Biomarkers in pursuit of precision medicine for acute kidney injury: hard to get rid of customs

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Traditional acute kidney injury (AKI) classifications, which are centered around semi-anatomical lines, can no longer capture the complexity of AKI. By employing strategies to identify predictive and prognostic enrichment targets, experts could gain a deeper comprehension of AKI’s pathophysiology, allowing for the development of treatment-specific targets and enhancing individualized care. Subphenotyping, which is enriched with AKI biomarkers, holds insights into distinct risk profiles and tailored treatment strategies that redefine AKI and contribute to improved clinical management. The utilization of biomarkers such as N-acetyl-β-D-glucosaminidase, tissue inhibitor of metalloprotease-2-insulin-like growth factor-binding protein 7, kidney injury molecule-1, and liver fatty acid-binding protein garnered significant attention as a means to predict subclinical AKI. Novel biomarkers offer promise in predicting persistent AKI, with urinary motif chemokine ligand 14 displaying significant sensitivity and specificity. Furthermore, they serve as predictive markers for weaning patients from acute dialysis and offer valuable insights into distinct AKI subgroups. The proposed management of AKI, which is encapsulated in a structured flowchart, bridges the gap between research and clinical practice. It streamlines the utilization of biomarkers and subphenotyping, promising a future in which AKI is swiftly identified and managed with unprecedented precision. Incorporating kidney biomarkers into strategies for early AKI detection and the initiation of AKI care bundles has proven to be more effective than using care bundles without these novel biomarkers. This comprehensive approach represents a significant stride toward precision medicine, enabling the identification of high-risk subphenotypes in patients with AKI.

Keywords: Acute kidney injury, Biomarkers, Dialysis, Precision medicine

Introduction

The burgeoning field of translational science has ushered in a new era in the diagnosis and management of acute kidney injury (AKI), advancing toward the realm of precision medicine [1]. Traditionally, AKI has been perceived as a monolithic entity, often classified along semi-anatomical lines, namely, prerenal, intrinsic, or postrenal AKI. This...
simplistic classification scheme is gradually making way for more precise categorizations, encompassing conditions like hepatorenal syndrome (HRS), cardiorenal syndrome, and sepsis-related AKI [2].

The prevailing diagnostic criteria for AKI predominantly rely on changes in serum creatinine (sCr) concentration and/or alterations in urine output. However, these criteria primarily reflect alterations in kidney function without necessarily explicitly indicating injury or damage [3]. Furthermore, the current AKI criteria are primarily centered on duration and severity, providing limited insights into the pathophysiology and prognosis of the condition [4].

Relying solely on sCr as a diagnostic marker may lead to diagnostic delays in specific scenarios, such as cases involving muscle wasting, liver diseases, or sepsis [5]. Consequently, the Acute Disease Quality Initiative 2020 has advocated for the concurrent utilization of functional and damage biomarkers in the early diagnosis of AKI [5]. This approach, which amalgamates damage and functional biomarkers, holds the potential to facilitate precise AKI diagnosis, differentiate underlying pathophysiological mechanisms, elucidate the etiology of AKI, and gauge the severity of the condition [6].

Simultaneously, the stratification of critical illness into distinct subphenotypes has emerged as a guiding principle in the quest for individualized medicine, a principle that also extends to the diagnosis of AKI (Fig. 1). Such stratification not only holds promise in the personalized management of AKI but also serves as a conduit for the discovery of distinct endotypes and treatable traits within this multifaceted condition [7]. In this review, we endeavor to synthesize the current methodologies into a comprehensive framework for the management of patients with AKI.

Reconsidering the classification and diagnostic challenges in acute kidney injury

Recent research has consistently demonstrated a notable association between AKI severity or chronic kidney disease (CKD) progression stages and a less favorable prognosis. This encompasses various critical facets, including the potential for renal function recovery, the imperative need for renal replacement therapy (RRT), and the ultimate mortality risk. Nevertheless, the existing definition of AKI portrays it as a solitary diagnostic entity, disregarding the intricate reality that AKI is a multifaceted syndrome influenced by

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Figure 1. Biomarkers for AKI subgrouping—dinosaur parkour illustration. The clinical use of biomarkers in AKI is influenced by the heterogeneity of patient groups and outcomes. Biomarkers have a range of advantages, including the early detection of kidney injury, the identification of AKI subphenotypes (subsets of clinical features within a shared phenotype), the recognition of AKI endotypes (subsets of patients with distinct biological disease mechanisms), and the predictive enrichment of high-risk patient groups for specific care pathways or interventions.

