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CKJ REVIEW

Update on persistent acute kidney injury in critical illnesses

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ABSTRACT

Acute kidney injury (AKI) affects about half of patients admitted to the intensive care unit (ICU), and worsens their short- and long-term outcomes. Apparently self-limiting AKI episodes initiate a progression toward chronic kidney disease (CKD) through cellular and molecular mechanisms that are yet to be explained. In particular, persistent AKI, defined in 2016 by the Acute Dialysis Quality Initiative as an AKI which lasts more than 48 h from its onset, has been correlated with higher morbidity and mortality, and with a higher progression to acute kidney disease (AKD) and CKD than transient AKI (i.e. AKI with a reversal within 48 h). This classification has been also used in the setting of solid organ transplantation, demonstrating similar outcomes. Due to its incidence and poor prognosis and because prompt interventions seem to change its course, persistent AKI should be recognized early and followed-up also after its recovery. However, while AKI and CKD are well-described syndromes, persistent AKI and AKD are relatively new entities. The purpose of this review is to highlight the key phases of persistent AKI in ICU patients in terms of both clinical and mechanistic features in order to offer to clinicians and researchers an updated basis from which to start improving patients' care and direct future research.

LAY SUMMARY

Acute kidney injury (AKI) affects about half of patients admitted to the intensive care unit (ICU), and worsens their short- and long-term outcomes. Persistent AKI, defined in 2016 by the Acute Dialysis Quality Initiative as an AKI which lasts more than 48 h from its onset, has been correlated with higher morbidity and mortality, and with a higher progression to acute kidney disease and chronic kidney disease than transient AKI (i.e. AKI with a reversal within 48 h). Due to its incidence and poor prognosis and because prompt interventions seem to change its course, persistent AKI should be recognized early and followed-up also after its recovery.

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Keywords: acute kidney disease, AKI-to-CKD transition, molecular mechanisms, persistent acute kidney injury, transient acute kidney injury

INTRODUCTION

Acute kidney injury (AKI) is estimated to occur in approximately 50% of intensive care unit (ICU) patients [1]. AKI has been associated with an increased morbidity and mortality, and, over the past decade, a higher risk of chronic kidney disease (CKD) [2]. A growing body of evidence supports a bidirectional relationship between AKI and CKD [3]. CKD, characterized by a decreased number of functioning nephrons [4], is probably the most important factor that defines the susceptibility of a subject to developing AKI under nephrotoxic exposure [5]. Furthermore, baseline renal function is the most significant variable in assessment of patients' AKI risk; therefore, it is a component of several risk scores used in different clinical settings [6, 7]. However, AKI is a recognized risk factor for CKD [8], by damaging nephrons and reducing first renal functional reserve (RFR) and then glomerular filtration rate (GFR) [9]. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI workgroup defined AKI and CKD as syndromes mainly differentiated by the timing of kidney function impairment (i.e. a period of $\leq$7 days for AKI and >90 days for CKD) and its reversibility [10]. Additionally, KDIGO also defined the persistence of kidney functional impairment for a duration of between 7 and 90 days as acute kidney disease (AKD). In 2016, the Acute Disease Quality Initiative (ADQI) group further defined AKI as persistent if variations of serum creatinine (sCr) and/or urine output, according to KDIGO criteria, last beyond 48 h from AKI onset. On the contrary, a rapid reversal of AKI within 48 h has been defined as transient AKI [11]. However, persistent AKI needs to be consistently defined in the literature. While AKI and CKD are well-described syndromes, transient or persistent AKI and AKD are relatively new entities. This review aims to highlight the critical phases of persistent AKI in ICU patients in terms of both clinical and mechanistic features to offer to clinicians and researchers an updated basis from which to start improving patients' care and direct future research.

BEFORE AN AKI EPISODE: RISK FACTORS FOR PERSISTENT AKI IN CRITICALLY ILL PATIENTS

The traditional classification by which transient AKI is due to a brief kidney injury while persistent AKI is due to a prolonged kidney injury is partially obsolete. Depending on patients' susceptibility, a short kidney injury may evolve into persistent AKI and AKD, triggering the AKI-to-CKD transition. While patient-related risk factors determine the individual patient's susceptibility to developing AKI, procedure-related risk factors are the exposure of a patient to potentially nephrotoxic agents. Susceptibility and exposure together define each patient's risk of AKI. According to this concept, it is reasonable to assume that persistent versus transient AKI occurs when a patient has a high susceptibility to developing kidney damage and/or undergoes intensive, repeated potentially nephrotoxic exposures. The first case is due to patient-related risk factors that limit the adaptability to conditions potentially harmful for the kidneys (i.e. pre-existing CKD or low/absent RFR, comorbidities and clinical conditions that may contribute to AKI development). The exposures to which the patient can be subjected vary in intensity, number and frequency (e.g. nephrotoxic agents, emergency surgery, liver failure, sepsis, etc.) [12]. As patients' susceptibility increases, the intensity of exposure that can lead to persistent AKI decreases. On the contrary, in the presence of severe nephrotoxic exposure (e.g. sepsis), even a lowly susceptible subject may develop persistent AKI, AKD and CKD.

