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The concept of acute kidney disease and its place in the renal continuum

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ABSTRACT

The paper discusses the concept of acute kidney disease, a relatively new concept in clinical medicine, the introduction of which is due to the presence of kidney diseases that do not meet strict criteria for acute kidney injury or chronic kidney disease. The article presents the criteria and severity stratification of acute kidney disease proposed by the Kidney Disease: Improving Global Outcomes Foundation, interpretation of the criteria and severity stratification by the Scientific Society of Nephrologists of Russia, associations of nephrologists and anesthesiologists-resuscitators of Russia, the National Society of Specialists in Hemapheresis and Extracorporeal Hemocorrection in accordance with the classification system of the Acute Dialysis Quality Initiative group. The role of acute kidney disease in the modern renal continuum is outlined. The article reviews the results of studies of acute kidney disease in patients with septic shock, patients who underwent total joint replacement, myocardial infarction with *ST* segment elevation and having acute kidney injury, patients with ischemic stroke, after coronary angiography, after acute surgery for type A aortic dissection, which demonstrate the prevalence of acute kidney disease and its outcomes. Despite the fact that acute kidney disease has a high prevalence among patients with various pathologies, worsens the prognosis and increases the risk of death or complications, its significance in modern medicine remains extremely underestimated. The article identifies the most common and studied biochemical markers that can potentially increase the proportion of patients at risk of adverse outcomes when used in clinical practice.

Keywords: acute kidney disease; renal continuum; acute kidney injury; chronic kidney disease.

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Концепция острой болезни почек и её место в почечном континууме

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АННОТАЦИЯ

В работе рассмотрена концепция острой болезни почек — относительно нового понятия в клинической медицине, внедрение которого обусловлено наличием заболеваний почек, которые не удовлетворяют строгим критериям острого повреждения почек или хронической болезни почек. В статье приведены критерии, стратификация тяжести острой болезни почек, предложенные фондом Kidney Disease: Improving Global Outcomes, интерпретация критериев и стратификации тяжести Научным обществом нефрологов России, ассоциациями нефрологов и анестезиологов-реаниматологов России, Национальным обществом специалистов в области гемафереза и экстракорпоральной гемокоррекции в соответствии с классификационной системой группы Acute Dialysis Quality Initiative. Обозначена роль острой болезни почек в современном почечном континууме. Рассмотрены результаты исследований острой болезни почек у пациентов с септическим шоком, пациентов, перенёвших тотальное эндопротезирование суставов, перенёвших инфаркт миокарда с подъёмом сегмента ST и имеющих острое повреждение почек, пациентов с ишемическим инсультом, после выполнения коронароангиографии, после острой операции по расслоению аорты типа А, которые демонстрируют распространённость острой болезни почек и её исходы. Несмотря на то обстоятельство, что острая болезнь почек имеет высокую распространённость среди пациентов с различной патологией, ухудшает прогноз и увеличивает риск смерти или развития осложнений, её значение в современной медицине по-прежнему остаётся крайне недооценённым. В статье обозначены наиболее распространённые и исследуемые биохимические маркёры, потенциально позволяющие повысить долю выявления пациентов с риском неблагоприятных исходов при использовании в клинической практике.

Ключевые слова: острая болезнь почек; почечный континуум; острое повреждение почек; хроническая болезнь почек.

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Acute kidney disease (AKD) is a new concept in clinical medicine, which was introduced owing to the presence of kidney disease that did not meet the acute kidney injury (AKI) or chronic kidney disease (CKD) criteria and the need to develop an approach that integrates the established concepts of AKI and CKD.

AKD was first defined by the Kidney Disease: Improving Global Outcomes (KDIGO) Foundation in 2012 in the first clinical practice guideline for the diagnosis and management of AKI (Clinical Practice Guideline for Acute Kidney Injury), which also reflected the basic principles in identifying AKD as a new concept [1]. The authors of the guidelines believed that AKD can be diagnosed if functional or structural criteria are met, namely, the presence of AKI, a change in glomerular filtration rate (GFR) <60 mL/min/1.73 m² in less than 3 months, and a decrease in GFR $\geq 35\%$ or an increase in serum creatinine (SCr) >50 in less than 3 months [1].

