as I-II stages of acute kidney damage in patients after surgical treatment and patients of intensive care units. This method, unlike the determination of N-acetyl-β-D-glucosaminidase (NAG) and β1-microglobulin in urine, belongs to the most specific and highly sensitive diagnostic methods. It should be noted that in acute kidney injury, an increase in serum concentration of cystatin C occurs 10 h after the detection of increased NGAL excretion.

Cystatin C is a 13 kDa polypetide chain consisting of 120 amino acids. It belongs to the inhibitors of lysosomal proteinases and is produced by all nuclear cells of the body, protecting it from uncontrolled activation of proteolysis of its own proteins. Cystatin C enters the bloodstream uniformly from the cells, and its serum concentration is maintained at a constant level [14, 25]. The small molecular weight and low affinity to other serum proteins determine the ability of this molecule to filter freely in the renal

Таблица 2 / Table No. 2

Роль NGAL в диагностике острого повреждения почек*
Role of NGAL in the diagnosis of acute kidney damage*

Вариант ОПП / Acute kidney damage variant	Биоматериал / Biomaterial	AUC, мкг/ мл × мин / AUC, μg/ml × min	PPV, %	NPV, %	Se, %	Sp, %
После кардиохирургических вмешательств / After cardiac surgery interventions	Кровь / Blood	0,76	52,3	90,6	67,9	83,0
	Моча / Urine	0,77	48,4	67,7	75,7	76,0
У пациентов ОРИТ** / In ICU patients	Кровь / Blood	0,79	64,7	81,5	78,5	77,5
	Моча / Urine	0,76	87,7	82,0	70,6	79,9
Постконтрастное ОПП / Postcontrast acute kidney damage	Кровь / Blood	0,73	20,0	97,0	–	–
	Моча / Urine	–	–	–	–	–
У пациентов приемного отделения / In emergency room patients	Кровь / Blood	0,82	70,0	99,0	–	–

Примечание (здесь и далее): *p <0,05; ** ОРИТ – отделение реанимации и интенсивной терапии; AUC (area under curve) –среднее значение площади под характеристической кривой диагностического теста (ROC-кривой –receiver operating characteristics); PPV (positive predictive value) – среднее значение прогностической ценности положительного результата (отношение истинно положительных результатов к положительным результатам, определенным с применением диагностического теста); NPV (negative predictive value) – среднее значение прогностической ценности отрицательного результата (отношение истинно отрицательных результатов к отрицательным результатам, определенным с применением диагностического теста); Se (sensitivity) – чувствительность диагностического теста (доля лиц с заболеванием, имеющих положительный результат диагностического теста); Sp (specificity) – специфичность диагностического теста (доля лиц без заболевания, имеющих отрицательный результат диагностического теста); данные представлены на основании обзоров исследований, опубликованных в 2013 г. [22, 23, 25]

Note (hereafter): *p < 0.05; ** ICU —intensive care unit; AUC (area under curve) —mean value of the area under the diagnostic test characteristic curve (ROC curve –receiver operating characteristics); PPV (positive predictive value) — mean value of the prognostic value of a positive result (ratio of true positive results to positive results determined using a diagnostic test); NPV (negative predictive value) — mean value of the prognostic value of a negative result (ratio of true negative results to negative; Se (sensitivity) is the sensitivity of the diagnostic test (the proportion of people with the disease who have a positive diagnostic test result); Sp (specificity) is the specificity of the diagnostic test (the proportion of people without the disease who have a negative diagnostic test result); data are based on reviews of studies published in 2013 [22, 23, 25]

Таблица 3 / Table No. 3

Информативность некоторых биомаркеров при остром повреждении почек
Informativity of some biomarkers in acute kidney damage

Биомаркеры Biomarkers	Варианты и стадии ОПП / Variants and stages of acute kidney damage			
	послеоперационное ОПП / postoperative acute kidney damage	РКС-нефропатия X-ray contrast nephropathy	пациенты ОРИТ, в т.ч. с сепсисом / ICU patients, including those with sepsis	СИР после трансплантации почки Ischemia reperfusion syndrome after kidney transplantation
NGAL, плазма, моча NGAL, plasma, urine	++ I	++ I	++ I	++ I
Цистатин С, плазма, моча Cystatin C, plasma, urine	+ I–II	+ I–II	++ I–II	+ I–II
ИЛ-18, моча Interleukin-18, urine	++ I–II	Не информативно Not informative	++ I–II	++ I–II
KIM-1, моча KIM-1, urine	++ I–II	Не информативно Not informative	Не изучено Not explored	Не изучено Not explored