Critically ill patients are exposed to various potential nephrotoxic substances, including prescribed therapeutic agents, that could be responsible for underrecognized persistent AKI. In addition, although several studies have identified conditions that predispose to persistent AKI [13, 14], risk factors are currently under investigation limiting the designing of simplified risk prediction models.

DURING AN AKI EPISODE: CLINICAL AND MECHANISTIC FEATURES OF PERSISTENT AKI IN CRITICALLY ILL PATIENTS

Predictive and early diagnostic criteria of persistent versus transient AKI

The early diagnosis of transient/persistent AKI has a key role in critical care management. Assessing the variation of sCr for AKI diagnosis requires ascertaining its change from a known baseline. In literature, four different baseline SCr definitions are described: (i) pre-admission sCr: sCr measured in a time-period of a maximum of 365 days and a minimum of 7 days from the moment of hospital admission; (ii) admission sCr: the first sCr measured at hospital admission; (iii) nadir sCr: the lowest measured value of sCr during the first 3 days of the ICU stay; (iv) estimated sCr: calculated using a back-estimation equation, starting from an assumed GFR of 75 or 100 mL/min, or assigning GFR from age- and sex-standardized reference tables [15, 16]. In clinical practice, the most used definitions are pre-admission sCr and admission sCr, while nadir sCr and estimated sCr are mostly used in experimental settings. However, it needs to be clarified which is the best method for assessing baseline sCr.

Based on the increase in sCr levels that starts when >50% of nephrons are impaired, it is evident that sCr is a late marker of kidney dysfunction [17]. Nevertheless, equations for GFR estimation have a limited use in critically ill patients in which sCr is not at a steady state [18]. Numerous other methods for renal function assessment have been proposed, such as the Jelliffe equation [19], the kinetic eGFR [20] and the point-of-care determination of GFR through a fiberoptic ratiometric fluorescence analyzer [21], but they are still under investigation, while more established methods, such as GFR measurement with inulin or iohexol, are cumbersome and time-consuming. However, measured GFR would allow a rapid diagnosis of AKI and quantification of the extent of injury without the limits due to sCr and urine output. In addition to the late increase of sCr during a kidney damage, both sCr and urine output can be influenced by non-renal factors. This is particularly obvious in ICU patients with frequent muscle wasting syndrome, hyperhydration, hypovolemia and diuretic use [15, 22].

Recently, the 23rd ADQI expert group proposed expanding the AKI definition and staging by considering both kidney dysfunction and early kidney damage [23]. Although new biomarkers, functional tests [e.g. RFR assessment, furosemide stress test (FST), etc.] and ultrasonographic markers have been widely

Table 1: Potential markers of persistent versus transient AKI in different settings.

AKI settings	Biomarkers	Functional tests	Clinical meaning
Cardiac surgery Vascular surgery Coronary angiography Cardiac surgery ICU	uDKK3:uCr[a] suPAR[a] [90]	RFR assessment [50] IRRIV test [79] RRI	Before an AKI episode. The alterations of biomarkers or functional tests identify subjects with a high susceptibility to developing persistent AKI after a kidney injury
ICU Cardiac surgery ICU Sepsis	 Nefrocheck Nefrocheck pCysC CCL14[a] PenK [91] NGAL	Furosemide stress test RRI [25] RRI	During an AKI episode. The alterations of biomarkers or functional tests, performed after a kidney injury, allow early diagnosis of persistent AKI
Cardiac surgery ICU Sepsis	uDKK3:uCr[a] [88] pCysC CCL14[a] [87, 92] PenK [91] uDKK3:uCr[a] CCL14[a]	RFR assessment [75]	After an AKI episode. The alterations of biomarkers or functional tests, performed after a persistent AKI episode, identify patients with a high risk of AKI-to-CKD transition

[a]Biomarkers not yet available for clinical use.
uDKK3:uCr, urinary dickkopf-3:urinary creatinine; suPAR, soluble urokinase plasminogen activator receptor; pCysC, plasma cystatin C; CCL14, Chemokine (C-C motif) ligand 14; PenK, Proenkephalin; NGAL, Neutrophil Gelatinase-Associated Lipocalin.

investigated with the aim to improve early diagnosis of AKI, they are still underused, even in critical care settings. Among ultrasonographic markers, the renal resistive index (RRI) value, measured in a segmental artery, is commonly used to assess blood flow in renal intra-parenchymal vessels. RRIs are calculated using the formula:

$$\mathrm{RRI} = (\text{peak systolic velocity} - \text{end-diastolic velocity}) / \text{peak systolic velocity},$$

thus being a valuable indicator of the resistance to flow within the kidney. In addition, studies suggest that RRI value may predict persistent AKI in some clinical settings [24].

