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Acute Kidney Injury in the Emergency Department: Role of Proenkephalin A 119-159

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Abstract

In the emergency department (ED) and critically ill patients in general, acute kidney injury (AKI) is a common complication, and obtaining timely information about kidney function is crucial for initiating protective measures as early as possible. Creatinine-based estimations of the glomerular filtration rate are currently the standard of care, but they are imprecise, prone to errors, and have significant time delays in the identification of reduced kidney function and kidney damage. Emerging research indicates that proenkephalin A 119-159 (penKid) may overcome these drawbacks by indirectly assessing the hormone enkephalin, which stimulates kidney function. This approach offers a more precise evaluation of the kidney. As a novel biomarker for detecting AKI, penKid can be measured immediately upon a patient's arrival at the ED or intensive care unit (ICU), allowing for the early prediction of declining renal function up to 48 h ahead of current diagnostic practices. In summary, penKid offers rapid access to vital information about kidney function for physicians in the ED and ICU. This information complements current diagnostic tools and enables early assessment of renal function. Consequently, penKid can assist clinicians in various clinical scenarios, such as guiding the administration of nephrotoxic drugs or aiding decisions regarding the discontinuation of renal replacement therapy.

Keywords: Acute kidney injury, proenkephalin, emergency department

Introduction

Reduction in kidney function significantly impacts several critically ill patients and is an important contributor to fatal outcomes (1).

More than 13 million cases of acute kidney injury (AKI) are reported annually worldwide, and approximately 30% of patients admitted to an intensive care unit (ICU) develop AKI (2,3). Obtaining timely information about renal function is crucial for initiating nephroprotective strategies early and avoiding nephrotoxic drugs, as these drugs account for approximately one-third of AKI cases in the ICU (4).

This condition refers to an abrupt decrease in kidney function associated with the retention of urea and other nitrogenous waste products and dysregulation of extracellular volume and electrolytes. AKI is currently defined and diagnosed using serum creatinine (sCr) and urine output (5,6), although these data provide limited and delayed information regarding changes in kidney injury and exhibit low sensitivity and specificity (7).

The Kidney Disease: Improving Global Outcomes (KDIGO) definition is the preferred and defines AKI as follows (8):

- Increase in sCr by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 h or,

- Increase in sCr to ≥1.5 time baseline, which is known or presumed to have occurred within the previous 7 days, or,

- Urine volume <0.5 mL/kg/h for 6 h.

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Despite its usefulness for epidemiologic studies, the clinical utility of this definition and staging system remains to be validated. Furthermore, this definition carries several limitations for an emergency physician. Baseline kidney function among patients presenting to the ED is often unknown, and the evaluation of urinary output is not easy to measure with precision in that setting. Finally, such classification does not help in the identification of the etiology of AKI.

The Dark Side of Creatinine

The current standard for renal function evaluation relies on determining an estimated glomerular filtration rate (eGFR) (9). This method suffers from the influence of several factors, such as age, sex, and muscle mass, and is based only on the value of sCr. Several formulas have been developed to account for these confounders, but eGFR may remain imprecise. With the most accurate eGFR equations, the proportion of values that are within 30% of the measured GFR values (P_{30}) generally does not exceed 90%, which is the performance goal for eGFR (6,10,11).

Finally, sCr is unable to detect mild renal failure; its concentration starts to rise above the normal range when almost 50% of the function is already lost. This was described in 1985 as the creatinine-blind area (12).

The Quest for a New Biomarker

In recent years, significant progress has been made in the research of biomarkers aimed at the early identification of AKI (7). Ideally, a good biomarker should be independent of other clinical conditions and possess attributes of easy and precise measurement, and rapid results. It is crucial for this biomarker to exhibit high diagnostic accuracy and be associated with prognostic implications. In addition, there is a need for a reliable biomarker that can help clinicians make informed decisions regarding medical therapy adjustments.

Several candidates are being investigated by different study groups. Among others, some promising biomarkers are proenkephalin A (penKid), cystatin C, neutrophil gelatinase-associated lipocalin, and insulin growth factor binding protein 7 (IGFBP7).

