Proenkephalin A 119-159 (penKid)

A unique biomarker for real-time assessment of kidney function

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The Biomarker Company

Table of Content

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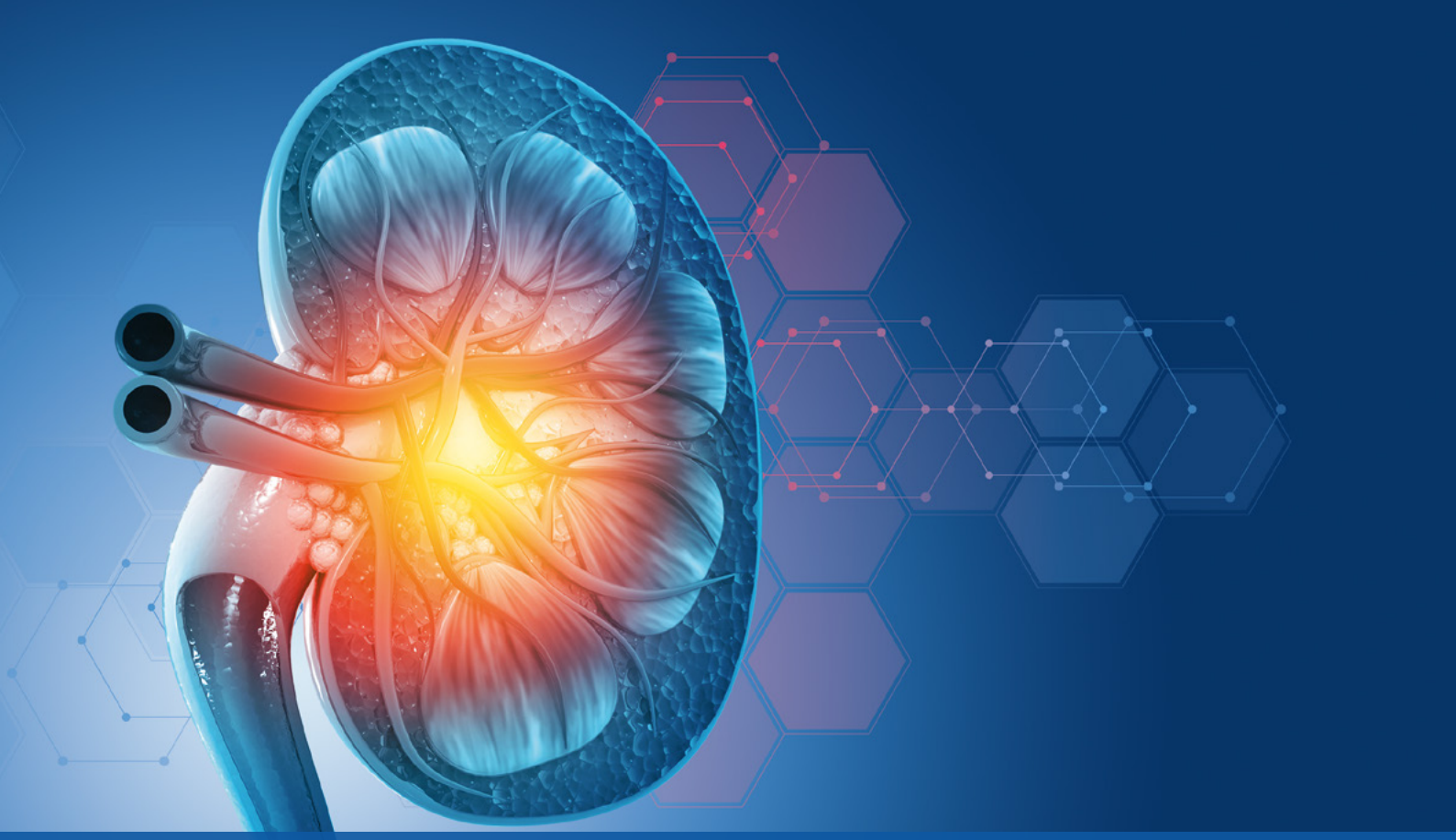