AKI, acute kidney injury; CCL14, chemokine ligand 14; HJV, hemojuvelin; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; PROENK, proenkephalin.
several contributory factors. This underscores the pressing need for the exploration of alternative AKI classifications.

The untimely detection of AKI is a major diagnostic challenge. Notably, sCr levels only become abnormal when much of the patient’s kidney function (often >50%) has already been compromised [8]. This inherent delay in its responsiveness poses a notable hindrance to early diagnosis and intervention.

In contrast, in conditions like angina pectoris, troponin-based diagnostic strategies have led to notable achievements in survival rates by expediting diagnosis and subsequent treatment [9]. However, when considering renal angina, a similar approach that relies on creatinine-based markers may not yield comparable improvements in patient prognosis. The inherent delay in the presentation of elevated creatinine levels in response to kidney injury may explain this disparity. As such, it is imperative to reevaluate the diagnostic criteria for AKI, considering its complex nature and the limitations of current biomarkers.

Redefining acute kidney injury: the imperative of subphenotypes

The prevailing definition of AKI does not sufficiently provide insight into the trajectory of the condition, the utility of measured biomarkers, and the critical question of when a return to baseline renal function may be anticipated. Relying solely on sCr and urine output data does not provide enough information to elucidate the intricate pathophysiological underpinnings and the inherent heterogeneity of AKI [10].

To ensure better prognostic accuracy, it is vital to identify distinct AKI subphenotypes [11]. A subphenotype can be characterized as a discrete subset of AKI patients, who exhibit shared characteristics, risk factors, biomarker profiles, responses to treatment, or outcomes that distinguish them from other patient groups within the broader AKI phenotype [12]. These etiological subphenotypes such as LIION (low perfusion, inflammation/immune, obstruction, nephrotoxin/envenomation) [1] could be delineated based on shared etiological factors (Table 1) [13] or specific outcomes, such as the need for RRT [14]. The process of subphenotyping AKI not only unveils variances in clinical outcomes [15] but also paves the way for the development of treatment strategies tailored to the distinct needs of each patient group.

### Table 1. AKI subphenotyping category

<table>
<thead>
<tr>
<th>Old classification for AKI</th>
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<tbody>
<tr>
<td><strong>Prerenal</strong></td>
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<tr>
<td>1. Absolute decrease in effective blood volume: hemorrhage, volume depletion</td>
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<tr>
<td>2. Relative decrease in blood volume (ineffective arterial volume): CHF, decompensated liver cirrhosis</td>
</tr>
<tr>
<td>3. Arterial occlusion or stenosis of renal artery</td>
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<tr>
<td>4. Hemodynamic form: NSAIDs, ACE-I, ARB in renal artery stenosis or CHF</td>
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<tr>
<td><strong>Intrinsic</strong></td>
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<tr>
<td>Vascular: vasculitis, malignant HTN</td>
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<tr>
<td>Acute glomerular nephritis: PSGN</td>
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<tr>
<td>AIN: drug-associated ATN</td>
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<tr>
<td>Ischemic Nephrotoxic</td>
</tr>
<tr>
<td>Exogenous: cisplatin, contrast</td>
</tr>
<tr>
<td>Endogenous: rhabdomyolysis, myeloma</td>
</tr>
<tr>
<td><strong>Postrenal</strong></td>
</tr>
<tr>
<td>Obstruction of collecting system or extra renal drainage: bladder outlet and ureteral obstruction</td>
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**LIION [1]**

| Low perfusion a AKI          |
| Volume: volume depletion, hypervolemia |
| Vascular Dilatation |
| Local: hepatorenal syndrome |
| Systemic: shock and sepsis |
| Constriction: eclampsia, HTN, rhabdomyolysis |
| Interruption: IAP ↑ |
| Ventricular ↓ RV output |
| ↓ LV output |
| **Inflammatory immune**      |
| Sepsis |
| Vasculitis |
| Nephritis |
| **Obstructive**              |
| Pressure necrosis |
| **Nephrotoxin/envenomation** |
| Direct toxin: ATN |
| Indirect toxin: AIN |

