Proenkephalin A 119-159 (penKid)

A unique biomarker for real-time assessment of kidney function

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Abstract

Acute kidney injury (AKI) affects many critically ill patients, making timely information on kidney function important for early intervention, such as kidney replacement therapy (KRT) and nephroprotective strategies (1). The current AKI diagnostic criteria rely on the changes in serum creatinine and urine output, although they are neither sensitive nor specific for AKI (2).

An emerging body of evidence demonstrates that Proenkephalin A 119-159 (penKid), a dynamic biomarker for kidney glomerular function, overcomes these limitations (3). As a biomarker for diagnosing AKI, penKid measured at admission to the emergency department (ED) (4, 5) or intensive care unit (ICU) (6-9), enables timely anticipation of worsening renal function within 48 hours before current diagnostic criteria based on creatinine are met (10, 11).

More than 70 peer-reviewed publications report on the significance of penKid in more than 80,000 patients, allowing a clear understanding of the value of using penKid in critical care medicine. Above all, penKid levels demonstrate a strong correlation with glomerular filtration rate (GFR) measured through iohexol/iothalamate clearance, providing real-time assessment of kidney function and offering a fast blood-based alternative for the in vivo measurement of true GFR (3, 12, 13).

In summary, penKid provides physicians at the ED and ICU with critical information on kidney function, complementing the current diagnostic tools. As studies have shown, penKid contributes to clinical decision-making for patients under KRT by enabling the monitoring of renal function under therapy (8, 14, 15), and supports the management of patients following kidney transplantation (16, 17).

Introduction

Impaired kidney function affects a broad number of critically ill patients and contributes to morbidity and mortality. In fact, one in three ICU patients develops AKI (18, 19), making it a global burden with estimated 13 million cases per year (18). AKI accounts for many complications in patients with sepsis or septic shock (1). It is furthermore concerning that approximately 30% of hospitalized patients with AKI discharged from the hospital continue to experience persisting renal dysfunction (20).

The underlying causes of AKI include, among others, sepsis, complex surgical interventions, cardiogenic shock, and acute heart failure (2). It is associated with a high mortality rate and extensive hospital costs. In the United States, additional expenses related to AKI complications are estimated to be approximately $42,000 per case (21). Therefore, timely information on renal function is essential to initiate and adapt treatment options like KRT and nephroprotective strategies early. Although several additional biomarkers of kidney damage have been developed, they have not made it to clinical routine.
In clinical practice, serum creatinine (sCr) and urine output are the cornerstones of the current diagnostic approach for defining AKI (2). However, they give limited and delayed information on changes during kidney injury and have low sensitivity and specificity (2, 22).

Scientific experts agree on the significant need for new biomarkers that timely mirror kidney function, thereby improving the prediction and monitoring of AKI, major adverse kidney events (MAKE), graft failure and the necessity of KRT (22, 23). When translated into clinical practice, these insights may inform decision-making related to the discontinuation of KRT, the guidance of nephrotoxic drug administration, hospitalization decisions after catheterization-laboratory procedures, the prediction of delayed graft function in kidney transplant recipients, and assessment of contrast-induced nephropathy. GFR is considered to be the best indicator of kidney function (24).

However, the gold standard technique for determining the true GFR is based on a complex and resource-intensive procedure using inulin, iothalamate, or iohexol that are not feasible in daily practice. Today's routine standard relies on determining an estimated GFR (25).

This method is often based on sCr, which is known to be affected by non-renal factors (age, gender, muscle mass, and others) and therefore inaccurate. SCr is unable to detect mild kidney insufficiency because its levels only begin to rise above the normal value when approximately 50% of renal function is already impaired; this is known as the creatinine-blind area (26).
Scientific evidence showed that penKid predicts the future change in sCr up to two days in advance independently from inflammation or common comorbidities (e.g., hypertension, Diabetes mellitus) (3, 27).

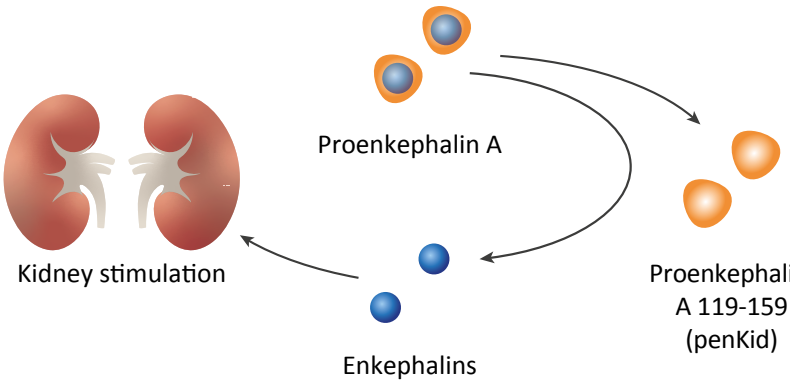
PenKid is a stable prohormone fragment of the enkephalin family, with a long in vivo half-life. It is stable after collection and is not influenced by sex or age in adults (12).
Studies have shown that penKid strongly correlates with kidney function and measured GFR. PenKid does not bind to plasma proteins and is freely filtered in the glomerulus, making it a promising biomarker for assessing kidney function in critically ill patients (3, 12, 27, 28).