Abstract

Acute kidney injury (AKI) affects many critically ill patients, making timely information on kidney function important for early intervention, such as renal replacement therapy (RRT) 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 sensitive biomarker for kidney glomerular function,** overcomes these limitations (3). As a new biomarker for diagnosing AKI, penKid measured at admission to the emergency department (ED) (4, 5) or intensive care unit (ICU) (6, 7), enables timely anticipation of worsening renal function within 48 hours before current diagnostic criteria based on creatinine are met (8, 9).

More than 60 peer-reviewed publications and additional submitted clinical studies investigated 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, 10, 11).

In summary, penKid rapidly provides physicians at the ED and ICU with urgently needed information on kidney function, which is complementary to the current diagnostic toolbox. Thus, as studies show, penKid may aid in guiding nephrotoxic drug administration (12), contribute to clinical decisions around renal replacement therapy (RRT) by monitoring renal function under therapy (13), management of patients after major vascular surgery (14).

As CE_{0123} IVD marked quantitative immunoassay, **sphingotest® penKid® aids in the diagnosis of acute kidney injury in patients with sepsis or septic shock (15).**

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 (16, 17), making it a global burden with estimated 13 million cases per year (16). AKI accounts for many complications in patients with sepsis or septic shock (1). It is furthermore concerning that around 30% of hospitalized AKI patients discharged from the hospital continue to experience with persisting renal dysfunction (18).

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 (19). Therefore, timely information on renal function is essential to initiate and adapt treatment options like RRT 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, 20).

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), and the necessity of RRT (20).

Translated into clinical practice these insights might provide benefit in the guidance to start or stop RRT, the guidance of nephrotoxic drug administration, hospitalization decisions after catheterization-laboratory procedures, the prediction of delayed graft function, and assessment of contrast-induced nephropathy.

GFR is considered to be the best indicator of kidney function (21). 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 (22).

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 (23).

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, 24).

PenKid is a stable prohormone fragment of the Enkephalin family, with a long in vivo half-life, is stable after collection and is not influenced by sex or age (10).

Studies have shown that penKid strongly correlates with the kidney function and measured GFR. As penKid does not bind to proteins in the plasma and it is freely filtered in the glomerulus, it is a promising biomarker for assessing kidney function in critically ill patients (3, 10, 24, 25).

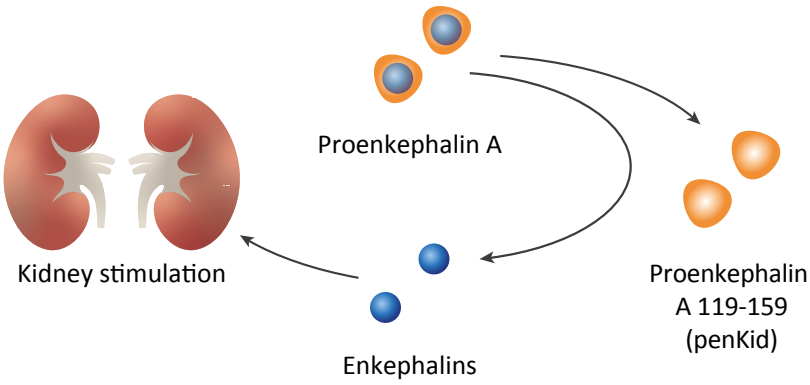
PenKid may, therefore, provide physicians with urgently needed information on top of the standard of care, with a potential role to predict kidney recovery (6, 26).

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 (28).