ACE-I, angiotensin-converting enzyme inhibitor; AIN, acute interstitial nephritis; AKI, acute kidney injury; ARB, angiotensin receptor blockers; ATN, acute tubular necrosis; CHF, congestive heart failure; HTN, hypertension; IAP, intraabdominal pressure; LIION, low perfusion, inflammation/immune, obstruction, nephrotoxin/envenomation; LV, left ventricle; NSAIDs, nonsteroidal anti-inflammatory drugs; PSGN, post-streptococcal glomerulonephritis; RV, right ventricle.

“Previously labeled “prerenal,” the term “low perfusion” is introduced here to highlight the treatment approaches that are tailored to the pathogenesis of the condition.
subphenotype [16].

**Biomarkers and acute kidney injury phenotype (Fig. 2)**

**Biomarkers in postcardiac surgery**

The PrevAKI randomized controlled trial (RCT) implements the Kidney Disease Improving Global Outcomes (KDIGO) care bundle (optimization of volume status and hemodynamics, functional hemodynamic monitoring, avoidance of nephrotoxic drugs, and prevention of hyperglycemia) in high-risk patients after cardiac surgery. High-risk patients were defined as those with urinary (tissue inhibitor of metalloprotease-2, TIMP-2)•(insulin-like growth factor-binding protein 7, IGFBP7) > 0.3. The rates of moderate-to-severe AKI were significantly reduced by the intervention compared to standard care [17]. Another multicenter RCT later also demonstrated a lower prevalence of moderate-to-severe AKI in the intervention group [18].

**Biomarkers in acute advanced cardiorenal syndrome**

When speaking to the dynamic change in renal function in patients with heart failure, the term (worsening of renal function, WRF) was used [19]. Rao et al. [20] demonstrated that in patients with acute heart failure decompensation who have preexisting WRF, aggressive volume removal with a consequent rise in tubular markers (N-acetyl-β-D-glucosaminidase [NAG], kidney injury molecule-1 [KIM-1], and neutrophil gelatinase-associated lipocalin [NGAL]) did not increase risks of post-discharge mortality or rehospitalization. The extent of the elevation of these tubular “injury” biomarkers is far less than in true AKI [21]. Novel biomarkers such as galectin-3, soluble suppression of tumorigenicity 2 (ST2), fibroblast growth factor 23 (FGF-23), soluble urokinase plasminogen activator receptor (suPAR), microRNA, growth differentiation factor 15, and NAG may have prognostic value in kidney disease progression. Liver fatty acid-binding protein (L-FABP) and suPAR may help predict AKI. ST2 and NAG may be helpful in diuretic resistance [22].

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**Figure 2. Biomarkers for clinical features in patients sharing a common syndrome or condition.**

AKI, acute kidney injury; CXCL9, C-X-C motif chemokine ligand 9; FGF-23, fibroblast growth factor 23; GDF-15, growth differentiation factor 15; IGFBP7, insulin-like growth factor-binding protein 7; IL-9, Interleukin 9; KDIGO, Kidney Disease Improving Global Outcomes; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid-binding protein; miRNA, microRNA; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; ST2, suppression of tumorigenicity 2; suPAR, soluble urokinase plasminogen activator receptor; TIMP-2, metalloproteinase 2; TNF, tumor necrosis factor.

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Biomarkers in hepatorenal syndrome

AKI in cirrhosis has a spectrum of etiologies, of which HRS carries the worst prognosis [23]. AKI is managed according to its etiology: prerenal AKI is treated with volume resuscitation, HRS is managed using intravenous albumin and vasoconstrictors, and supportive care is used for acute tubular necrosis (ATN).