PenKid may, therefore, provide physicians with urgently needed information on top of the standard of care, with a potential role to predict kidney recovery (6, 29).
In the consensus statement of the ADQI workgroup, penKid was recognized as a relevant functional biomarker able to detect subclinical AKI in critically ill patients (30).

PenKid physiology in the kidney

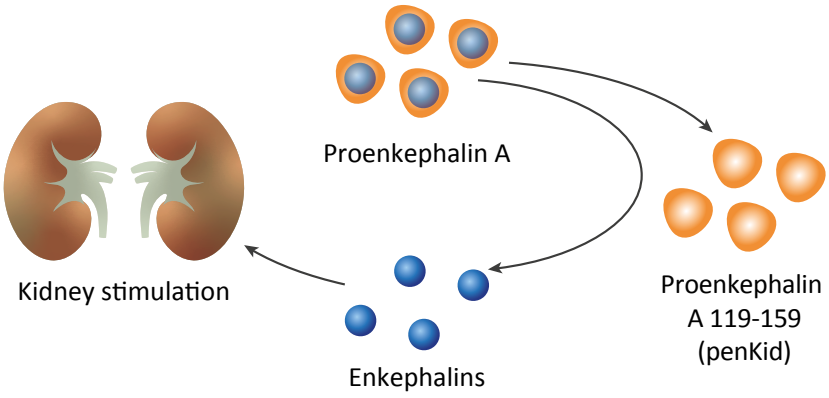
Enkephalins are endogenous opioids widely expressed in the human body with primary activity on delta opioid receptors (31). Interestingly, a high concentration of opioid receptors is found in the kidney (3, 32). Studies suggest a possible regulatory role for enkephalins in the kidneys, such as the induction of diuresis and natriuresis through receptor agonism (33) or inhibition of antidiuretic hormone activity (34). Several studies have shown a strong correlation of plasma penKid with mGFR, indicating that penKid might be a suitable and accurate surrogate maker to estimate the true GFR (28).

PenKid in the healthy state



Kidney function is modulated by the hormone enkephalin which remains difficult to detect due to its short half-life (12). PenKid overcomes this limitation, as it is the stable fragment of the Proenkephalin A precursor protein, therefore being a suitable surrogate measure of enkephalins (35).

PenKid in the disease state



Impaired renal function triggers the expression of Proenkephalin A, which is causative for the increase in plasma penKid levels. Thus, high penKid levels indicate impaired kidney function (28, 35).

Sphingotest® penKid®

Research use only product developed by SphingoTec

The research use only sphingotest® penKid® is a microtiter plate assay designed for the measurement of Proenkephalin A 119-159 in human plasma. The 97.5th percentile in healthy individuals is 89 pmol/L (Figure 1).

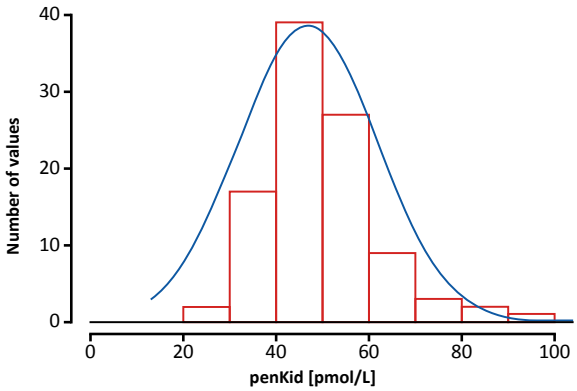


Figure 1. PenKid reference range of 120 healthy adults based on European population; age 31-82 (mean 51) years, 46% female. Median 29.9 pmol/L; 97.5th percentile: 89 pmol/L (95% CI 85-118) (36).

Microtiter plate (MTP)-based immunoassay sphingotest® penKid® (12)

Figure 2. The MTP is an appropriate platform for manual high-throughput analysis for research use. Results are obtained in 1 hour. Detection range: 30 - 1,172 pmol/L. Sample volume: 50 µL EDTA plasma (12).

Diagnostic solutions of our licensing partners

SphingoTec collaborates with leading diagnostic companies to bring advanced biomarker assays to laboratories and clinics around the world. Through strategic licensing agreements, our partners make SphingoTec's biomarkers available on their proprietary diagnostic platforms. These assays combine SphingoTec's scientific innovation with the manufacturing and distribution capabilities of our partners, offering healthcare professionals reliable, widely accessible solutions for critical patient needs.

Figure 3. AFIAS sphingotest® penKid® assay on the AFIAS diagnostic platform. This CE IVDR-certified fluorescence immunoassay quantitatively measures Proenkephalin A 119-159 (penKid). Commercialized by Boditech Med Inc., a global leader in point-of-care diagnostics.

Figure 4. IB10 sphingotest® penKid® assay on the Nexus IB10 diagnostic platform. This CE IVD-released immunoassay quantitatively measures Proenkephalin A 119-159 (penKid). Commercialized by Nexus Dx, a provider of near-patient testing systems and advanced diagnostic solutions.