Moreover, they identified markers of damage typical of AKD, including red blood cells/red blood cell casts, white blood cells/white blood cell casts, tubular epithelial cells/casts, small and large granular casts, urine protein, and, using diagnostic imaging techniques, enlarged kidneys, hydronephrosis, cysts, and stones [1].

AKD includes AKI and conditions characterized by kidney injury markers wherein the rate of GFR decline is not as high as in AKI [1]. The differences between AKD, AKI, and CKD and their possible combinations are unclear; thus, KDIGO experts proposed approaches to differential diagnosis of these conditions [1].

The term AKI was further developed in 2017 in the consensus document of the International Working Group of the Acute Dialysis Quality Initiative (ADQI) [2]. It states that AKD is stage 1 or greater AKI present ≥ 7 days after an AKI-initiating event and that AKD persisting beyond 90 days is considered CKD [2].

Additionally, the working group proposed a concept of the renal continuum, combining AKI, AKD, and CKD [2]. In the proposed system, AKI is defined as an acute decline in kidney function lasting ≥ 7 days, and CKD is a persistent kidney disease lasting >90 days [2]. AKD may be an acute or sub-acute injury and/or loss of renal function within 7–90 days after AKI onset [2]. The concept further implies that AKI and AKD can co-exist with CKD [2].

The ADQI experts were the first to stratify AKD by severity, which they believed should be consistent with AKI severities and include the following stages [2]:

- Stage 0: partial recovery from AKI and divided into the following stages:
 - OA (complete recovery from AKI, but the risk of long-term events retains)
 - OB (serum creatinine has returned to baseline, but ongoing kidney damage is evident)
 - OC (SCr above baseline, but within 1.5 times baseline)
- Stage I: SCr increase to 1.5-fold of baseline)
- Stage II: SCr increase to 2–2.9-fold of baseline)
- Stage III: SCr increase to 3-fold of baseline or an absolute increase of 356.6 mmol/L or need for renal replacement therapy)

Figure 1 shows the severity stratification.

A consensus document of European and North American nephrologists (Improving Global Outcomes Consensus Conference) in 2020 included both alternative definitions of AKD. Notably, harmonizing AKD with AKI and CKD was a priority and would be addressed at a future KDIGO consensus conference [3].

In 2022, a Russian research team clarified the position of AKD in the renal continuum and suggested dividing it into two groups [4]:

- With preserved function and biomarkers of renal damage or structural kidney changes
- With decreased function

Each type can be transient (up to 7 days) or persistent (7–90 days). The authors presented the modified concept, which elucidates the positions of AKD and AKI in the renal continuum based on generally accepted criteria, allowing for rapid routine clinical practice implementation [4].

The draft Russian guidelines for AKI treatment (2020), developed by the Russian Scientific Society of Nephrology, associations of nephrologists and anesthesiologists–resuscitators of Russia, and the National Society of Specialists in Hemapheresis and Extracorporeal Hemocorrection, described an approach comparable to the international ADQI group consensus document. In this approach, AKD is a condition that has not resolved within 7 days of AKI, lasts 7–90 days, and is characterized by persistent renal injury or dysfunction of varying severity [5]. The AKD severity stratification in the Russian clinical guidelines corresponds to ADQI group's classification system (2017) [2, 5].

In 2023, the KDIGO consensus document further discussed the AKD concept [6]. The final opinion of the congress participants demonstrated that AKD includes AKI and involves all patients who have a functional and/or structural disorder with health-related consequences that lasted for ≤ 3 months. The experts determined an AKD criteria comparable to those in the KDIGO Clinical Guidelines for the Diagnosis and Management of AKI (2012): AKI or GFR <60 mL/min/1.73 m² or decrease in GFR $\geq 35\%$ or increase in SCr $> 50\%$ and/or markers of renal injury (most commonly albuminuria, hematuria, and pyuria) ≤ 3 months.