Like CKD, AKI does not have early specific symptoms. Beyond the issue related to "when" to use markers, another critical concern is "which" marker/s to use. In fact, AKI is a very heterogeneous syndrome with different etiologies, pathophysiological pathways and clinical features, thus it is difficult to generalize. Therefore, for instance, RRI is a good predictor of persistent cardiac surgery–associated AKI [25], but its role is less defined in sepsis-associated AKI [26, 27]. Then, the predictive capability of different biomarkers varies depending on the etiology of AKI and the group of patients considered. In addition to all these reasons, the main issue concerning the scarce clinical use of biomarkers is the need for more awareness of the importance of early AKI diagnosis and treatment among healthcare team members, as revealed by a recent Italian survey [28, 29].

Table 1 summarizes potential markers of persistent vs transient AKI in different settings, some of which are not yet available for clinical use.

Cellular and molecular differences between persistent and transient AKI

Immediately after a kidney injury, repair processes are activated. Some of them allow a rapid return of renal function, and others lead to a persistence of renal dysfunction. The 13th ADQI Consensus Conference defined as "adaptive repair" as those processes that lead to a "resolution of the renal structure free of long-term sequelae" and as "maladaptive repair" a "process that results in a durable reduction in kidney function usually associated with a change in renal structure" [30]. Adaptive and maladaptive repair processes together with the injury mechanisms determine the number of irreversibly lost nephrons and then the long-term prognosis of kidney function. Several pathophysiologic processes that promote maladaptive repair and AKI-to-CKD transition have been identified and gained growing attention, such as microvascular damage and loss of peritubular capillaries, systemic inflammation and pro-fibrotic cytokine secretion, cell cycle arrest and cellular senescence [31], pericyte activation with myofibroblasts generation [32] and metabolic reprogramming of tubular epithelial cells (TECs). Some of these mechanisms, such as cell cycle arrest and metabolic reprogramming of TECs, start as adaptive repair processes, but, if persistent, become maladaptive [33] .

When not completely repaired, TECs undergo cell cycle arrest at G2/M, as a protective mechanism for maintaining genomic stability. Nonetheless, TECs with arrested cell cycle acquire a pro-fibrotic secretory phenotype known as senescence-associated secretory phenotype, which promotes the development of kidney fibrosis [34].

It has been demonstrated that AKI leads to a permanent loss of TECs even when full clinical renal recovery occurs (see below). Kidney function can be augmented by polyploidization of TECs in unaffected nephrons (i.e. compensatory hypertrophy) [35]. However, TECs polyploidy promotes TECs senescence, progressive interstitial fibrosis and AKI-to-CKD transition [36].