Примечание. РКС – рентгеноконтрастная нефропатия; СИР – синдром ишемии – реперфузии; ИЛ-18 – интерлейкин-18; IKM-1 (KIM – kidney injury molecule-1 – молекулы почечного повреждения-I)
Note. KIM-1 (KIM – kidney injury molecule-1)

tubules, enter the tubules, where it is reabsorbed by megalin-cubulin-mediated endocytosis and then completely metabolized in the proximal tubule epithelial cells. As a consequence, cystatin C is excreted in minimal amounts in the urine in normal conditions.

The average parameters of diagnostic significance of cystatin C in patients with acute kidney injury are presented in Table 4.

L-FABP (liver fatty acid binding protein) is a cytoplasmic protein with a molecular weight of 15 kDa that is expressed in tissues with increased fatty acid metabolism. It belongs to the family of fatty acid transporter proteins that are involved in the transport of long-chain fatty acids between the intra- and extracellular space and regulate oxidative stress by binding lipophilic products, limiting their damaging effects on cell membranes.

In humans, this molecule is mainly synthesized in the liver; in small amounts, it is found in the kidneys and small intestine. Under normal conditions, L-FABP is not present in the urine. Since, filtered in the glomeruli, it is then completely reabsorbed in the proximal tubules, which allows the diagnosis of acute kidney damage. This was first demonstrated in an animal model of ischemic tubular necrosis. This marker proved to be a sensitive predictor of acute kidney damage in children after cardiac surgical interventions with the use of a heart-lung machine. In patients with acute kidney damage against the background of septic shock, L-FABP levels are elevated and determine the relative risk of mortality. The study of urinary concentrations of this marker suggested it as an acceptable biomarker of acute kidney damage in patients admitted to intensive care units (AUC, 0.95; PPV, 100%; NPV, 85%) - [21, 25].

KIM-1, the renal injury molecule or cell receptor-1 of hepatitis A virus, is also a biomarker of early renal damage. It is a membrane protein that is not detected in normal renal tissue and urine, but is detected in damaged proximal tubule epithelium due to ischemia or nephrotoxic effects. High sensitivity of KIM-1 determination in urine enables to differentiate acute kidney damage of ischemic and toxic origin from prerenal hyperazotemia, chronic kidney disease, urinary tract infection, X-ray-contrast-induced nephropathy. In acute kidney injury, a high concentration of KIM-1 in the urine is prognostically unfavorable.

Interleukin-18 is a proinflammatory cytokine that is localized in renal macrophages, podocytes, and dendritic cells. An increase in interleukin-18 provokes the formation of free oxygen radicals, which alters the epithelium of the convoluted tubules. Increased urinary excretion of interleukin-18 in ischemic acute tubular necrosis and ischemia-reperfusion syndrome is correlated with enzymuria (α-glutathione-S-transferase, NAG) and preempts changes in serum creatinine concentration. Given its high (over 90%) specificity and by dynamically monitoring IL-18 levels, we can distinguish between: ischemic acute kidney injury, including renal transplant ischemia-reperfusion syndrome; chronic kidney disease; urinary tract infection; prenatal acute renal failure. In patients who are in the intensive care unit with adult respiratory distress syndrome (ARDS), increased urinary excretion of interleukin-18 becomes a marker of acute renal failure, outpacing hyperazotemia by two days.

Таблица 4 / Table No. 4

Роль цистатина С в диагностике острого повреждения почек*
Role of cystatin C in the diagnosis of acute kidney damage*

Вариант ОПП Acute kidney damage variant	Биоматериал Biomaterial	AUC, мкг/ мл × мин / AUC, μg/ml × min	PPV, %	NPV, %
После кардиохирургических вмешательств After cardiac surgery	Кровь/Blood	0,73	63	84
	Моча/ Urine	0,65	52	82
У пациентов ОРИТ In ICU patients	Кровь/Blood	0,80	42	85
	Моча / Urine	0,68	75	95
Постконтрастное ОПП / Postcontrast acute kidney damage	Кровь/Blood	0,93	56,7	98,0
У пациентов приемного отделения In emergency room patients	Кровь/Blood	0,87	48,0	94,0
	Моча / Urine	0,59	32,0	84,0