Fagundes et al. [24] used the levels of urinary tubular markers such as urinary NGAL to predict elevations across the different AKI causes, with prerenal AKI being the lowest, followed by the slightly higher levels seen in HRS and the significantly elevated levels seen in ATN. They also used the cutoff value of 194 g/g creatinine of urinary NGAL to separate type-1 HRS from ATN. If HRS was diagnosed, terlipressin use was recommended [25]. Furthermore, the urinary NGAL can predict the therapeutic response to terlipressin and albumin for HRS-AKI and is an independent predictor of in-hospital mortality [26].

Biomarkers in acute interstitial nephritis

Moledina et al. [27] found that urinary tumor necrosis factor alpha (TNF-α) and interleukin (IL) 9 levels were higher in the patients whose biopsies revealed acute interstitial nephritis (AIN). They concluded that urinary TNF-α and IL-9 were used to differentiate AIN from other causes of acute kidney disease [27]. They also evaluated the relationship between corticosteroid use and 6m-eGFR (the estimated glomerular filtration rate [eGFR] 6 months after the diagnosis of AIN) and concluded that corticosteroid use was associated with higher 6 m-eGFR values in patients with high urinary IL-9 levels [28]. Thus, urinary IL-9 levels could be measured to predict the corticosteroid treatment response. Recently, a diagnostic biomarker for AIN, urinary C-X-C motif chemokine ligand 9 (CXCL9), was identified and validated [29]. They adopted urinary CXCL9-to-creatinine ratios, in which values above 58.9 ng/g were diagnostic of AIN while those below 14.2 ng/g suggested other causes for AKI [30].

Identifying the causes of acute kidney injury subphenotypes (Fig. 3)

1. In the low-perfusion subphenotype, cellular hypoxia is primarily triggered by hypoperfusion, which predominantly affects proximal tubular cells. When tubular injury occurs, certain proteins from the tubular cells, such as L-FABP, NGAL, TIMP-2, and IGFBP7, are released.

2. In the inflammatory subphenotype, both plasma and urine may show elevated levels of inflammatory markers such as IL-6, soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), L-FABP, and KIM-1.

The practical application of these biomarkers can facilitate the timely diagnosis of AKI compared to creatinine-based methods, leading to earlier intervention and better prognoses. Although several biomarkers have been put forth as potential predictors of AKI, their efficacy varies across distinct trials [31]. Notably, biomarkers incorporating NGAL demonstrated superior predictive accuracy for AKI occurrence, irrespective of whether adjustments were made based on urinary creatinine levels. However, the predictive utility of urinary NGAL was comparatively restrained in surgical patients, with urinary NGAL/creatinine ratios emerging as the most precise biomarkers within this cohort [32].

Acute kidney injury subphenotypes: predictive and prognostic enrichment targets (Fig. 3)

In essence, the subphenotypes of AKI not only enhance our understanding of the underlying pathophysiology but also unveil potential treatment-specific targets. Considering the intrinsic heterogeneity characterizing AKI, there is an ardent call to arms to craft customized clinical study designs, meticulously perform choreograph timing, and meticulously devise robust thresholds for the intervention. In this rigorous journey, we move closer to providing personalized healthcare.

Biomarkers for predicting subclinical acute kidney injury

The utilization of biomarkers to predict subclinical AKI, which is characterized by elevated biomarker levels that do not align with KDIGO classification criteria, has gained considerable attention. Studies by Haase et al. [33] have demonstrated that individuals with subclinical AKI, specifically those with NGAL-positive/sCr-negative profiles, face an elevated risk of subsequent RRT initiation, prolonged
intensive care unit (ICU) and in-hospital stays, and increased mortality.

In a multicenter prospective cohort study [34], it has been established that patients with elevated levels of urinary NGAL and urinary KIM-1 without concurrent sCr elevation are at increased risk of a composite outcome; namely, dialysis initiation or death during hospitalization. This risk is significantly higher than that in patients without elevations in NGAL, KIM-1, or creatinine levels.