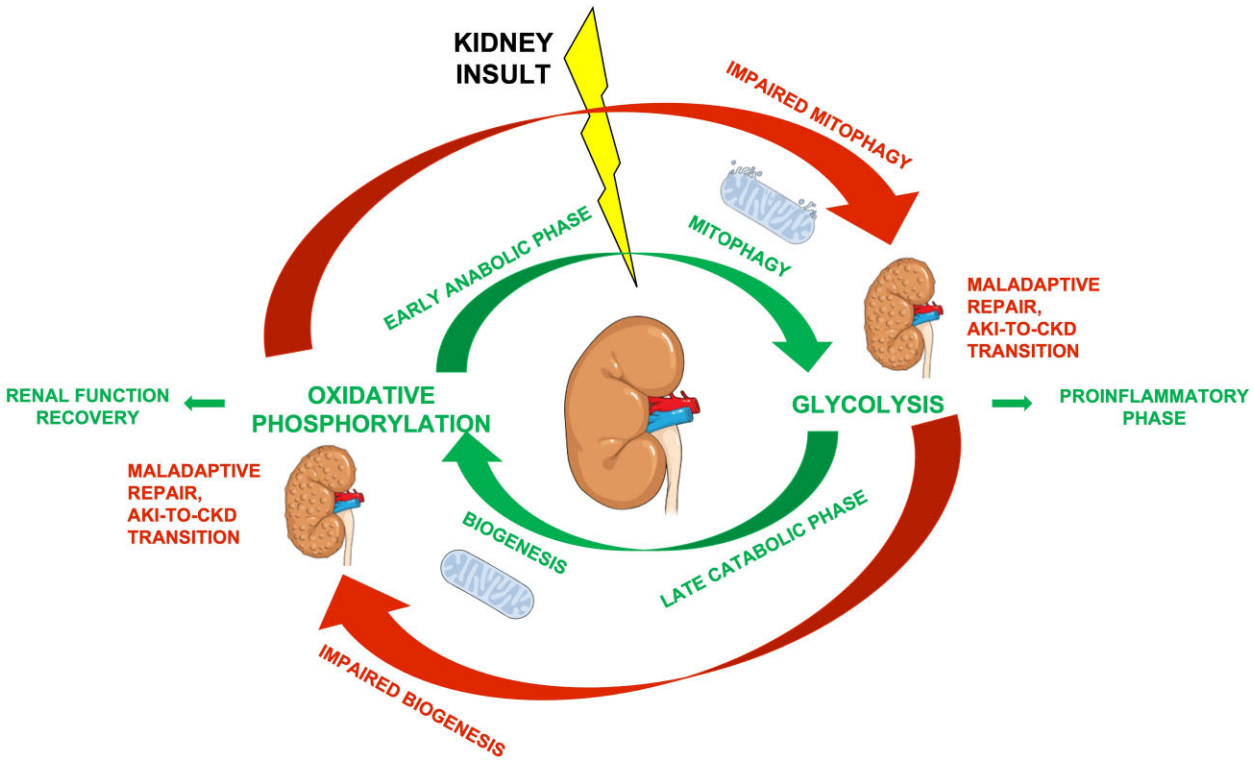

Figure 1: Biphasic response to sepsis-associated AKI. After a kidney injury, dysfunctional mitochondria are removed from the cytosol via mitophagy. After this first proinflammatory phase, the restitution of a functioning mitochondria pool via biogenesis promotes renal recovery. There is evidence that an impaired mitophagy and an impaired biogenesis lead to maladaptive repair and transition to CKD [42, 44].

Although the exact mechanisms are still unknown, the metabolic reprogramming of TECs during an AKI episode seems to play a pivotal role in inhibiting AKI-to-CKD transition.

In the early 2000s, activated T cells were found to switch their metabolism to glycolysis, thus adjusting their energetic and biosynthetic needs in response to changing conditions [37]. Some data suggest that, like immune cells, TECs can also reprogram their metabolism in response to kidney injuries. In particular, investigations focused on sepsis-associated AKI [38, 39]. It has been hypothesized that proximal TECs act as danger sensors by responding to pathogen-associated molecular patterns (PAMPs), secreting pro-inflammatory cytokines into the tubule, and activating TECs in other nephron segments, thus amplifying tubular inflammation [40]. These findings suggest the presence of an early proinflammatory phase followed by a later catabolic phase, probably related to mitochondrial functions. They are respectively characterized by a shift in metabolism to aerobic glycolysis, generating appropriate inflammatory responses, limiting oxidative damage and rearranging substrates to prevent cell death, and to oxidative phosphorylation, promoting renal function recovery [41] (Fig. 1). Mitochondria regulate intracellular calcium homeostasis and reactive oxygen species (ROS) levels, and control cell cycle, cellular differentiation and death through their biogenesis, dynamics, mitophagy, bioenergetics and mitochondrion endoplasmic reticulum cross-talk. During the early glycolytic phase, TECs remove dysfunctional mitochondria from the cytosol via mitophagy (i.e. a form of autophagy that selectively eliminates damaged mitochondria) to avoid ROS generation. In experimental models of AKI, impaired mitophagy has been associated with a reduced renal recovery [42] while a diminished AKI progression and improved survival have been found in conditions of increased mitophagy [43]. After the first proinflammatory phase, the restitution of a functioning mitochondria pool via biogenesis (i.e. the generation of new mitochondrial mass) is mandatory to cope with the increased metabolism and energy demands, thus promoting renal recovery and survival. Recent findings suggest that impaired biogenesis leads to a maladaptive repair after AKI and renal fibrosis [44] (Fig. 1). As the glycolytic phase is fundamental for appropriate responses to kidney injuries, the capacity to turn off the inflammation is required for renal recovery. In fact, cytokines and damage-associated molecular patterns (DAMPs), released by injured TECs and endothelial cells in the proinflammatory state, participate in the development of a pro-fibrotic milieu. This activates pericytes to proliferate and evolve into myofibroblasts, thereby inducing matrix deposition and subsequent decreased capillary density, thus leading to maladaptive repair, renal fibrosis and AKI-to-CKD conversion [45].

In immune cells the early switch to glycolysis is also required to develop a trained immunity (i.e. the process by which the innate immune system develops memory and adjusts its response to future insults). The fascinating hypothesis of a biological memory that drives the kidney to respond to future insults in humans has been postulated, but it is still a subject of debate [46].