Примечание (здесь и далее): * p <0,05; AUC (area under curve) среднее значение площади под характеристической кривой диагностического теста (ROC-кривой – receiver operating characteristics); PPV (positive predictive value) – среднее значение прогностической ценности положительного результата (отношение истинно положительных результатов к положительным результатам, определенным с применением диагностического теста); NPV (negative predictive value) – среднее значение прогностической ценности отрицательного результата (отношение истинно отрицательных результатов к отрицательным результатам, определенным с применением диагностического теста) – данные представлены на основании обзоров исследований, опубликованных в 2013 г. [25]

Note (hereafter): * p < 0.05; AUC (area under curve) —average value of area under the diagnostic test characteristic curve (ROC curve receiver operating characteristics); PPV (positive predictive value) average value of prognostic value of a positive result (ratio of true positive results to positive results determined using a diagnostic test), NPV (negative predictive value) —average value of prognostic value of a negative result (ratio of true negative results to negative results determined using a diagnostic test) [25]

Other marker proteins are used in experimental work on acute renal failure and have not yet been tested clinically. These include, for example, uromodulin or Tamm-Horsfall protein found in the epithelium of the distal renal tubules. In the early stages of acute renal failure, the concentration of uromodulin is significantly reduced.

The detection of several markers in the urine at the same time is very promising. In particular, detection of NGAL, KIM-1, matrix metalloproteinase makes it possible with high sensitivity to early diagnose acute renal failure as a consequence of cardiac surgery in pediatric patients.

In a multicenter study, simultaneous assessment of urinary excretions of NGAL and KIM-1 has been shown to predict the initiation of renal replacement therapy and the relative risk of mortality [11, 25]. A two-center study of 529 patients admitted to the intensive care unit compared the role of 6 urinary biomarkers-Gamma glutamyl transpeptidase, alkaline phosphatase, NGAL, cystatin C, KIM-1, and IL-18. The biomarkers NGAL, cystatin C, and IL-18 were predictors of the need for dialysis therapy, whereas all markers except KIM-1 were predictors of mortality risk [16, 25]. Currently, there is no answer to the question which combination of biomarkers is optimal. According to some authors, that should be a combination of markers with high sensitivity on the one hand, and with specificity on the other.

REFERENCES

1. Miziev I.A., Zhigunov A.K., Baksanov Kh.D., et al. Treatment of Patients with Injuries of the Abdominal Organs and the Musculoskeletal System in Polytrauma. Bulletin of St. Petersburg University. Ser. 11. Medicine. Appendix: Pirogovskaya Surgical Week. Materials of the All-Russian Forum. 2010. 688 p. (In Russ.).

2. Miziev I.A., Makhov M.Kh., Hatshukov A.Kh., Dabagov O.Yu., Akhkubekov R.A. Detection of Early Laboratory Manifestations of Renal Dysfunctions in Patients with Concomitant Trauma Using the Endogenous Marker Cystatin C. Urology. 2015;1:20-22 (In Russ.).

3. Seleznev S.A. Traumatic Illness (Topical Issues, Problems). Eds. Seleznev S.A., Khudayberenov G.S. Ashgabat, Ylym Publ., 1984. 242 p. (In Russ.).

4. Sokolov V.A., Kartavenko V.I., Ivanov P.A., Garaev D.A. The Value of the Syndrome of Mutual Aggravation of Injuries in Victims with Concomitant and Multiple Trauma. Emergency Med. Help. 2004;3:188-189 (In Russ.).

5. Ronco C, Bellomo R, Kellum JA. Acute Kidney Injury. Lancet. 2019;Nov;23;394;10212:1949-1964. doi: 10.1016/S0140-6736(19)32563-2. PMID: 31777389.

6. Proletov Y.U., Saganova E.S., Cmirnov A.V. Biomarkers in Acute Kidney Injury Diagnostics. Nephrology. 2014;18;4:25–35 (In Russ.).

7. Poston JT, Koyner JL. Sepsis associated acute kidney injury. BMJ. 2019;Jan;9;364:k4891. doi:10.1136/bmj.k4891. PMID: 30626586; PMCID: PMC6890472.

8. Wang H.E., Muntner P., Chertow G.M., Warnock D.G. Acute Kidney Injury and Mortality in Hospitalized Patients. Am. J. Nephrol. 2012;35:349–355.