However, the time of AKI progression to AKD has not been clearly defined, and duration and criteria of recovery from AKI have not been addressed. Nonetheless, a classification system that distinguished AKD without AKI from AKD with AKI was established; each type could develop in patients with or without CKD. The experts indicated that AKD with AKI could be stratified by severity based on AKI staging and AKD without AKI or AKD after AKI by GFR and albuminuria categories, similar to CKD.

Moreover, participants discussed AKD progression to CKD. Patients who met the AKI/AKD criteria and whose renal function remained below baseline but did not progress to CKD 3 months after exposure were classified as having a history of AKI/AKD [6].

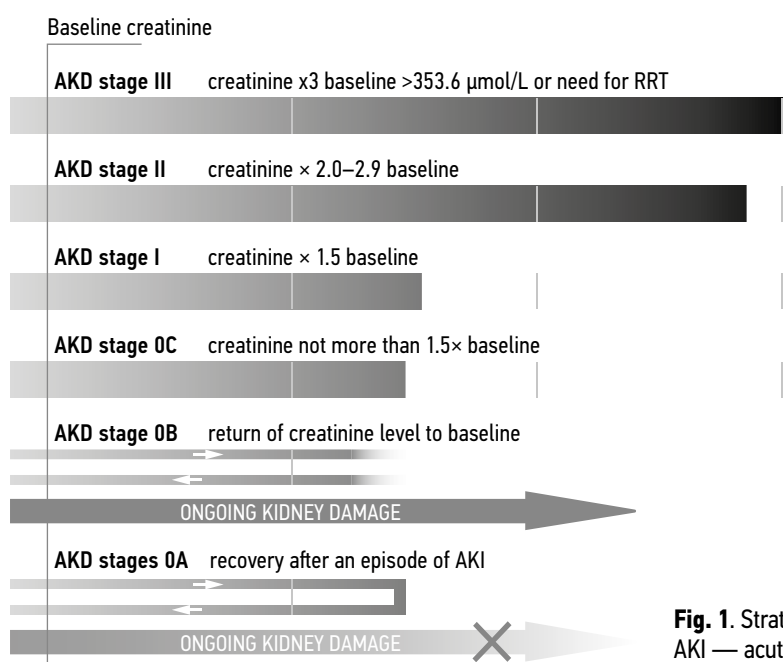


Fig. 1. Stratification of severity of acute kidney disease (AKD); AKI — acute kidney injury; RRT — renal replacement therapy

Presently, AKD has been found to be common. Despite the fact that this condition worsens the prognosis of pre-existing CKD and increases mortality and morbidity, its role remains underestimated [7, 8]. Differential diagnosis of AKI and AKD is challenging because of the low accuracy of diuresis assessment in AKI and assessment of baseline SCr, which results in a wide range of data in diagnosing AKI and AKD [7, 9]. The biomarkers in current guidelines have been extensively investigated; however, their use in predicting and diagnosing AKI remains limited [1, 8, 10].

How long SCr has been elevated during a patient's hospitalization is unclear; hence, whether the patient has AKI or AKD could not often be determined [3]. AKD and AKI studies conducted primarily in patients with cardiovascular disease had to be retrospective. However, the results presented were limited to mortality and de novo CKD incidence, with follow-up from 90 days to 10 years. Nonetheless, these studies confirm that AKD increases the possibility of CKD and risk of death [11].

AKD and AKI can develop outside the hospital, with more common cases of community-acquired AKI, and some episodes involve AKD without AKI [12–14]. Numerous studies on CKD and AKI have been published over the past decades; however, AKD remains poorly understood [7, 8].

Classifying AKD as a separate stage in the renal continuum is based on the need to isolate this period to prevent AKI progression to CKD. The current concept of the renal continuum indicates that the pathogenesis of CKD following AKI is multifactorial, and the role of hemodynamic factors, proteinuria, oxidative stress, metabolic dysfunction, inflammation, hypoxia, and other factors is debatable [4]. This led to a complete understanding of the association between AKI, AKD, and CKD [15–20].