Moreover, the incorporation of normalized urinary hemojuvelin and uKIM-1 levels (assessed 3 hours after cardiovascular surgery) into Liano’s score has proven to be a valuable strategy for identifying patients who are predisposed to advanced AKI and adverse composite outcomes [35].

Collectively, these findings emphasize the crucial role of tubular damage biomarkers in clinical practice. Their utilization facilitates the early diagnosis of subclinical AKI, enabling timely and effective interventions to improve patient outcomes [36].

**Biomarkers for predicting the persistence of acute kidney injury (non-recovery of acute kidney injury)**

Urinary motif chemokine ligand 14, in particular, exhibited promising predictive performance, with a pooled sensitivity of 0.81 (95% confidence interval [CI], 0.72–0.87) and specificity of 0.71 (95% CI, 0.53–0.84). Furthermore, the pooled positive likelihood ratio (LR) stood at 2.75 (95% CI, 1.63–4.66), and the negative LR at 0.27 (95% CI, 0.18–0.41) [37]. Establishing standardized cutoff levels for these biomarkers holds significant potential in guiding AKI management and facilitating the design of clinical trials [38].

**Biomarkers for predicting weaning from acute dialysis therapy**

The use of biomarkers to predict the successful weaning of ICU patients with AKI from RRT has been a subject of interest. A retrospective single-center cohort study demonstrated that a daily urinary urea excretion that exceeds 1.35
mmol/kg/24 hr is the most reliable indicator of successful weaning from intermittent hemodialysis in ICU patients with AKI [39]. The urinary L-FABP/creatinine ratio at the time of weaning off RRT has shown promise in predicting both successful weaning from RRT and 90-day mortality [40]. Additionally, in patients with advanced CKD, plasma C-terminal FGF-23 levels have emerged as an independent risk factor for forecasting both 90-day mortality and progression to end-stage kidney failure requiring renal transplantation within the same timeframe [41].

Distinct subgroups in the progression of acute kidney injury

Advanced statistical techniques such as the latent class analysis (LCA) are being employed to subdivide AKI into distinct subgroups. For instance, Bhatraju et al. [42] employed LCA in their analysis of patients with AKI in the VASST trial (Vasopressin and Septic Shock Trial; n = 271), identifying two unique subphenotypes: AKI-SP1 and AKI-SP2. Remarkably, the AKI-SP1 group exhibited lower 90-day mortality rates when vasopressin was introduced early in conjunction with norepinephrine than norepinephrine alone did. Conversely, vasopressin therapy did not significantly impact mortality in the AKI-SP2 subgroup. Furthermore, the authors identified a genetic variant near the ANGPT2 gene, correlating with plasma angiopoietin-2 concentrations and the development of AKI-SP2 in critically ill patients [43]. The utilization of unsupervised consensus clustering to distinguish subphenotypes holds substantial clinical significance, particularly within the context of sepsis-associated AKI requiring dialysis, where it emerges as an invaluable outcome predictor. This method exemplifies a considerable leap forward in the pursuit of precision medicine, offering the capacity to pinpoint high-risk subphenotypes among patients grappling with sepsis-associated AKI [44].

Biomarkers for oliguric acute kidney injury without azotemia

After excluding obstruction, reduced urine output becomes a clinically valuable biomarker for decreased GFR. Consensus definitions of AKI incorporate urine output criteria along with biochemical markers of renal excretory function. Isolated oliguria, even without an increase in sCr, is linked to higher mortality [45]. Despite efforts to enhance risk stratification for poor kidney outcomes using biomarkers like NGAL in oliguric patients [46,47], they did not surpass the predictive performance of sCr [48]. Distinctions in risk among episodes of oliguria were acknowledged, and NGAL successfully differentiated functional oliguria from AKI based on sCr criteria in a separate study [49]. However, assessments of fluid responsiveness using urinary sodium, fractional excretion of sodium, and fractional excretion of urea in oliguric patients lacked significant predictive value [46]. Further research is warranted to refine risk stratification in oliguric patients.