For instance, plasma cystatin C seems to be more sensitive than sCr in detecting reduced kidney function (13,14).

Proenkephalin A 119-159

In healthy states (Figure 1A), kidney function is stimulated by the hormone enkephalin and endogenous opioid peptide. This peptide is derived from the cleavage of proenkephalin A 1-243, but it is unstable and difficult to measure. During this process, another peptide, proenkephalin A 119-159 (penKid), is produced in equimolar concentrations and can be used as a surrogate marker because of its stability (Figure 2).

When kidney function is low (Figure 1B), enkephalin levels rise to stimulate the kidneys. By indirectly measuring enkephalin production, high penKid levels indicate impaired kidney function (15).

Studies have shown that this novel biomarker, penKid, strongly correlates with the measured GFR, the gold standard for the evaluation of kidney function, and its levels are not influenced by age or sex (Figure 3) (16-18).

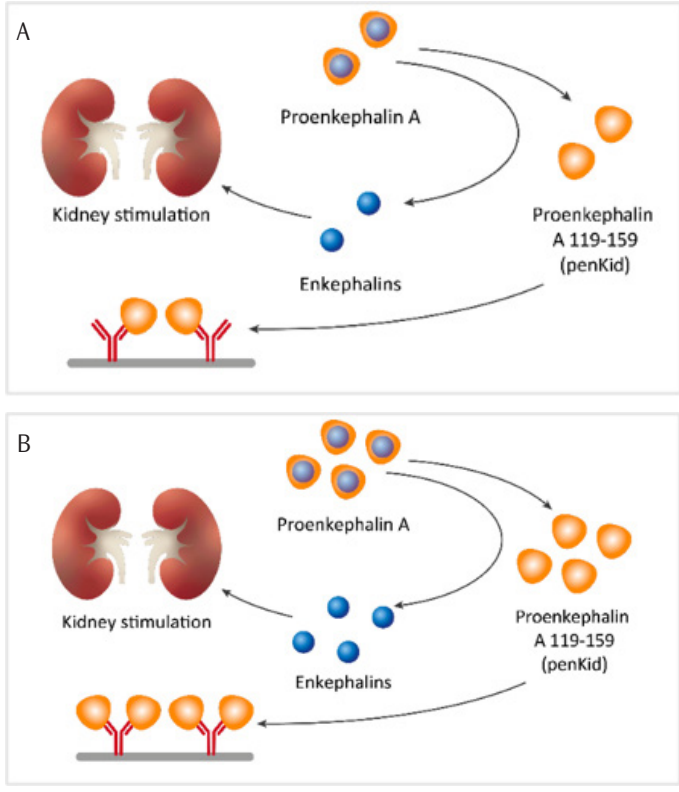

Figure 1. Proenkephalin A production in healthy (A) and ill (B) patients

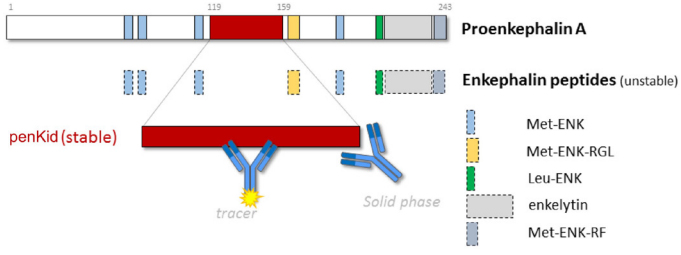

Figure 2. Cleavage of proenkephalin 1-243 results in the release of enkephalin and penKid, among other peptides. PenKid is detected through monoclonal antibodies directed against its middle portion (tracer antibody) and C-terminus (capture antibody on solid phase) (16)

Hollinger et al. (19) showed that penKid predicts future changes in sCr up to two days in advance independently from common comorbidities (e.g. chronic kidney disease, hypertension, and diabetes mellitus), providing physicians with urgently needed information on top of the standard of care. Similar results on the incidence of AKI at 48h and 7 days were reported by Caironi et al. (20) (Figure 4).