PenKid physiology in the kidney

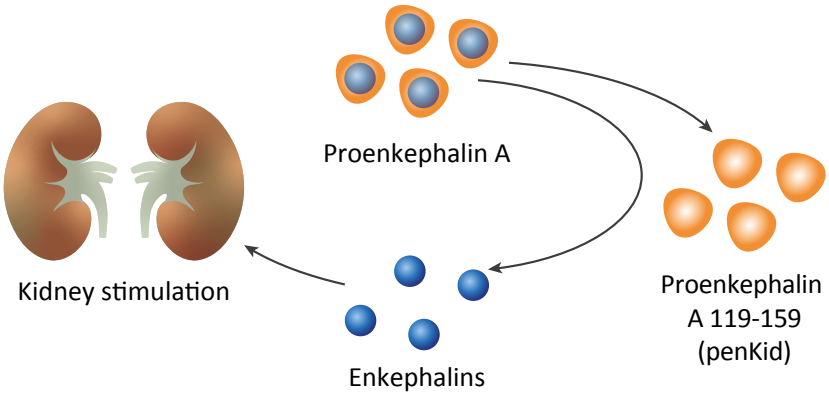
The enkephalins are endogenous opioids widely expressed in the human body with primary activity on delta opioid receptors (29). Interestingly, a high concentration of opioid receptors is found in the kidney (3, 30). Studies suggest a possible regulatory role for enkephalins in the kidneys, such as the induction of diuresis and natriuresis through receptor agonism (31) or inhibiting antidiuretic hormone activity (32). Several studies have shown a strong correlation of plasma penKid with the mGFR, which indicate that penKid might be a suitable and accurate maker to estimate the true GFR (25).

PenKid in the healthy state



Kidney function is modulated by the hormone enkephalin which remains difficult to detect due to its short half-life (10). PenKid overcomes this limitation, as it is the stable fragment of the Proenkephalin A precursor protein, therefore being a suitable surrogate measure of enkephalins (33).

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 (33, 25).

Sphingotest® penKid® diagnostics

Proenkephalin A 119-159 is detected in the plasma with the diagnostic assay sphingotest® penKid®. The clinical performance of the CE_{0123} certified IVD sphingotest® penKid® was demonstrated in the patient cohort from the AdrenOSS-1 trial (i.e., adult patients with severe sepsis or septic shock) (35), using a cut-off at 89 pmol/L, resembling the upper normal limit of healthy subjects. Primary endpoint of this study was diagnosis of all-stage AKI within 48 hours after enrolment (n=529 patients).

Intended use: The sphingotest® penKid® is a non-automated immunoluminometric assay (ILMA) for the in vitro diagnostic quantitative measurement of Proenkephalin A 119-159 in human EDTA plasma. Proenkephalin A 119-159 measurement in conjunction with clinical assessments and other laboratory findings is used as an aid in the diagnosis of acute kidney injury in adult patients with sepsis or septic shock. The sphingotest® penKid® is intended for use by professional users in laboratory settings.

Sphingotest® penKid® performance in diagnosing AKI within 48 hours

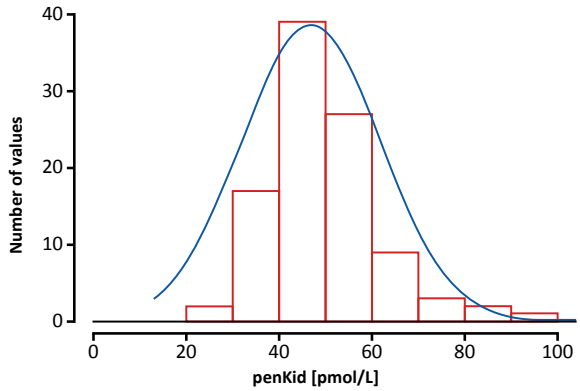


Figure 1. PenKid reference range of 120 healthy adults based on European population; age 31-82 (mean 51) years, 46% female. Median 29.9 pmol/L; 97.5th percentile: 89 pmol/L (95% CI 85-118) (15).