Acute kidney injury subphenotypes: proposed acute kidney injury management flow chart (Fig. 4)

“The less there is to justify a traditional custom, the harder it is to get rid of it” from Mark Twain’s wisdom, as expressed in The Adventures of Tom Sawyer, illustrates this difficulty. It can be challenging for us to transition from using creatinine to adopting novel biomarkers for AKI diagnosis. Due to evolving concepts in critical illness [50], we should adopt a new perspective on AKI management. The incorporation of AKI subphenotyping and corresponding biomarkers into clinical practice should be adopted.

Biomarkers for risk stratification in acute kidney injury

Cartin-Ceba et al. [51] demonstrated that critically ill patients were at increased risk of AKI in the following conditions: older age, diabetes, hypertension, higher baseline creatinine, heart failure, systemic inflammatory response syndrome, use of nephrotoxic drugs, higher severity of disease scores, use of vasopressors/inotropes, high-risk surgery, emergency surgery, use of intra-aortic balloon pump, and more time spent on a cardiopulmonary bypass pump. Thus, the identification of patients at high risk of AKI is vital to AKI management.

The various risk hold prediction models for AKI at ICU admission such as Coritsidis et al. [52], renal angina index [53], and the USCD (the University of California, San Diego) Mayo model [54], were mentioned previously. Recently, Mohebi et al. [55] added four biomarkers (KIM-1, IL-18, osteopontin, and cystatin C) to the contrast-induced AKI
The incorporation of osteopontin and cystatin C into the CA-AKI clinical model significantly increased the c-statistic level from 0.69 to 0.73 (p for change <0.001). Therefore, the application of biomarkers in the risk prediction model could identify high-risk patients and enhance risk classification [56].

Biomarkers to predict renal recovery

The amount of irreversible nephron loss determines the long-term outcome of kidney function. However, it is difficult to appreciate nephron loss in clinical practice. Some tools and biomarkers are reported to predict renal recovery. First, the furosemide stress test (FST) can predict AKI progression and the need for RRT [57]. In a study conducted by Chawla et al. [57], 77 patients from two cohorts were administered a single dose of furosemide (1.0 mg/kg for loop diuretic-naïve patients and 1.5 mg/kg for those who had received loop diuretics before). The optimal cutoff for the prediction of AKI progression during the first 2 hours following FST was a urine output of less than 200 mL.

Figure 4. Proposed strategies for managing AKI. The definition of AKI encompasses an escalation in serum creatinine levels, a decrease in urine output, and the presence of kidney damage and stress biomarkers. Various biomarkers, some of which are accessible at the point of care, may assist in the early detection of AKI. These biomarkers can facilitate the timely identification of patients who exhibit potential endotypes, amenable traits for targeted interventions, or suitability for specific preventive measures. AKI subphenotypes, which are delineated by their clinical attributes, have already been integrated into routine clinical practice, including considerations such as etiology, AKI staging, severity, and duration. However, the integration of biomarkers into these subphenotypes may offer a more comprehensive and informative framework, culminating in predictive and prognostic insights. This refined definition of subphenotypes aims to distinguish patient subgroups with comparable outcomes (prognostic enrichment) or similar responses to therapeutic interventions (predictive enrichment). The evolution of treatment strategies requires further development and fine-tuning. Moreover, the nuanced categorization of AKI subphenotypes will advance with the discovery of novel biomarkers and more precise clinical and biomarker-derived subphenotypes.
(100 mL/hr) with 87.1% sensitivity and 84.1% specificity. The FST can also predict renal recovery and the cessation of continuous RRT in patients recovering from AKI [58]. Koyner et al. [59] demonstrated that (urinary NGAL of >150 ng/mL [n = 44] or IGFBP7 × TIMP of >0.3 [n = 32]) in whom the 2-hour urine output after FST was analyzed, the area under the curve (AUC) for progression to stage 3 improved to 0.90 ± 0.06 and the AUC for receipt of RRT improved to 0.91 ± 0.08. The above findings suggested that the combination of FST and biomarkers provides higher positive predictive values. Not long ago, Hasson et al. [60] proved that AKI is associated with increased urinary olfactomedin 4 (OLFM4), and urinary OLFM4 is associated with furosemide unresponsiveness. Furthermore, TIMP2 and IGFBP7 demonstrated strong predictive capabilities in the diagnosis of AKI associated with cardiac surgery. It is noteworthy that these biomarkers can also serve as predictors of long-term outcomes.