PenKid in Critical Care

In emergency settings, it is crucial for the clinician to obtain as much information as possible about patient status. This information will be necessary to make an accurate diagnosis, identify patients at risk of progression, and guide clinical decision-making.

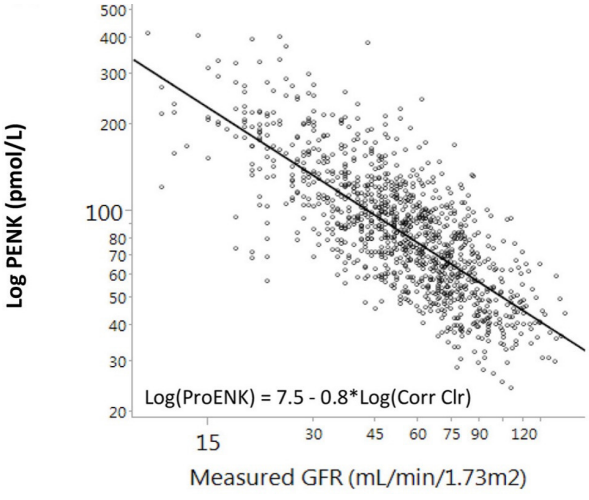

Figure 3. Correlation between penKid and measured GFR (16)
GFR: Glomerular filtration rate

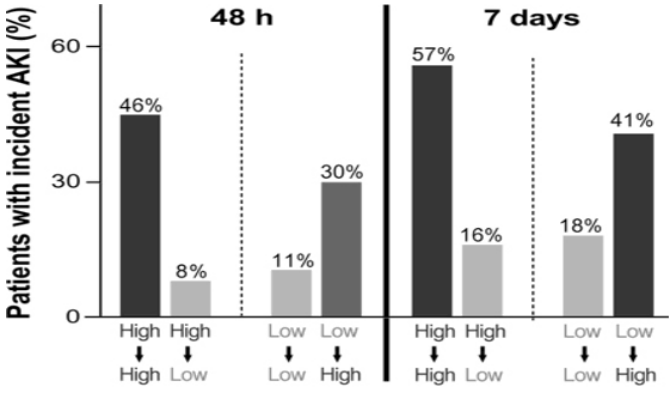

Figure 4. Incidence of AKI at 48 h or 7 h in relation to penKid concentrations on days 1 and 2. Patients were divided into 4 groups, below or above their respective median concentrations on days 1 (78.5 pmol/L) and 2 (70.2 pmol/L) (20)
AKI: Acute kidney injury

Biomarkers, such as high-sensitivity cardiac troponins or procalcitonin (PCT), are well implemented in clinical practice and help clinicians make informed decisions.

PenKid was measured in several cohorts of patients in the ED, and here we provide a summary of the most robust evidence in support of the use of this biomarker for these pathologies.

Acute Heart Failure

Acute heart failure (AHF) is one of the most frequent reasons for presenting to the ED in patients older than 65 years. This condition is defined as a clinical syndrome characterized by a rapid onset of signs and symptoms that reflect an increase in intracardiac pressure or inadequate cardiac output (22). One of the major challenges is identifying patients at risk. To help clinicians correctly stratify the risk of those patients, several scores have been developed, but none of them are still able to predict hospital readmissions with enough precision in the short term (23,24). The guidelines reflect a lack of high-quality data for acute settings (25).

Furthermore, AHF is often complicated by worsening renal function (WRF) and reduced response to diuretic therapy (Figure 5). Therefore, a reliable marker of kidney function would be helpful.

Ng et al. (26) measured penKid in 1,908 patients with AHF, and multivariable Cox regression models showed that penKid level was an independent predictor of 1-year mortality and 1-year death and/or heart failure (HF) [hazard ratio: 1.27; 95% confidence interval (CI): 1.10 to 1.45; p=0.001]. In addition, penKid levels independently predicted outcomes at 3 or 6 months and were independent predictors of in-hospital mortality.