AFTER AN AKI EPISODE: PROGNOSIS OF PERSISTENT AKI IN CRITICALLY ILL PATIENTS

Persistent AKI has been correlated with higher morbidity and mortality, and a higher progression rate to AKD and CKD than transient AKI [47]. It seems that prompt interventions can change the course of AKI and improve patients' outcomes [47]. The continuum of AKI-to-CKD proposed by 23rd ADQI consensus group is based on the AKD definition that can be considered the evolution of a persistent AKI episode that has not been promptly and appropriately treated or, more generally, in which the abovementioned mechanisms (and probably many others) have reduced functioning nephrons, thus affecting RFR and/or GFR [11]. Unfortunately, like persistent AKI, the AKD definition also depends on sCr level variations and its incidence is probably underestimated because of muscle wasting, hyperhydration, hyperfiltration, etc. Plasma cystatin C has been proposed in critical settings as an alternative marker to assess renal recovery. Despite promising preliminary results, it is still far from being routinely used in clinical practice [15, 48]. Moreover, even in the case of sCr levels returning to baseline, a complete recovery of baseline renal conditions, in terms of both kidney structure and function, may not occur. A subclinical damage may be identified by new-onset or worsening proteinuria, arterial hypertension and/or a drop in RFR [11, 49]. Moreover, patients with AKD in whom sCr levels returned to baseline have been demonstrated to be more prone to further kidney damage and other adverse events [50].

PERSISTENT AKI IN TRANSPLANTED PATIENTS

The classification of transient vs persistent AKI has also been used in the setting of liver and lung transplantation. In these settings, AKI has a high incidence, reaching more than the half of transplanted patients (studies have reported an incident of AKI up to 64% in the liver [51] and 69% in lung transplant recipients [52]) and a worse prognosis in terms of morbidity and mortality [51, 53].

In kidney transplantation, AKI, manifesting as either delayed graft function (DGF) or *de novo* post-transplant acute deterioration of graft function, occurs in 30% of kidneys coming from deceased donors and in 50% of those coming from deceased donors after cardiac death [54], and affects short- and long-term transplant outcomes [55].

In transplanted patients, multifarious risk factors contribute to the development of AKI. They can be classified as pre-transplant comorbidities, related to both donor and recipient, perioperative problems and post-transplant factors, mainly associated with exposure to nephrotoxic agents, such as calcineurin inhibitors and antimicrobial drugs [56].

There is growing evidence demonstrating that persistent AKI after lung transplantation is associated with worse renal and non-renal outcomes [57], including a higher mortality [57, 58]. A recent study on liver-transplanted patients showed that persistent AKI is associated with an increased incidence rate of graft failure and a decreased graft survival time [59].

According to recently published data, a linear association between duration of DGF and graft loss has been found. In particular, a prolonged DGF beyond 7 days posttransplant has been associated with a >40% greater risk of death-censored graft loss [60]. These data confirm the results of prior studies [61, 62] and underline the importance of clinical interventions that aim to prevent or reduce the duration of DGF.

CLINICAL APPROACH TO CRITICALLY ILL PATIENTS WITH PERSISTENT AKI

Prevention and diagnosis

According to the varied pathophysiology of AKI, the choice of which clinical parameters and risk scores, biomarkers and functional tests to use should be considered and tailored to the AKI setting, clinical phase and center availability or local expertise.

The rapid diagnosis of persistent AKI may allow reconsideration of all causes of AKI, their correction when possible and remodulation of the therapy [11]. In critically ill individuals, AKI is frequently multifactorial and depends on both patient- and agent-related factors. Although patient-related factors are commonly unmodifiable, the ones related to nephrotoxic agents, when possible, must be reassessed according to the literature evidence. The timely recognition of persistent AKI potentially enables the physician to promptly withdraw potential nephrotoxic drugs and to interrupt the pathogenetic mechanisms of kidney injury, thus preventing further renal impairment [63].

AKI awareness programs could help to improve AKI awareness and recognition, and they should include a broader and more appropriate use of early biomarkers of kidney damage [23] and functional tests in critical care settings and the involvement of all healthcare team members, each for their own competence [28].

Treatment and follow-up

The treatment of persistent AKI largely depends on its cause(s) and the setting in which it occurs, and varies according to the clinical phase.

Therapeutic indications for AKI due to specific kidney diseases, such as acute glomerulonephritis, acute renal vascular disease, etc., are beyond the scope of this review.

At the beginning of an AKI episode, therapeutic indications for persistent AKI do not differ from the ones for transient AKI. They mainly concern the optimization of fluid management and hemodynamic support and the withdrawal of nephrotoxic agents, when it is possible. In cases in which agents potentially harmful for the kidneys are required, benefits and risks should be balanced and they should be administered for as long as needed with a close monitoring of renal function [22]. The risk of drug (or metabolites) accumulation and toxicity due to kidney dysfunction, altered protein binding and variable volume of distribution should be considered [5]. Simultaneously, the risk of therapeutic failure due to drug under-dosing should be balanced, particularly in patients undergoing renal replacement therapy (RRT).