The current understanding regarding the renal continuum is that AKD can be a cause or a consequence of CKD influenced by risk factors, with some possibility of recovery or

death [15]. AKI, with or without direct influence of risk factors, may cause AKD [18].

Long-term studies conducted by European initiative groups revealed that AKI is a common and often fatal clinical syndrome associated with a high rate of in-hospital mortality, approximately 25% in the general population and $>50\%$ in critically ill patients [16, 21, 22]. These studies showed that adverse outcomes such as severe acute kidney injury requiring dialysis or non-recovery or incomplete recovery of renal function (end-stage renal disease or CKD, respectively) may occur in AKI survivors [21]. Patients with AKI are at risk for long-term complications and poor outcomes, even with full recovery [18–20].

Available data present multiple variations in renal continuum progression. In 2022, the International Society of Nephrology published a study of patients with septic shock [22]. AKI was detected in 45% of the examined patients, 19.9% died within 7 days, and 53.2% had early resolution of AKI within the first 7 days, and 26.9% of patients with AKI developed AKD [22]. In patients with early reversal, 14.2% had recurrent AKI, and only about one-third of them recovered [22]. Among those who had AKD, 9.3% had renal function recovery before discharge [22].

In 2021, a similar study of patients with severe sepsis and/or septic shock was published by Flannery et al., with selection of patients with impaired renal function [23]. Patients who survived sepsis-related AKI often did not return to baseline renal function following hospital discharge; 47% of patients developed AKD stage 0C or higher [23]. These AKD stages were significantly and progressively associated with the primary outcome compared to stage 0A [23]. CKD was more possibly developed or progressed at higher stages of AKD [23].

In 2017, a study of AKD was conducted in patients after total joint arthroplasty. The study showed a 6.8% incidence of

postoperative AKD [24]. Perioperative use of angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors, vancomycin, and higher body mass index increased the possibility of postoperative AKD [24]. Other data reveal that exposure to angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers following AKI is associated with a lower risk of all-cause mortality, recurrent AKI, and progression to CKD [25].

In 2019, Tonon and Rosi investigated the incidence and outcomes of AKD (with or without AKI) in patients with cirrhosis [26]. AKD was diagnosed in 29% of patients who did not have AKI, which was approximately 4 times more common than AKD with/after AKI. Only 52.5% of patients with AKD recovered, 35% died, and the remaining patients developed CKD [26].

In 2019, Kofman et al. evaluated AKD incidence after AKI in 225 patients with ST-segment elevation myocardial infarction [27]. The patients were examined for AKD incidence and long-term renal outcomes based on SCr levels measured 7 days after hospital discharge and 90–180 days after AKI [27]. Mortality was investigated at 90 days and for $1,271 \pm 903$ days.

AKD was detected in 81 (36%) of 225 patients with myocardial infarction and AKI and was associated with higher 90-day (35% vs. 11%, $p < 0.001$) and long-term (35 vs. 17%, $p < 0.001$) mortality rates. At ≥ 90 days after AKI, 41% of patients with AKI had an SCr level equal to or lower than that at admission, whereas the remaining 59% developed or progressed to CKD [27]. Notably, in the absence of AKD, progression to CKD was observed in only 7% of patients [27].

The results of the Third China National Stroke Registry were published in 2022 [28]. One subgroup included patients with in-hospital testing for SCr and serum cystatin C levels who had repeat testing at 3 and 12 months of follow-up [28]. The primary clinical outcome was 1-year all-cause mortality rate, and the secondary outcomes included stroke recurrence and post-stroke disability [28].

AKD was determined in 3.9%, 6.7%, 9.9%, and 6.2% of patients based on SCr, estimated GFR based on SCr, estimated GFR based on cystatin C, and combined estimate of estimated GFR based on SCr and cystatin C, respectively. AKD diagnosed by SCr or estimated GFR based on SCr was independently attributed to 1-year all-cause mortality and post-stroke disability in Chinese patients with ischemic stroke [28].