9. Srisawat N, Kellum JA. The Role of Biomarkers in Acute Kidney Injury. Crit Care Clin. 2020;Jan;36;1:125-140. doi: 10.1016/j.ccc.2019.08.010. PMID: 31733675.

10. Schrezenmeier EV, Barasch J, Budde K, Westhoff T, Schmidt-Ott KM. Biomarkers in Acute Kidney Injury – Pathophysiological Basis and Clinical Performance. Acta Physiol (Oxf). 2017;Mar;219;3:554-572. doi: 10.1111/apha.12764. Epub 2016 Aug 25. PMID: 27474473; PMCID: PMC5575831.

11. Nickolas T., Schmidt-Ott K.M., Canetta P., et al. Diagnostic and Prognostic Stratification in the Emergency Department Using Urinary Biomarkers of Nephron Damage: a Multicenter ProSpective Cohort Study. J. Am. Coll. Cardiol. 2012;59;3:246-255.

12. Teo SH, Endre ZH. Biomarkers in acute kidney injury (AKI). Best Pract Res Clin Anaesthesiol. 2017 Sep;31(3):331-344. doi: 10.1016/j.bpa.2017.10.003. PMID: 29248140.

13. Kane-Gill SL, Meersch M, Bell M. Biomarker-Guided Management of Acute Kidney Injury. Curr Opin Crit Care. 2020;Dec;26(6):556-562. doi: 10.1097/MCC.0000000000000777. PMID: 33027146.

14. Kayukov I.G., Smirnov A.V., Emmanuel V.L. Cystatin C in Modern Medicine. Nefrologiya = Nephrology. 2012;16;1:22-39. (In Russ.).

15. Vijayan A., Faubel S., Askenazi D.J., et al. Clinical Use of the Urine Biomarker [TIMP-2] x [IGFBP7] for Acute Kidney Injury Risk Assessment. Am. J. Kidney Dis. 2016;68;1:19-28. doi: 10.1053/j.ajkd.2015.12.033.

16. Siew E.D., Ikizler T.A., Gebretsadik T., et al. Elevated Urinary IL-18 Levels at the Time of ICU Admission Predict Adverse Clinical Outcomes. Clin. J. Am. Soc. Nephrol. 2010;5;8:1497-1505.

17. Edelstein C.L. Biomarkers in Kidney Disease. Elsevier Inc, 2011.

18. Cavalcante CTMB, Cavalcante MB, Castello Branco KMP, Chan T, Maia ICL, Pompeu RG, de Oliveira Telles AC, Brito AKM, Libório AB. Biomarkers of Acute Kidney Injury in Pediatric Cardiac Surgery. Pediatr Nephrol. 2021;May;25. doi: 10.1007/s00467-021-05094-9. Epub ahead of print. PMID: 34036445.

19. Engelman DT, Crisafi C, Germain M, Greco B, Nathanson BH, Engelman RM, Schwann TA. Using Urinary Biomarkers to Reduce Acute Kidney Injury following Cardiac Surgery. J Thorac Cardiovasc Surg. 2020;Nov;160(5):1235-1246.e2. doi: 10.1016/j.jtcvs.2019.10.034. Epub 2019 Oct 17. PMID: 31757451.

СПИСОК ИСТОЧНИКОВ

1. *Мизиев И.А., Жигунов А.К., Баксанов Х.Д. и др.* Лечение больных с повреждениями органов брюшной полости и опорно-двигательного аппарата при политравме // Вестник Санкт-Петербургского университета. Сер. 11. Медицина. Приложение: Пироговская хирургическая неделя: материалы Всероссийского форума. 2010. 688 с.

2. *Мизиев И.А., Махов М.Х., Хатшуков А.Х., Дабагов О.Ю., Ахкубеков Р.А.* Выявление ранних лабораторных проявлений нарушений функций почек у больных с сочетанной травмой с использованием эндогенного маркера цистатина С // Урология. 2015. №1. С. 20-22.

3. *Селезнев С.А., Худайберенов Г.С.* Травматическая болезнь (актуальные вопросы, проблемы). Ашхабад: Ылым, 1984. 242 с.

4. *Соколов В.А., Картавенко В.И., Иванов П.А., Гараев Д.А.* Значение синдрома взаимного отягощения повреждений у пострадавших с сочетанной и множественной травмой // Скорая медицинская помощь. 2004. №3. С. 188-189.