As an accelerated RRT strategy in critically ill patients with AKI has failed to demonstrate a lower risk of death [64], RRT should be considered when metabolic and fluid demands exceed the kidney's capacity to meet them [10]. The choice of modality depends on the patient's clinical status, the center's available resources and the expertise of personnel. Although conclusive randomized clinical trials are missing, in hemodynamically unstable patients, continuous RRT is more appropriate than intermittent RRT. As a consequence, also for maintenance hemodialysis and peritoneal dialysis patients, modality transitions should be considered based on their status [5].

As early diagnosis is fundamental to addressing preventive strategies, transitioning care from ICU to other hospital departments and from hospital to community is crucial to defining optimal follow-up care. It should be personalized according

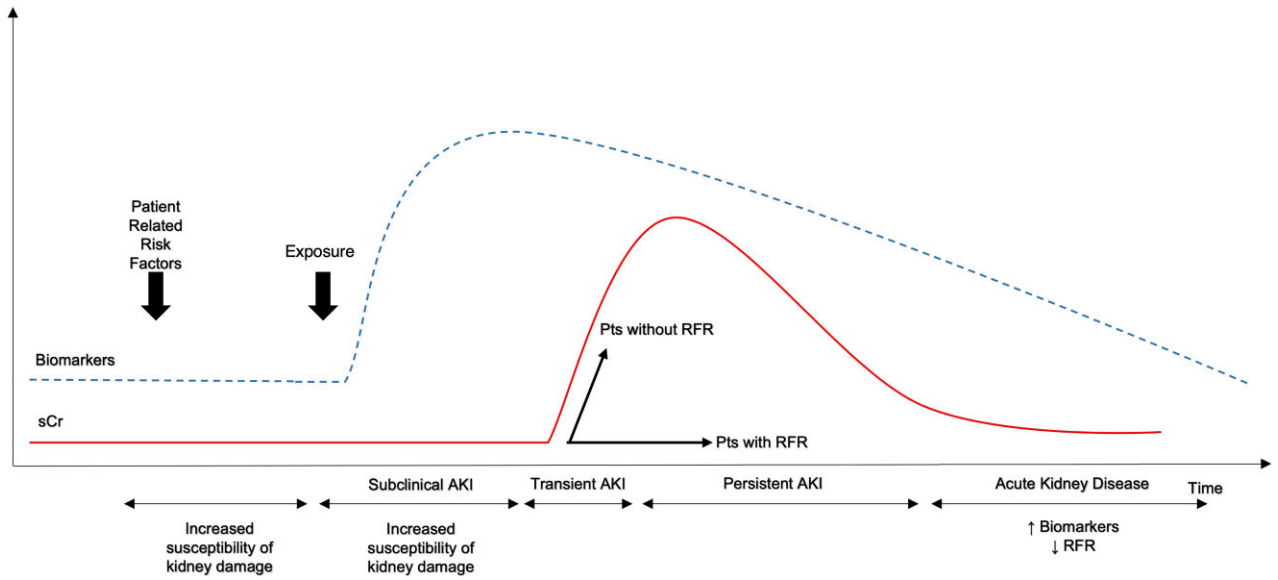

Figure 2: The continuum of AKI and AKD in patients with and without RFR. Before an AKI episode, patient-related risk factors define the kidney's susceptibility to kidney damage. Based on this, a different intensity of exposure is required to lead to subclinical or clinical AKI. Baseline renal function, including RFR, is critical among patient-related risk factors for AKI. In the presence of an intact RFR, even in case of intensive, repeated potentially nephrotoxic exposures, the damage to the kidney may remain subclinical. In contrast, if RFR is lost, even in mild exposure, the kidney damage may become clinically manifest [9]. In addition, persistent AKI has a high rate of progression to AKD. Also, in the case of sCr levels returning to baseline, these patients may yet have increased biomarkers and impaired RFR, thus having a higher risk of further kidney damage [75].

to patients' overall risk (e.g. pre-existent CKD, age, etc.), AKI severity and duration (e.g. need for RRT, persistent vs transient AKI) and renal recovery [65]. Despite several medical advances meaning that critically ill patients with AKI increasingly have better survival [66], they are nevertheless at risk of adverse outcomes, including renal failure [2], progression to CKD, and cardiovascular events such as new-onset arterial hypertension or myocardial infarction [67]. Unfortunately, few patients benefit from early nephrological evaluation that could decrease mortality among survivors of dialysis-receiving AKI [68]. The improvement of care includes appropriate risk stratification, monitoring of kidney function, the management of CKD complications, blood pressure control, medication reconciliation and education [69]. Risk stratification and a kidney function monitoring plan at discharge are needed to improve post-AKI care. In their randomized controlled trial, Silver *et al.* [70]. compared structured nephrologist follow-up versus usual care in survivors of AKI and showed that the enrollment of fully eligible patients was a barrier, primarily due to the requirement for post discharge, in-person visits. The reason was that eligible patients had long hospital travel times/hospital-related fatigue. Additionally, they did not identify any difference in major adverse kidney events at 1 year. However, the high frequency of events highlights the vulnerability of this population and the urgent need for feasible and effective interventions for survivors of AKI. Strategies for optimal follow-up care of patients post-AKI are still under investigation.