Sepsis and Septic Shock

Sepsis is a leading cause of death worldwide and a major challenge for physicians to predict and manage. The 2021

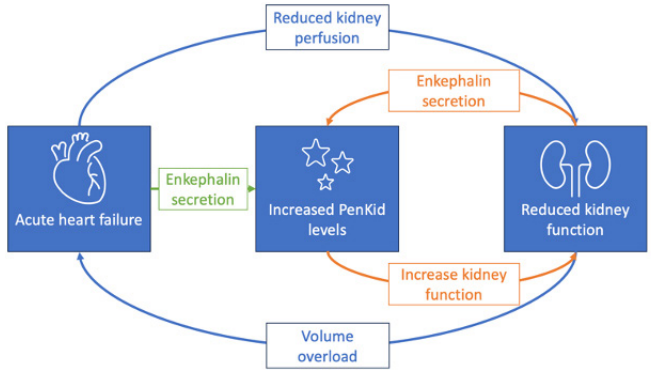

Figure 5. PenKid in acute heart failure (26)

Table 1. Stages of AKI, adapted from the KDIGO Clinical Practice Guidelines for AKI (5)		
Stage	**Serum creatinine**	**Urine output**
1	1.5-1.9 times the baseline *or* ≥0.3 mg/dL (≥26.5 micromol/L) increase	<0.5 mL/kg/h for 6-12 h
2	2.0-2.9 times the baseline	<0.5 mL/kg/h for ≥12 h
3	3 times the baseline *or* ≥4.0 mg/dL (≥353.6 micromol/L) increase or Initiation of RRT *or* Decrease in eGFR <35 mL/min/1.73 m^2 (in patients <18 years)	<0.3 mL/kg/h for ≥24 h *or* Anuria ≥12 h
AKI: Acute kidney injury, KDIGO: Kidney Disease: Improving Global Outcomes, eGFR: Estimated glomerular filtration rate, RRT: Renal replacement therapy		

surviving sepsis campaign guidelines endorse the use of two biomarkers to guide medical therapy (27). Serum lactate levels are recommended to detect peripheral hypoperfusion, and PCT should be used to decide when to stop antimicrobial therapy. These markers alone are not enough.

Recently, new biomarkers have been investigated in this setting, such as bio-adrenomedullin, which can be useful to identify patients at high risk of progression and could be a target for new drugs (28,29).

In septic patients, monitoring renal function is crucial for several reasons. First, kidney function is predictive of mortality and is one of the items in the Sequential Organ Failure Assessment (SOFA) Score, which is used to evaluate the severity of organ failure and predict mortality. Second, antibiotic therapy can be nephrotoxic; therefore, physicians need to tailor it to each patient. Finally, AKI requiring renal replacement therapy (RRT) is one of the most common complications of sepsis and septic shock.

In an analysis involving 956 septic patients, it was observed that penKid exhibited independent predictive abilities for the development of AKI within 48 h and 7 days of hospital admission (20). The adjusted odd ratios were 3.3 (CI: 2.1-5.1) and 2.1 (CI: 1.7-2.8), respectively. Furthermore, the median levels of penKid demonstrated a correlation with the severity of AKI based on the KDIGO stage and renal SOFA score (Figure 6).

High levels of penKid were also associated with all-cause mortality at 28 days in septic patients (Figure 7) (30).

Strong evidence for sepsis also comes from ICU trials, such as the AdrenOSS or the FROG-ICU. In Figure 8 boxplots show the association between the biomarker and different outcomes: major adverse kidney events (MAKEs), AKI, WRF, and need for RRT.