Parameter	Observed performance
Diagnostic sensitivity	71.8% (95% CI 65.7%-77.2%)
Diagnostic specificity	83.1% (95% CI 78.4%-86.9%)
PPV	77.1% (95% CI 71.0%- 82.2%)
NPV	78.8% (95% CI 73.9%-83.0%)
Diagnostic odds ratio	12.5 (95% CI 8.2-18.9)

Figure 2. Sensitivity, specificity, PPV, NPV and diagnostic odds ratio for sphingotest® penKid® values for diagnosis of AKI within 48 hours. Clinical cut-off: 89 pmol/L.

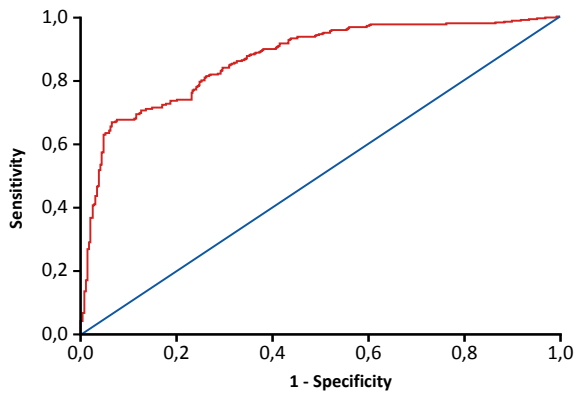


Figure 3. ROC plot for sphingotest® penKid® and endpoint diagnosis of AKI within 48 hours. AUC 0.868 (95% CI 0.837-0.899), p<0.0001.

Microtiter plate (MTP)-based immunoassay sphingotest® penKid® (10)

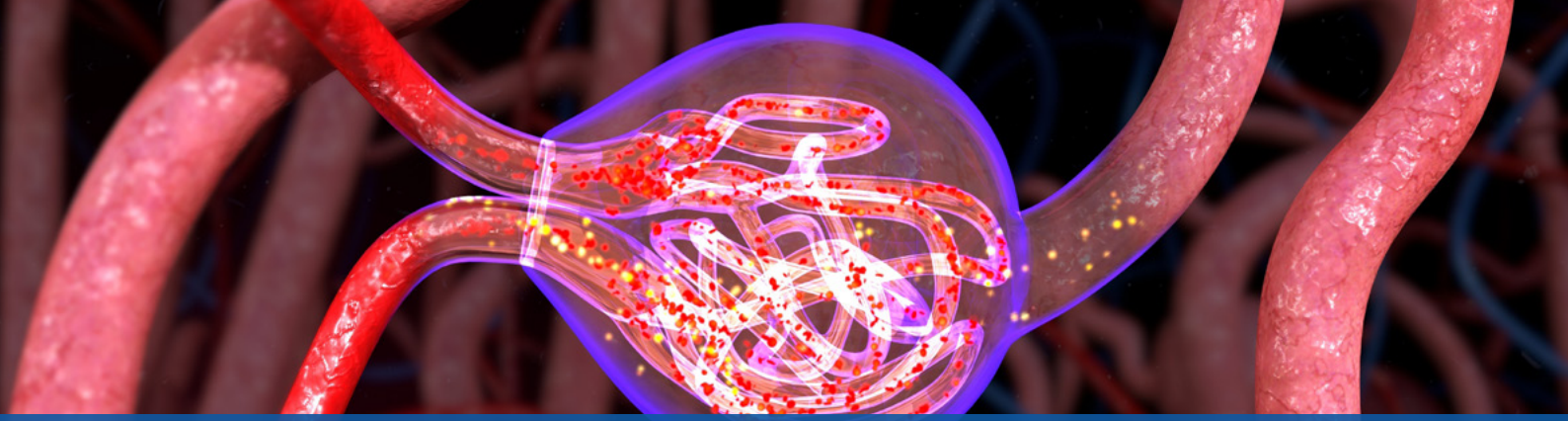
Figure 4. The MTP is an appropriate platform for manual high-throughput analysis in the central laboratory. Results are obtained in 1 hour. Detection range: 30 - 1,172 pmol/L. Sample volume: 50 µL EDTA plasma (10) .