ONGOING RESEARCH ON PERSISTENT AKI

Prevention and diagnosis

Several studies have assessed promising tools as prediction models for AKI based on machine-learning methodologies [71, 72]. However, the performance of models may vary in different scenarios, and the abovementioned studies do not focus on the critical care setting. Furthermore, few studies involving comparisons of models have concentrated on AKI prediction in the ICU and the majority of them lack external and prospective validation [73]. Liang *et al.* [74] built models to predict AKI within 48 h in critically ill patients by using three transcontinental databases, and then they evaluated the clinical effect of the model through a 1-year prospective validation. A total of 2532 patients were admitted to the center for prospective validation; 358 positive results were predicted and 344 patients were diagnosed with severe AKI, with the best sensitivity of 0.72, specificity of 0.80 and area under the receiver operating characteristic of 0.84. However, the AKI predictions using artificial intelligence is still controversial.

The assessment of RFR, i.e. the capability of the kidney to increase GFR under conditions of physiologic or pathologic higher functional demand, thus being an indicator of renal functioning mass, allows better definition of susceptibility to developing acute damage. Different methods to measured RFR have been proposed, such as oral protein load and infusion of amino acids. In the presence of an intact RFR, even in case of intensive, repeated potentially nephrotoxic exposures, the damage to the kidney may remain subclinical. On the contrary, if RFR is progressively lost, the susceptibility of the kidney progressively increases and even in the presence of a mild exposure, the kidney damage may become clinically manifest [9] (Fig. 2). However, although RFR is an important tool to assess the kidney's capacity to respond to conditions of higher functional demand, the exam is challenging and may be stressful for some patients. For this reason, based on the pathophysiological hypothesis of kidney damage during intra-abdominal hypertension [76], the intraparenchymal renal resistive index variation (IRRIV) test was designed to predict the presence of RFR [77]. Samoni *et al.* found a correlation between IRRIV test and RFR measured by using an oral protein loading test in healthy volunteers [78] and in