Finally, a recent analysis underlined the predictive role of penKid 30-day mortality in patients with Coronavirus disease-2019

Table 2. Publications on European reference populations		
Population	**Median**	**95th percentile**
Infants (<1 year) (21)	584 (444.4-700.5) pmol/L	
Adults (16)	45 pmol/L	83 pmol/L

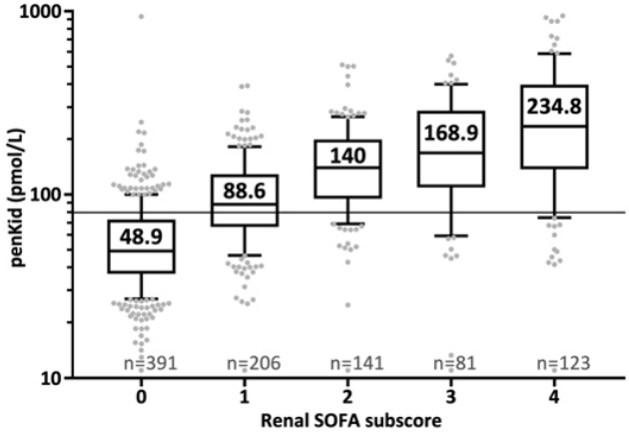

Figure 6. PenKid concentrations at admission in relation to the rSOFA score (20)

rSOFA: Renal Sequential Organ Failure Assessment

(COVID-19) or non-COVID-19 interstitial pneumonia at ED admission (31). The authors did not find a significant difference in penKid concentrations between COVID-positive and COVID-negative patients at admission. A major finding of this study is that higher levels of PenKid at admission correlated with mortality at 30 days, regardless of the etiology of interstitial pneumonia.

Major Burns

Dépret et al. (32) demonstrated, in a cohort of severely ill burned patients (median burn total body surface area was 35%), that

Table 3. Utility of penKid in different conditions and settings	
Disease	**Evidence**
Heart failure	**Acute:** - WRF, in-hospital mortality (33); - 1-year mortality, heart failure rehospitalization, WRF (26); - WRF, 180-day mortality (34).
	Chronic: - MACE (35); - AMI, MACE, hospitalization, 2-years mortality after AMI (36); - In HFpEF patients, rehospitalization at 2 years (37).
Sepsis and septic shock	**ED:** - Progression of renal SOFA, 28-day mortality (30); - 7-day mortality in ED (38).
	ICU: - MAKE, transient AKI, WRF, renal recovery (19); - Need for RRT, improvement in renal function, 90-day mortality (20); - Need for RRT and 30-day mortality (39); - 1-year mortality after ICU discharge (40).
	RRT: - Need for RRT on day one or later during hospitalization (20,41). - Prediction of early and successful liberation from RRT in critically ill patients (42).
Major burns	PenKid highly associated with 90-day mortality and with the development of AKI (32).
Neonates and children	Establishment of penKid reference value in healthy infants; discrimination between AKI and non-AKI children (KDIGO) (21). PenKid levels in neonates and children correlate well with iohexol GFR measurements; discriminates between AKI and non-AKI (43).

WRF: Worsening of renal function, MACE: Major adverse cardiac events, MAKE: Major acute kidney events, HFpEF: Heart failure with preserved ejection fraction, AMI: Acute myocardial infarction, TAAA: Thoraco-abdominal aortic aneurysm, SOFA: Sequential Organ Failure Assessment, RRT: Renal replacement therapy, ICU: Intensive care unit, KDIGO: Kidney Disease: Improving Global Outcomes, ED: Emergency department

Table 4. Selected variables by all-cause mortality within 7 days after admission of patients with sepsis in the ED (38)				
Variable median [interquartile range]	**All (n=101)**	**Dead within 7 days (n=28)**	**7-day survivors (n=73)**	**p value**
PCT (ng/mL)	2.8 [0.6-10.7]	4.1 [1.3-13.0]	2.2 [0.6-9.0]	0.102
penKid (pmol/L)	87 [50-205]	209 [77-499]	75 [47-124]	<0.001
NGAL (µg/mL)	0.6 [0.4-1.2]	1.3 [0.5-2.1]	0.6 [0.3-0.8]	<0.001
Creatinine clearance (mL/min)	48 [23-77]	33 [15-69]	56 [29-81]	0.071
APACHE II score (points)	16 [13-21]	23 [18-27]	14 [12-18]	<0.001

Values are median and interquartile range; p value from non-parametric Kruskal-Wallis test.
PCT: Procalcitonin, NGAL: Neutrophil gelatinase-associated lipocalin, APACHE II: Acute physiology and chronic health evaluation II, ED: Emergency department

high concentrations of penKid at admission correlated with 90-day mortality. Furthermore, this biomarker provided added value to the sCr and SOFA scores in predicting 90-day mortality (combined c-index of 0.738 versus 0.707; p=0.024 and 0.787 versus 0.752; p<0.001).