Kidney function

SCIENTIFIC EVIDENCE

PenKid has been evaluated as a biomarker of kidney function in several clinical conditions (6, 12, 37), and correlates with the gold standard measurement of GFR (12, 27). A penKid-based formula to estimate the GFR was developed and validated in a broad patient cohort (13). The assessment of penKid identifies patients with impaired kidney function, at high risk of AKI and delivers information on the GFR in healthy subjects and hospitalized patients (3, 6, 7). PenKid values reflect the measured GFR and are independent of inflammation (7, 12, 13).

PenKid as a surrogate biomarker for glomerular filtration rate

PenKid is a reliable surrogate for the measured GFR in adults with stable and unstable renal conditions (12).

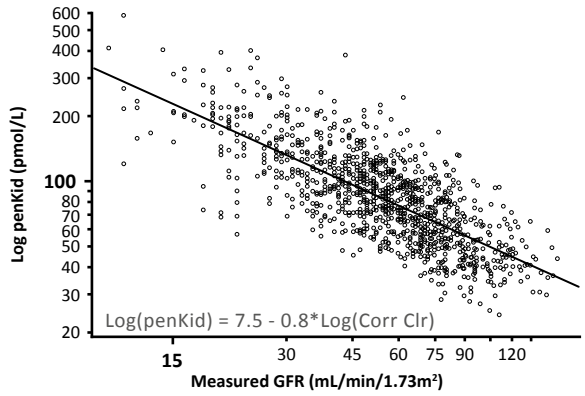


Figure 5. PenKid inversely correlates with the measured GFR (iothalamate clearance): the higher the penKid levels, the lower the mGFR. N = 1191 patients. Modified from (12).

PenKid has a high correlation with the measured GFR in neonates and children (38).

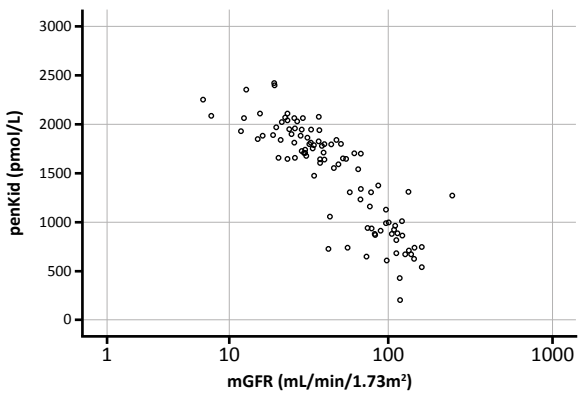


Figure 6. Correlation of penKid concentration as a function of measured GFR (iothalamate clearance). N= 37 patients: p= - 0.88, p<0.001. Modified from (38).

PenKid eGFR formula correlates with mGFR (13)

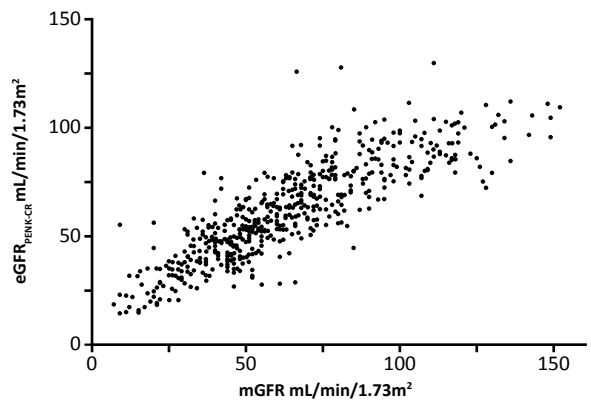


Figure 7. Correlation of mGFR and eGFR using the new penKid formula including penKid and sCr, developed from patients with corresponding assessment of GFR by iohexol or iothalamate clearance. Patient cohort: chronic kidney disease patients, healthy volunteers, sepsis and septic shock patients, kidney donors, and recipients. N=1354 patients. R-squared: 0.73 (p < 0.001). Modified from (13).

PenKid has high specificity for renal function (7)