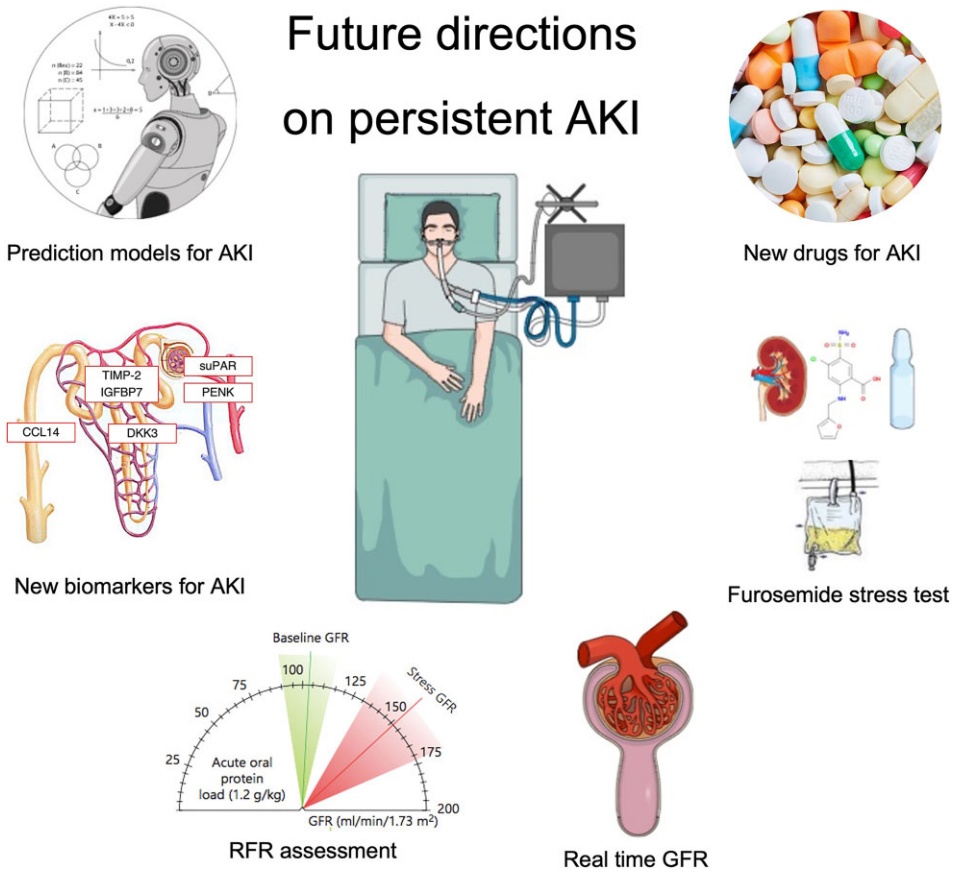

Figure 3: Future directions in persistent AKI. Future directions in persistent AKI include a better assessment of kidney susceptibility (prediction models, RFR assessment), an earlier and more accurate diagnosis (FST, new biomarkers, real-time GFR), and a pharmacological therapy, thus improving the care of AKI and AKD patients.

cardiac surgery patients [79]. However, these findings must be confirmed in large patient cohorts and different settings.

Among functional stress tests to early diagnose persistent versus transient AKI, the FST, based on the pharmacokinetic properties of furosemide, assesses the functional integrity of the renal tubule, and it may be a reliable predictor of AKI progression to severe stages and requirement of dialysis in ICUs [80]. It could help clinicians identify patients with tubular injury and at higher risk of AKI or CKD progression. Chen *et al.* [81]. in their systematic review and meta-analysis showed that the FST is a simple tool for the identification of AKI populations at high risk of AKI progression and the need for RRT, and the diagnostic performance of FST in RRT prediction is better in early AKI population. Koyner *et al.* [82]. showed that, in the setting of early AKI, FST urine output outperformed biochemical biomarkers for prediction of progressive AKI, need for RRT and inpatient mortality. Using an FST in patients with increased biomarker levels improves risk stratification. However, several aspects can limit FST such as the retrospective nature of most studies, variability of doses and timing. Additionally, some of the published studies solely rely on AUC values to define the predictive capacity of the test, while actual or absolute predicted risk could be more appropriate to assess risk prediction models [83].

During an AKI episode, accurate ascertainment of GFR is crucial for the diagnosis of early kidney disease [84]. Patients at risk of early kidney disease when GFR is normal-to-elevated would benefit from having their GFR measured using more accurate and precise techniques. Recent advances in technology to measure fluorescent compounds through the skin are providing a new approach for real-time monitoring of GFR [85]. After the injection of an ideal GFR marker, its concentration in the plasma reaches a peak, followed by an exponential decay due to its diffusion into the extracellular space. Using transdermal sensors, the plasma disappearance rate can be measured rather than their steady state concentration. This eliminates the delay inherent in using an endogenous marker of filtration and permits continuous monitoring of GFR.

Treatment and follow-up

Without effective pharmacologic therapies, severe AKI is usually managed through RRT. Unfortunately, no specific therapy is currently available to prevent or treat AKI. However, various potential agents, including novel compounds, re-purposed drugs and cell-based therapies, are in ongoing early-phase clinical trials. Various pathways have been targeted for this purpose, including oxidative and mitochondrial stress, cellular metabolism and repair, inflammation, apoptosis and hemodynamics [63, 86].

After an AKI episode, the need for an appropriate follow-up of patients recovering from AKI or AKD is increasingly being recognized [65]. Kidney function and proteinuria monitoring, new biomarkers of renal tubular fibrosis measurement [e.g. Chemokine (C-C motif) ligand 14 (CCL14) [87], Dickkopf-3 (DKK3) [88], etc.] and functional tests application (e.g. RFR assessment)

are some of the tools proposed for a better risk stratification and prevention of new episodes of AKI. Simultaneously, drugs that act on the renin–angiotensin–aldosterone system, such as sodium-glucose co-transporter-2 inhibitors, have been shown to improve clinical outcome in CKD patients [89] and open a potential therapeutic strategy in post-AKI patients.

CONCLUSIONS

Persistent AKI has been associated with worse outcomes than transient AKI, including a higher rate of AKI-to-CKD transition. As prompt interventions can change its course, persistent AKI should be diagnosed early by measuring new biomarkers and applying functional tests.

In the absence of effective pharmacological therapies, the prevention of AKI has a crucial role, as well as the reconsideration of all causes of AKI, their correction when possible and modulation of the therapy. Furthermore, the follow-up post-AKI should be personalized according to patients' overall risk, AKI severity and duration, and renal recovery, considering that, also in case of full clinical recovery, subclinical damage may be present and predispose to further kidney damage and other adverse event(s).

Ongoing research on persistent AKI may lead to a better assessment of kidney susceptibility, to an earlier and more accurate diagnosis, and to a pharmacological therapy, thus improving the care of AKI and AKD patients (Fig. 3).

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

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