5. *Ronco C, Bellomo R, Kellum JA.* Acute Kidney Injury // Lancet. 2019. Nov. V. 23. No. 394(10212). P. 1949-1964. doi: 10.1016/S0140-6736(19)32563-2. PMID: 31777389.

6. *Пролетов Я.Ю., Саганова Е.С., Смирнов А.В.* Биомаркеры в диагностике острого повреждения почек. Сообщение I // Нефрология. 2014. Т.18, №4. С. 25–35.

7. Poston JT, Koyner JL. Sepsis Associated Acute Kidney Injury // BMJ. 2019. Jan. V. 9. No. 364. P. k4891. doi: 10.1136/bmj. k4891. PMID: 30626586; PMCID: PMC6890472.

8. Wang H.E., Muntner P., Chertow G.M., Warnock D.G. Acute Kidney Injury and Mortality in Hospitalized Patients // Am. J. Nephrol. 2012. No. 35. P. 349–355.

9. Srisawat N, Kellum JA. The Role of Biomarkers in Acute Kidney Injury // Crit Care Clin. 2020. Jan. V. 36. No. 1. P. 125-140. doi: 10.1016/j.ccc.2019.08.010. PMID: 31733675.

10. Schrezenmeier EV, Barasch J, Budde K, Westhoff T, Schmidt-Ott KM. Biomarkers in Acute Kidney Injury – Pathophysiological Basis and Clinical Performance // Acta Physiol (Oxf). 2017. Mar. V. 219. No. 3. P. 554-572. doi: 10.1111/apha.12764. Epub 2016 Aug 25. PMID: 27474473; PMCID: PMC5575831.

11. *Nickolas T., Schmidt-Ott K.M., Canetta P., et al.* Diagnostic and Prognostic Stratification in the Emergency Department Using Urinary Biomarkers of Nephron Damage: a Multicenter Prospective Cohort Study // J. Am. Coll. Cardiol. 2012. V.59, No. 3. P. 246-255.

12. Teo SH, Endre ZH. Biomarkers in Acute Kidney Injury (AKI) // Best Pract Res Clin Anaesthesiol. 2017. Sep. V. 31. No. 3. P. 331-344. doi: 10.1016/j.bpa.2017.10.003. PMID: 29248140.

13. Kane-Gill SL, Meersch M, Bell M. Biomarker-Guided Management of Acute Kidney Injury // Curr Opin Crit Care. 2020. Dec. V. 26. No. 6. P. 556-562. doi: 10.1097/MCC.0000000000000777. PMID: 33027146.

14. *Каюков И.Г., Смирнов А.В., Эммануэль В.Л.* Цистатин С в современной медицине // Нефрология. 2012. Т.16, № 1. С. 22-39.

15. Vijayan A., Faubel S., Askenazi D.J., et al. Clinical Use of the Urine Biomarker [TIMP-2] x [IGFBP7] for Acute Kidney Injury Risk Assessment // Am. J. Kidney Dis. 2016. V. 68. No. 1. P. 19-28. doi: 10.1053/j.ajkd.2015.12.033.

16. Siew E.D., Ikizler T.A., Gebretsadik T., et al. Elevated Urinary IL-18 Levels at the Time of ICU Admission Predict Adverse Clinical Outcomes // Clin. J. Am. Soc. Nephrol. 2010. V.5. No. 8. P. 1497-1505.

17. Edelstein C.L. Biomarkers in Kidney Disease. Elsevier Inc. 2011.

18. Cavalcante CTMB, Cavalcante MB, Castello Branco KMP, Chan T, Maia ICL, Pompeu RG, de Oliveira Telles AC, Brito AKM, Libório AB. Biomarkers of Acute Kidney Injury in Pediatric Cardiac Surgery // Pediatr Nephrol. 2021. May. No. 25. doi: 10.1007/s00467-021-05094-9. Epub ahead of print. PMID: 34036445.

19. *Engelman DT, Crisafi C, Germain M, Greco B, Nathanson BH, Engelman RM, Schwann TA.* Using Urinary Biomarkers to Reduce Acute Kidney Injury Following Cardiac Surgery // J Thorac Cardiovasc Surg. 2020. Nov. V. 160. No. 5. P. 1235-1246.e2. doi: 10.1016/j.jtcvs.2019.10.034. Epub 2019 Oct 17. PMID: 31757451.