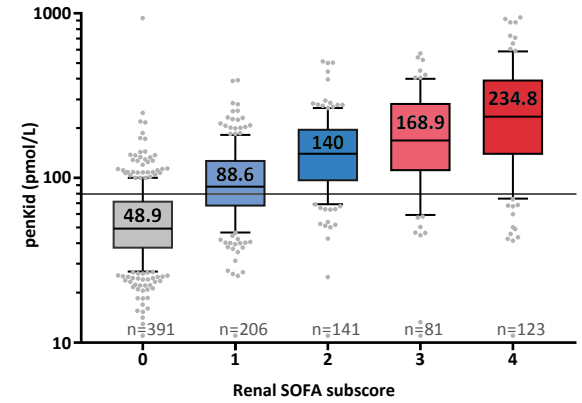
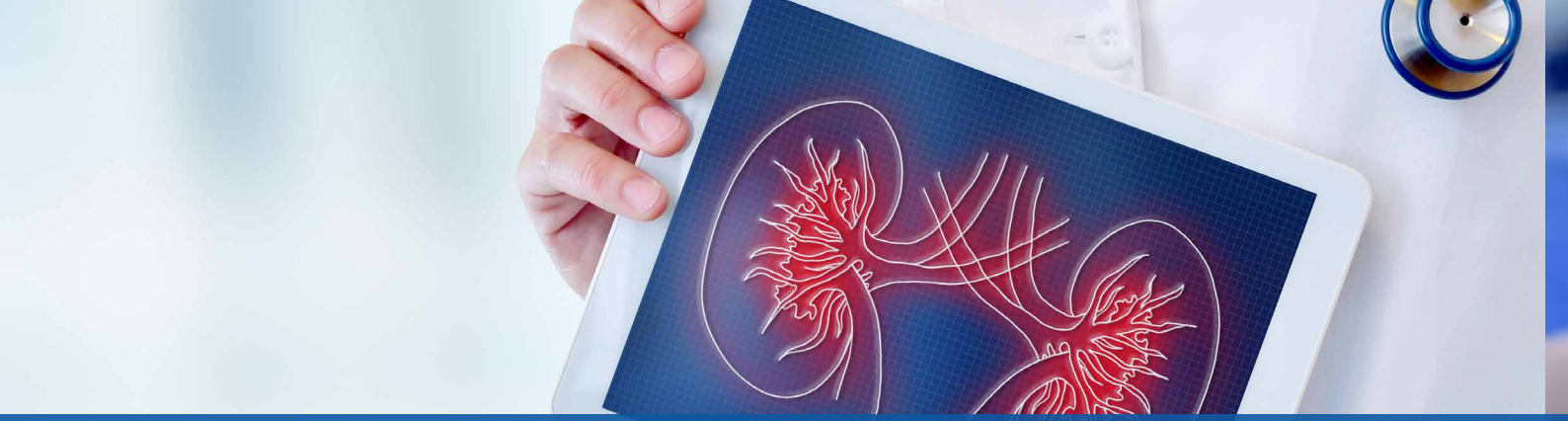


Figure 8. Association of penKid with renal SOFA score in severe septic and septic shock patients. PenKid increased only upon renal dysfunction (subscores 1 – 4), remaining within normal range even in the context of systemic inflammation, as in sepsis or septic shock (subscores 0). The line indicates the upper normal range. N = 956 patients. Modified from (7).



Moving beyond creatinine

SCIENTIFIC EVIDENCE

The current diagnostic criteria for AKI routinely employ serum creatinine and urine output (39). However, both criteria are known to have several limitations. An increase in serum creatinine occurs only after more than 50% of the GFR is lost (40), urging the need for novel biomarkers for reliable and timely detection of kidney dysfunction. Subclinical AKI (sub-AKI) is characterized by an increase in functional or damage biomarkers in the absence of clinical criteria of AKI. The prevalence of sub-AKI on ICU admission is still not properly explored (between 12-18% patients) (30), however existing evidence suggests an association with poor prognosis in affected patients. The current scientific evidence shows that penKid can detect sub-AKI, allowing early identification of patients at risk while not meeting current AKI criteria (10, 30, 40, 41).

PenKid identifies patients with sub-AKI and increased risk of death

PenKid identifies sub-AKI in critically ill patients (30)

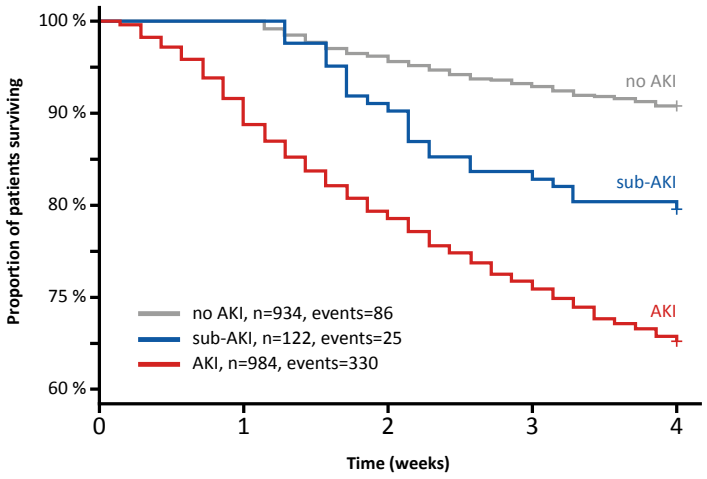


Figure 9. Survival of critically ill patients, based on presence of AKI, sub-AKI or no AKI. Sub-AKI defined based on penKid > 80 pmol/L. N=2087 patients. Modified from (30).