Biomarkers enhancing acute kidney injury care bundles

Incorporating kidney biomarkers into strategies for early AKI detection and initiating AKI care bundles has shown greater effectiveness than using care bundles without these novel biomarkers. This conclusion stems from a meta-analysis of RCTs [61].

For instance, Halmy et al. [62] divided patients into the following three risk-based groups: low risk (TIMP-2 × IGFBP7 of <0.3), moderate risk (TIMP-2 × IGFBP7 of 0.3–2.0), and high risk (TIMP-2 × IGFBP7 of >2.0). Then, they tailored interventions to align with these risk profiles [62].

Biomarkers identifying treatable endotype

For individuals with high renin levels, the administration of angiotensin II may serve a dual purpose. First, it can effectively reduce the renin concentration. Second, it holds the potential to enhance intra-renal hemodynamics and optimize signaling through the angiotensin II receptor 1. This tailored approach may identify patients for whom treatment with angiotensin II would positively affect clinical outcomes.

In essence, renin levels, when utilized as a biomarker, offer a way of identifying a specific endotype within AKI that is amenable to targeted treatment [63].

Based on the above points, we proposed the management flowchart for AKI (Fig. 4).

Limitations

The ideal characteristics of biomarkers for AKI encompass several key attributes: 1) organ specificity to differentiate between AKI subphenotypes; 2) early detection capability with predictive insights into the course and outcomes of AKI; 3) site specificity, providing information on pathologic changes across various segments of renal tubules during AKI; 4) noninvasive measurability; 5) stability within its matrix; and 6) cost-effectiveness.

However, challenges in the development of biomarkers for kidney injury and toxicity persist, primarily revolving around assay design, validation, and qualification for practical use. Further research is imperative to establish precise cutoff values for specific biomarkers mentioned earlier. Moreover, certain biomarkers present hurdles due to their elevated cost and complexity in clinical application. Addressing these challenges is paramount for the successful clinical integration of biomarkers.

Future directions

Due to the complexity of kidney disease, relying on a single biomarker may be insufficient for early diagnosis, understanding pathophysiology, and predicting outcomes. Combining multiple biomarkers in plasma, urine, or both has proven beneficial. In the future, biomarker test panels are anticipated to serve in diagnosing kidney injury, predicting outcomes, and acting as surrogate endpoints in clinical trials, expediting the evaluation of therapies for kidney diseases.

Conclusions

Within the domain of AKI, the odyssey toward precision medicine unfurls with the pressing necessity of subphenotyping, an approach that not only offers insights into discrete risk profiles but also makes it easier to tailor treatment strategies. This journey not only reshapes our understanding of AKI but profoundly elevates the standards of clinical management. Novel biomarkers are central to this transformative process, and their integration into subphe-
notype heralds the potential to illuminate and enrich our comprehension of AKI’s intricate landscape.

For example, consider the early diagnosis of subclinical AKI and the design of care bundles for interventions, which both profoundly underscore the potency of assimilating biomarkers into the tapestry of clinical practice. Questions surrounding the juxtaposition of traditional AKI criteria naturally arise, hinging on the bedrock of sCr and urine output, against the burgeoning significance of novel biomarkers such as urine NGAL and KIM1. These biomarkers not only demonstrate the potential to bolster AKI subphenotypes but also to guide interventions predicated on a profound grasp of pathophysiological nuances.

The wisdom encapsulated in the proverb “it is hard to get rid of traditional customs” finds contemporary resonance when contemplating the relinquishment of entrenched beliefs tied to the simplicity of creatinine. To boost this transformative potential, biomarkers could assume the role of fortune-tellers, forecasting the responsiveness of treatments.

**Conflicts of interest**

Vin-Cent Wu was supported by the Mrs. Hsiu-Chin Lee Kidney Research Foundation. All other authors have no conflicts of interest to declare.

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