Implementation in the Emergency Department

Given the evidence, several reasons support the use of penKid in the ED. First, for the early detection of AKI and therefore to allow healthcare providers to initiate prompt treatment and prevent further damage to the kidneys. Second, the role in risk stratification. In fact, penKid levels can help assess the severity and prognosis of AKI. Higher penKid levels often indicate more severe kidney injury and may be associated with a worse clinical outcome. By measuring penKid, healthcare providers can identify patients at a higher risk of complications and provide appropriate management strategies. Finally, to monitor the treatment response in patients with AKI.

These recommendations apply to all patients who may develop AKI, but especially in those with sepsis, AHF, and major burns for which the evidence is stronger and there is a clear risk of worsening kidney function.

Marino et al. (38) described how, in patients with sepsis in the ED, penKid was significantly higher in those who died within 7 days from presentation (Table 4). In contrast, there was no difference in the values of PCT and creatinine clearance between the groups,

	All patients	Quartile I	Quartile II	Quartile III	Quartile IV
penKid (pmol/L)	77.9 (10.9-843.0)	10.9-56.9	57.0-77.9	78.1-119.4	120.0-843.0

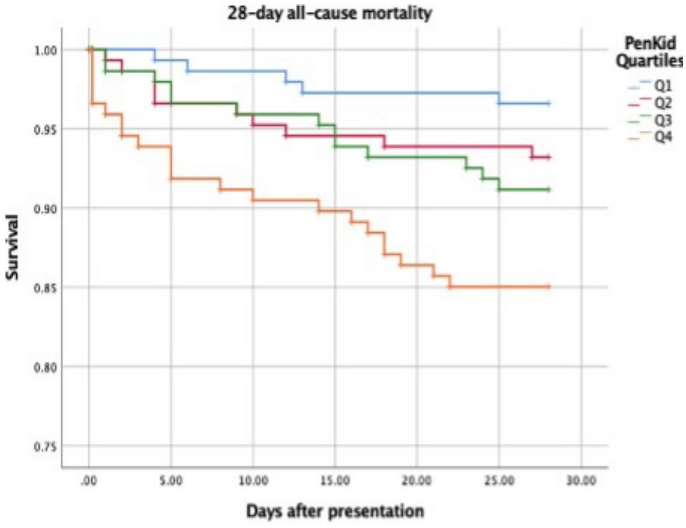

Figure 7. Unadjusted Kaplan-Meier plot showing 28-day all-cause mortality for penKid quartiles (30)