PenKid identifies sub-AKI in burned patients (41)

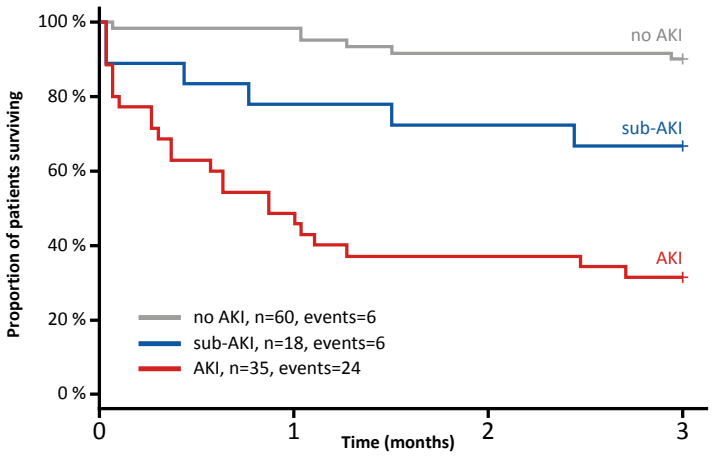


Figure 10. Survival of burned patients, based on AKI, sub-AKI or no AKI. The identification of sub-AKI allows the identification of patients who do not fall into the clinical AKI definition but still show a GFR decrease and increased risk of death. Sub-AKI defined based on penKid > 80 pmol/L. N=113 patients. Modified from (41).

Critically ill patients

SCIENTIFIC EVIDENCE

The assessment of penKid identifies patients at high risk of AKI and delivers information on kidney function in hospitalized patients (3-7, 23, 42, 43).

PenKid can detect AKI and its severity in sepsis patients at the ICU (8)

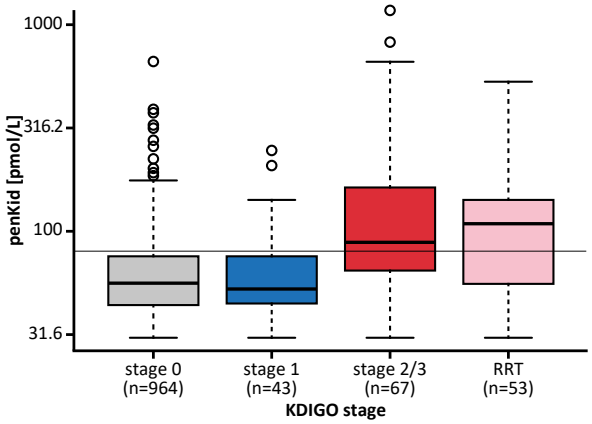


Figure 11. PenKid concentrations on ICU admission grouped by maximum AKI stage reached or need of RRT during ICU stay. Modified from (8).

PenKid rises progressively with the severity of AKI in sepsis patients on the ICU (7)

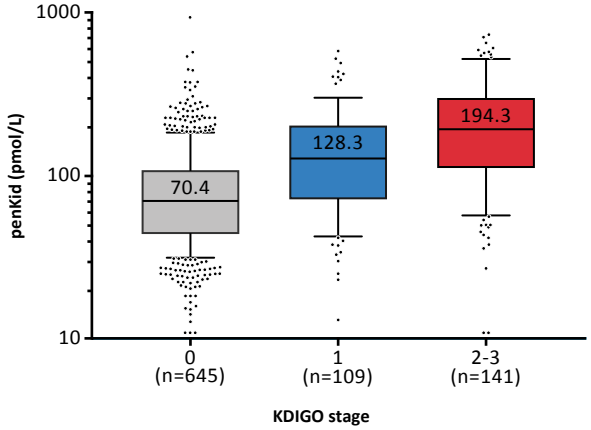


Figure 12. PenKid concentrations on day 1 grouped by AKI stage according to the KDIGO definition. N=956 ICU patients with severe sepsis or septic shock. Modified from (7).

High penKid levels on ED admission identify sepsis patients with poor outcome (43)

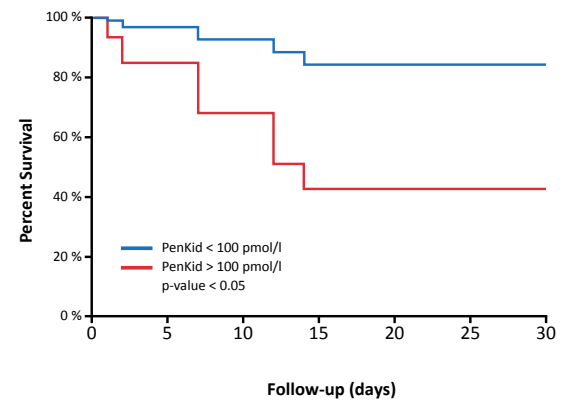


Figure 13. Survival of sepsis patients based on penKid levels on ED admission. N=153 patients. Modified from (43).