20. *Endre Z.H., Pickering J.W., Walker R.J.*, et al. Improved Performance of Urinary Biomarkers of Acute Kidney Injury in the Critically Ill by Stratifi-

20. Endre Z.H., Pickering J.W., Walker R.J., et al. Improved Performance of Urinary Biomarkers of Acute Kidney Injury in the Critically Ill by Stratification for Injury Duration and Baseline Renal Function. Kidney Int. 2011;79;10:1119-11130.
21. Matsui K1., Kamijo-Ikemori A., Hara M., et al. Clinical Significance of Tubular and Podocyte Biomarkers in Acute Kidney Injury. Clin. Exp. Nephrol. 2011;15;2:220-225.
22. Luft FC. Biomarkers and predicting acute kidney injury. Acta Physiol (Oxf). 2021;Jan;231(1):e13479. doi: 10.1111/apha.13479. Epub 2020 May 9. PMID: 32311830.
23. Vanmassenhove J., Vanholder R., Nagler E., Van Biesen W. Urinary and Serum Biomarkers for the Diagnosis of Acute Kidney Injury: an in-Depth Review of the Literature. Nephrol. Dial. Transplant. 2013;28;2:254-273.
24. Smirnov A.V., Dobronravov V.A., Rumyantsev A.Sh., Kayukov I.G. Acute Kidney Injury. Moscow, MIA Publ., 2015. 488 p. (In Russ.).
25. Acute Kidney Injury (AKI). Clinical Guidelines. Moscow Publ., 2020. P. 41-47 (In Russ.).
26. Tesch G.H. Review: Serum and Urine Biomarkers of Kidney Disease: A Pathophysiological Perspective. Nephrology (Carlton). 2010;15;6:609–616.
27. Noto A. Cibecchini F., Fanos V., Mussap M. NGAL and Metabolomics: The Single Biomarker to Reveal the Metabolome Alterations in Kidney Injury. Biomed. Res. Int. 2013;61:20–32.
28. Schneider A., Johnson L., Goodwin M., et al. Bench-to-Bedside Review: Contrast Enhanced Ul-Trasonography-a Promising Technique to Assess Renal Perfusion in the ICU. Crit. Care. 2011;15;3:157.

cation for Injury Duration and Baseline Renal Function // Kidney Int. 2011. V.79. No. 10. P. 1119-11130.
21. *Matsui K1., Kamijo-Ikemori A., Hara M.,* et al. Clinical Significance of Tubular and Podocyte Biomarkers in Acute Kidney Injury // Clin. Exp. Nephrol. 2011. V.15, No. 2. P. 220-225.
22. *Luft FC.* Biomarkers and Predicting Acute Kidney Injury // Acta Physiol (Oxf). 2021. Jan. V. 231. No. 1. P. e13479. doi: 10.1111/apha.13479. Epub 2020 May 9. PMID: 32311830.
23. Vanmassenhove J., Vanholder R., Nagler E., Van Biesen W. Urinary and Serum Biomarkers for the Diagnosis of Acute Kidney Injury: an in-Depth Review of the Literature // Nephrol. Dial. Transplant. 2013. V.28, No. 2. P. 254-273.
24. *Смирнов А.В., Добронравов В.А., Румянцев А.Ш., Каюков И.Г.* Острое повреждение почек. М.: Медицинское информационное агентство, 2015. 488 с.
25. Острое повреждение почек: Клинические рекомендации. М., 2020. С. 41-47.
26. *Tesch G.H.* Review: Serum and Urine Biomarkers of Kidney Disease: A Pathophysiological Perspective // Nephrology (Carlton). 2010. V.15. No. 6. P. 609–616.
27. *Noto A., Cibecchini F., Fanos V., Mussap M.* NGAL and Metabolomics: The Single Biomarker to Reveal the Metabolome Alterations in Kidney Injury // Biomed. Res. Int. 2013. No. 61. P. 20–32.
28. *Schneider A., Johnson L., Goodwin M.,* et al. Bench-to-Bedside Review: Contrast Enhanced Ul-Trasonography – a Promising Technique to Assess Renal Perfusion in the ICU // Crit. Care. 2011. V.15. No. 3. P. 157.

The material was received 17.08.21; the article after peer review procedure 15.10.21; the Editorial Board accepted the article for publication 13.12.21
Материал поступил в редакцию 17.08.21; статья принята после рецензирования 15.10.21; статья принята к публикации 13.12.21