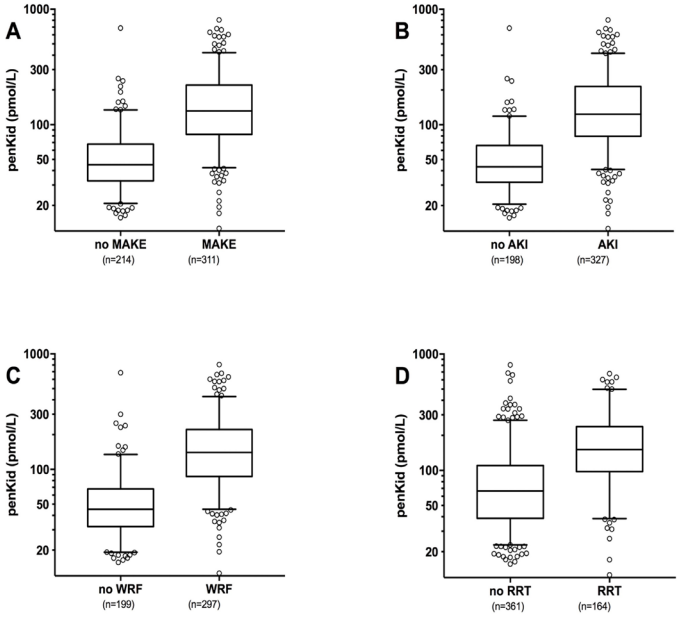

Figure 8. PenKid values at admission were compared in the FROG-ICU cohort across various groups: (A) patients with or without MAKEs at day 7, (B) patients with AKI compared with those without, (C) patients with WRF compared with those without, and (D) patients with or without RRT (19)

AKI: Acute kidney injury, ICU: Intensive care unit, MAKEs: Major adverse kidney events, WRF: Worsening of renal function, RRT: Renal replacement therapy

confirming that penKid could help clinicians identify high-risk patients, in addition to the already established biomarkers.

We suggest that patients with elevated penKid values should be carefully evaluated by a clinician to identify the possible cause of AKI. According to the findings, treatment strategies may include fluid resuscitation, medication adjustments, discontinuation of nephrotoxic drugs, and interventions to improve kidney perfusion. It is also important to closely monitor the patient, provide appropriate supportive care, and potentially consult a nephrologist for further management. Selected cases, such as severe AKI with high penKid levels, may require more aggressive interventions, such as RRT, to support kidney function and prevent complications such as electrolyte imbalances and fluid overload.

Although larger studies would be necessary to establish a standardized cut-off, Donato et al. (16) calculated the 95th percentile in a cohort of 100 adult healthy donors without (bleeding/clotting, diabetes, HF or other cardiovascular events, kidney disease, cancer, cardiovascular disorders) after a minimum 12-h fast. They derived a value of 83 pmol/L (70-92 pmol/L), with a median of 48.1 pmol/L (41.7-55.7 pmol/L), in that population.

In support of this finding, Hollinger et al. (19) reported that patients with a value above 84 pmol/L, the median value in their population, had a higher rate of MAKE and WRF and were at a higher risk of 28-day mortality compared with patients with a value below 84 pmol/L.

Other Settings

Scientific experts agree on the significant need for new biomarkers that timely mirror kidney function, thereby improving the prediction and monitoring of AKI, MAKE, and RRT (7). In addition, many other concrete clinical cases may also benefit from these developments, for instance, guidance on starting or stopping RRT, guidance on nephrotoxic drug administration, hospitalization decisions after catheterization-laboratory procedures, prediction of delayed graft function, and assessment of contrast-induced nephropathy.

Another setting that has been described in the literature is patients with chronic HF (CHF). Matsue et al. (34) measured penKid in a cohort of 95 patients with CHF together with other measures of kidney function, such as renal blood flow (RBF) and GFR, using ^{131}I-Hippuran and ^{125}I-iothalamate clearances, respectively. In these patients, penKid was strongly correlated with both RBF ($p<0.001$) and GFR ($p<0.001$), but not with renal tubular markers. Furthermore, in patients with acutely decompensated chronic HF and preserved ejection fraction, multivariate Cox regression models showed that penKid predicted the composite endpoint

of 2-year death/HF [HR 1.45 (95% CI: 1.12-1.88, p=0.005)], even after adjustment for troponin [HR 1.59 (1.14-2.20, p=0.006)], and body mass index [HR 1.63 (1.13-2.33, p=0.009)] (37).

Conclusion

AKI poses several challenges for physicians in clinical practice, from early identification to monitoring during treatment. In this setting, penKid can offer access to vital information about kidney function, providing added value to the existing standard of care, especially in the ED and ICU. This information complements current diagnostic tools and enables early assessment of renal function. Therefore, this novel biomarker can assist clinicians in various clinical scenarios, such as guiding the administration of nephrotoxic drugs or making decisions regarding the discontinuation of RRT.

Ethics

Authorship Contributions

Concept: L.C., Analysis or Interpretation: L.C., S.D.S., Literature Search: L.C., S.D.S., Writing: L.C., S.D.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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