PenKid to monitor treatment success in septic patients (7)

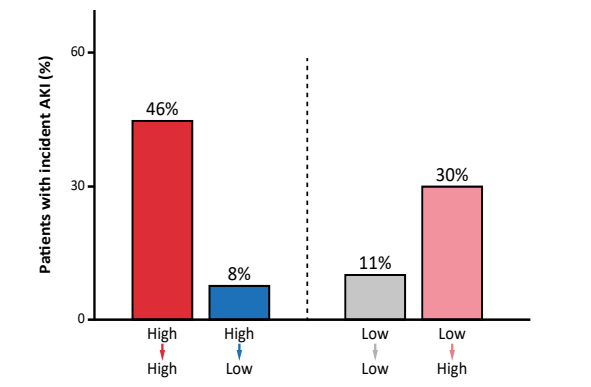


Figure 14. Patients with incidence AKI at 48h days based on the penKid concentrations on day 1 and day 2. Patients were divided into four groups according to their penKid concentrations on days 1 and 2, below or above their respective penKid median concentrations on day 1 (78.5 pmol/L) and day 2 (70.2 pmol/L), N=848 patients. Modified from (7).

Kidney replacement therapy

SCIENTIFIC EVIDENCE

Kidney replacement therapy (KRT) is the main therapy to to correct severe complications of AKI complications, such as electrolyte or acid-base disbalances, uremia, or fluid overload (14). The monitoring of kidney function under KRT is crucial to guide successful discontinuation of therapy. To date, the decision to discontinue KRT relies on the clinical assessment of patients, measurement of creatinine clearance and urine output – parameters which are not reliable for profound decision-making (44). PenKid is freely filtered by the glomerulus (45) and effectively cleared by extracorporeal therapies including convection (CVVH), diffusion (CVVHD) and adsorption (HA) (46). Despite this, plasma concentrations of patients receiving therapy are maintained, making it a valuable tool for monitoring patients under KRT and for guiding KRT discontinuation, thereby supporting successful liberation from KRT (7, 14).

PenKid is higher in patients requiring KRT (7)

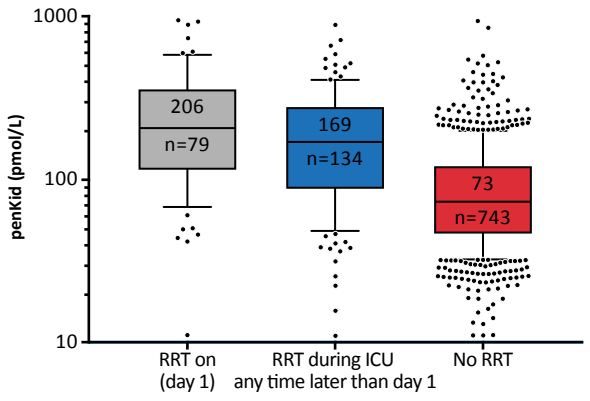


Figure 15. PenKid is higher in severe sepsis or septic shock patients requiring immediate KRT on day 1 or any time later. ALBIOS study. N=656 patients, p<0.0001. Modified from (7).

PenKid is a reliable kidney marker under KRT (8)

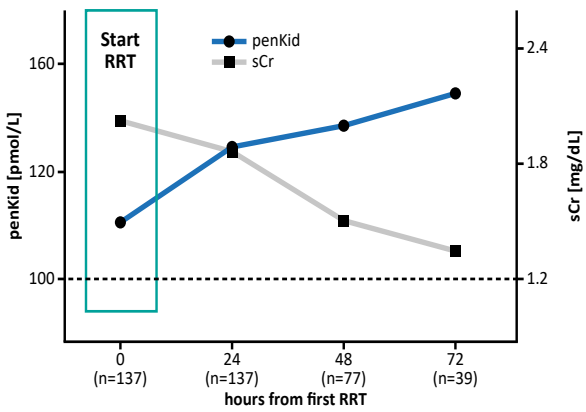


Figure 16. PenKid and serum creatinine trajectories in patients receiving KRT. Serum creatinine declines during KRT, whereas penKid continues to increase in these patients. N=137 patients. Modified from (8)

PenKid is associated with the successful liberation* from KRT (15)

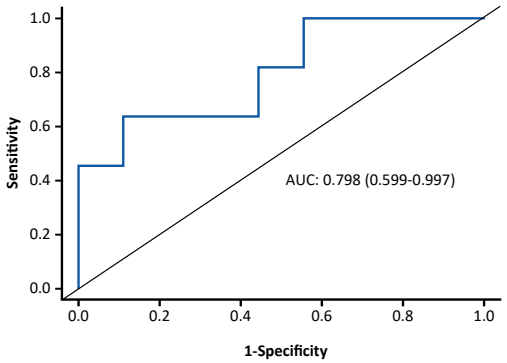


Figure 17. Receiver-operating characteristics analysis for penKid at CKRT discontinuation to determine successful CKRT discontinuation. N=20 patients (15).

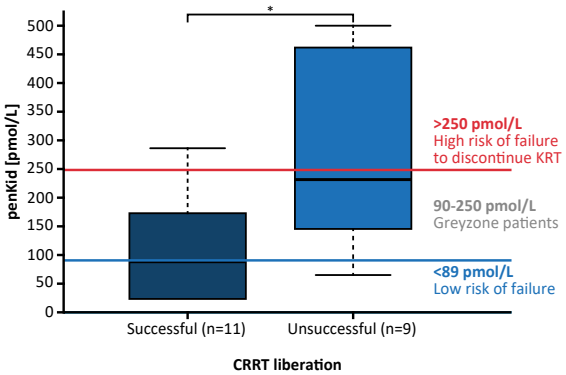


Figure 18. PenKid level at CKRT discontinuation discriminating between patients successfully (dark blue) and unsuccessfully (light blue) liberated from CKRT. N=20 patients, p<0.05. Modified from (15).