In 2022, a study was conducted in patients who had coronary angiography [29], wherein 16.7% were diagnosed with AKD. The mortality rate was higher in patients with AKD than in those without AKD (24.8 vs. 15.4%, $p < 0.001$) [29]. AKD was independently associated with an increased risk of all-cause mortality (adjusted hazard ratio: 1.57; 95% confidence interval (CI): 1.39, 1.78; $p < 0.001$) [29]. The study revealed that AKD commonly develops after AKI [29].

In a study conducted in China in 2021, 1,386 patients undergoing coronary angiography were evaluated for AKI at 7 days, AKD at 3 months, and CKD at 12 months [30]. AKI was observed in 23.9% of patients with normal preoperative renal function [30]. Even with early recovery of renal function within 3 days, AKI increased the risk of AKD (odds ratio: 3.21; 95% CI:

1.98, 5.20; $p < 0.001$) and CKD (odds ratio: 2.86; 95% CI: 1.68, 4.86; $p < 0.001$). Persistent AKI further increased the risk of AKD (odds ratio: 12.07; 95% CI: 5.56, 26.21; $p < 0.001$) and CKD (odds ratio: 10.54; 95% CI: 4.01, 27.76; $p < 0.001$). Multivariate analysis indicated that 3-month postoperative heart failure and high right ventricular systolic pressure are independent risk factors for CKD [30].

In October 2022, a study in patients who underwent acute surgery for type A aortic dissection was published [31]. In total, 54% of patients developed AKI, of which 35.9% progressed to AKD, and AKD developed in 10.6% of patients without AKI. Overall, 24.3% of participants were diagnosed with AKD [31]. Stage II–III AKD was associated with persistent decline in renal function for 1 year [31]. AKD was associated with a higher risk of serious adverse renal events (relative risk: 2.52; 95% CI: 1.90, 3.33) and all-cause rehospitalization rate (relative risk: 2.86; 95% CI: 2.10, 3.89) [31].

In the past decade, biological markers that predict and identify AKI earlier and more reliably than traditional estimates of renal function have been actively sought. Neutrophil gelatinase-associated lipocalin, cystatin C, interleukin-18, and kidney injury molecule-1 are among the most studied molecules [32].

More accurate analysis of complex biological systems is possible owing to recent advances in molecular biology, new methods to study the transcriptome, metabolomics and proteomics, and significant advances in genome sequencing [32]. This will hopefully lead to new studies using different molecules in the human biological environment to examine the renal continuum stages, including AKD and possibility of progression to CKD.

AKD is recognized as an independent entity [6] and is attracting increasing attention from researchers, especially in the context of renal function progression in patients. However, currently, studies on AKD are lacking, and in Russia, these studies are isolated, possibly because of the lack of a unified approach in diagnosing this disease.

Further research is warranted to characterize the clinical causes of AKD, identify their potential associations with outcomes, and understand how clinicians can apply them to effectively treat patients [6]. It is critical to increase clinician awareness of potential adverse renal outcomes of AKD, as most of these patients are not followed by a nephrologist. In the majority of these patients, AKD is not detected by monitoring clinical and outpatient hospital records [19].

Studies conducted by the action groups indicated that including AKD in clinical guidelines and kidney disease research programs will increase the proportion of identified patients at risk for adverse outcomes not identified by current criteria for AKI and CKD and will allow developing treatment strategies based on disease severity and specific AKD stages.

To improve outcomes, it is crucial to provide a clear definition of AKD, expand the use of the term, and develop research programs to assess outcomes and test interventions. This will provide evidence to support clinical guidelines.

ADDITIONAL INFORMATION

Authors' contribution. V.S.S. — formal analysis, methodology, investigation, writing — original draft; M.V.M. — conceptualization, writing — review and editing, supervision; A.Yu.D., S.F.K. and V.V.M. — formal analysis, investigation.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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