**Successful liberation: Patients who survived and did not receive any form of KRT for at least 7 days (relapse-free period) after CKRT discontinuation were classified as successfully liberated.*

Kidney transplantation

SCIENTIFIC EVIDENCE

Kidney transplantation remains the gold standard treatment for end-stage renal disease. However, early post-transplant management is critical, particularly when it comes to identifying patients at risk for delayed graft function (DGF), a common complication after kidney transplantation (47). PenKid provides a significant clinical advantage by identifying patients at risk for DGF well before traditional markers like serum creatinine show any changes (16). Moreover, penKid distinguishes between slow and delayed graft function with remarkable accuracy, up to eight days earlier than conventional assessments (16). This early and precise insight supports timely and personalized treatment decisions, giving clinicians a powerful tool to improve transplant outcomes.

PenKid identifies slow- and delayed graft function post transplant

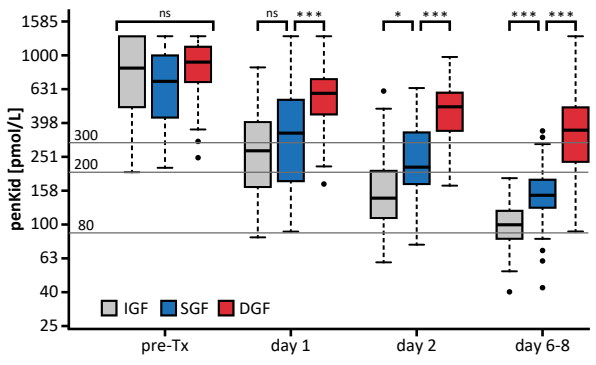


Figure 19. PenKid trajectories in kidney transplant recipients stratified by recovery of graft function. IGF - immediate graft function, SGF - slow graft function, DGF - delayed graft function. N=159 patients. *P≤0.05, ** P≤0.01, *** P≤0.001. Modified from (16).

PenKid indicates severity of delayed graft function post transplant

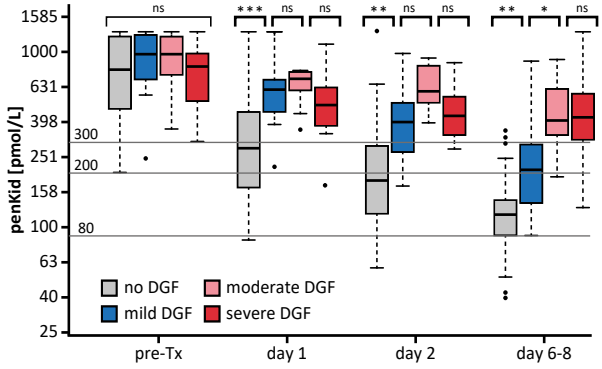


Figure 20. PenKid trajectories in kidney transplant recipients stratified by delayed graft function severity. DGF – delayed graft function. N=159 patients. *P≤0.05, ** P≤0.01, *** P≤0.001. Modified from (16).

PenKid predicts delayed graft function

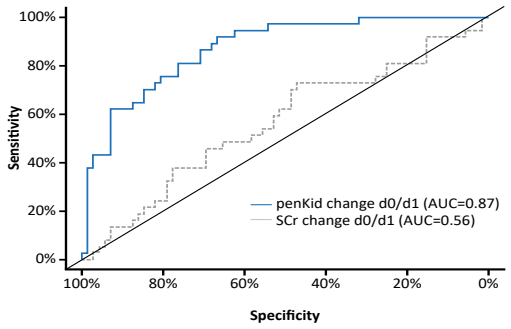


Figure 21. Receiver-operating characteristics analysis to predict delayed graft function. Calculated is the relative change in penKid and serum creatinine from pre-transplant to first post-transplant day. N= 159 patients receiving a kidney transplantation. Modified from (16).

High penKid levels indicate a higher risk of graft failure

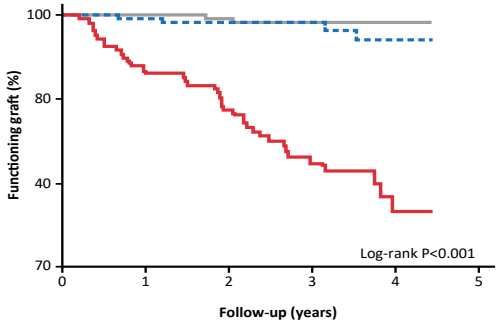


Figure 22. Kaplan-Meier curve for graft failure per tertiles of penKid. Black line: penKid >134 pmol/L, grey line: penKid <38 pmol/L, dotted line: penKid 38-134 pmol/L. N=664 kidney transplant recipients. Modified from (17).

***Mild DGF: Patients requiring kidney replacement therapy (KRT) within the first 24 h; Moderate DGF: Patients requiring KRT up to Day 7 post-transplant; Severe DGF: Patients requiring KRT beyond Day 7 post-transplant.*

Summary

Cutting edge research highlights on penKid

- PenKid is an innovative biomarker for the early diagnosis of AKI in critically ill patients.
- PenKid correlates with true GFR.
    - PenKid is reported to assess renal function under KRT.
    - PenKid indicates delayed graft function on day 1 post-transplant.
- PenKid is not influenced by inflammation in critically ill patients including sepsis and septic shock.
- Scientific evidence on penKid relies on measurement in over 80,000 patients.

Table 1: Pooled performance criteria of penKid for early detection of AKI. Results from a systematic review with meta-analysis incorporating 11 observational studies with 3,969 patients and 23.4% AKI incidence (48).

Pooled sensitivity	0.69 (95% CI 0.62-0.75)
Pooled specificity	0.76 (95% CI 0.68-0.82)
Positive likelihood ratio	2.83 (95% CI 2.06-3.88)
Negative likelihood ratio	0.41 (95% CI 0.33-0.52)
Area under the curve	0.77 (95% CI 0.73-0.81)

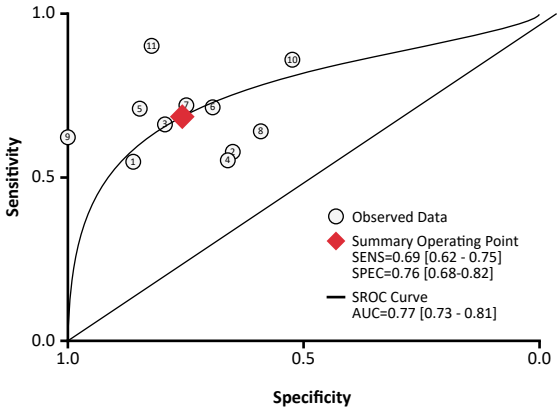
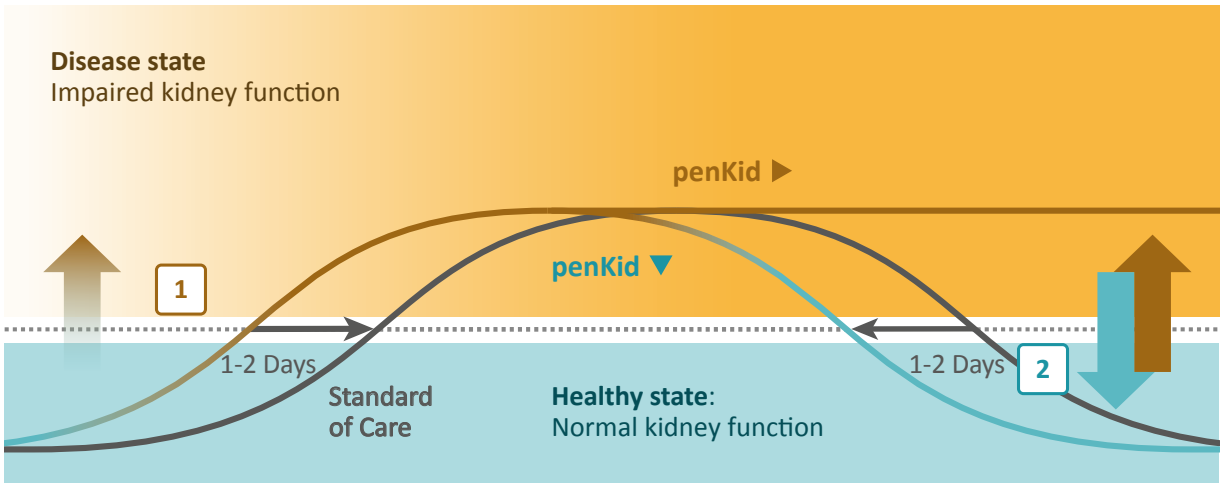


Figure 23. Receiver operating characteristics plot of penKid for the early detection of AKI (48).



Scheme displaying the rise of penKid blood levels [1] predicting worsening of kidney function up to 48 hours earlier than today's standard of care; the decrease of penKid levels [2] indicates the normalization of renal function.

Abbreviations

ADQI:	Acute Disease Quality Initiative
AKI:	Acute kidney injury
CKRT:	Continuous kidney replacement therapy
DGF:	Delayed graft function
ED:	Emergency department
GFR:	Glomerular filtration rate
ICU:	Intensive care unit
IGF:	Immediate graft function
KDIGO:	Kidney disease: improving global outcomes
KRT:	Kidney replacement therapy
MAKE:	Major adverse kidney events
mGFR:	measured glomerular filtration rate
NPV:	Negative predictive value
penKid:	Proenkephalin A 119-159
PPV:	Positive predictive value
ROC:	receiver operating characteristic
SA-AKI:	Sepsis associated- acute kidney injury
sCr:	Serum creatinine
SGF:	Slow graft function
SOFA:	Sepsis-relate organ failure assessment
WRF:	Worsening of renal function

References

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Your notes

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