Published clinical indications

Over 60 peer-reviewed publications have investigated penKid in more than 80,000 patients allowing a clear understanding of the characteristics of penKid levels and its value in critical care. PenKid has already compiled scientific evidence for many indications in critical care and beyond, proving value beyond standard of care markers.

Table 1: Main clinical indications where penKid showed additive value as a kidney function marker.

Investigated indications	PenKid value
Sepsis and septic shock	**ED:** Earlier detection of AKI in sepsis patients upon ED admission is an unmet need for timely stratification of patients with AKI. PenKid showed great value by effectively detecting the presence and severity of AKI in septic patients with normal serum creatinine levels at admission (4, 5). **ICU:** Patients with sepsis or septic shock admitted to the ICU require efficient management strategies to predict kidney deterioration and recovery of renal function. PenKid predicted major adverse kidney events, transient AKI, worsening of renal function, and renal recovery in septic ICU patients (6, 7).
Heart failure	**Acute heart failure (AHF):** Patients with AHF, renal dysfunction, and inadequate decongestion during hospitalization are at risk of prolonged hospitalization, rehospitalization, and death. The rapid increase of penKid aids in identifying patients who do not tolerate the intensified diuretic therapy and predicts the worsening of renal function, in-hospital mortality, and mortality during follow-up (36-39). **Chronic heart failure (CHF):** There is an unmet clinical need for biomarkers to monitor kidney function in patients with CHF, mainly for patients with heart failure with preserved ejection fraction (HFpEF) (i.e., the left ventricle is not filling correctly with blood). High levels of penKid in HFpEF were associated with heart failure rehospitalization (40) and recurrence of acute myocardial infarction (41). **Ambulatory patients:** Patients with heart failure have a poor prognosis, but outcomes might be improved by early identification of organ failure risk. Increased penKid levels have shown significant predictive value for risk stratification of stable ambulatory patients (42).
Major surgeries	AKI occurs in up to 40% of patients undergoing cardiac surgery and is a common postoperative complication in complex aortic surgery. Due to its dynamic nature, penKid is a biomarker for the prediction of AKI before and after invasive interventions such as cardiac and aortic surgery (9, 14, 43).
Organ transplantation	PenKid is associated with kidney function in renal transplant recipients (RTR) and in healthy kidney donors and may be a marker for determining long-term renal prognosis in RTR. High penKid levels may indicate an additional benefit in the early identification of RTR at risk of graft failure (44). In liver transplantation during preoperative period, penKid was significantly higher in patients with severe AKI, and detected AKI after transplantation 48h earlier than sCr (8).
RRT	Critically ill patients are often at risk of developing AKI and are likely in need of organ support, such as RRT. However, the most effective timing to start RRT remains uncertain (45). PenKid levels have been shown to predict the need for RRT on day one or later during hospitalization in sepsis patients (7, 46) as well as in liver transplant patients (8). The ELAIN and RICH studies scientifically proved that penKid remains informational during RRT, indicating kidney function recovery and supporting the decision to safely stop RRT/CRRT (13, 47).
Burned patients	PenKid levels in patients on admission to the ICU were associated with the risk of developing AKI in patients with severe burns, where mortality rates range from 30-70%. The data suggest that penKid levels could provide additional value to the currently available markers of renal function and AKI to better quantify kidney function in critically ill patients (48).
Pediatric ICU	Pediatric AKI is often diagnosed too late for successful therapeutic interventions, leading to adverse outcomes and chronic kidney impairment in the long term (49). PenKid identifies AKI in critically ill neonates and children under one year of age, offering a potential solution to the shortcomings in pediatric critical care (50, 51).



Kidney function

SCIENTIFIC EVIDENCE

PenKid has been evaluated as a biomarker of kidney function in several clinical conditions (6, 10, 52), and correlates with the gold standard measurement of GFR (10, 24). A penKid-based formula to estimate the GFR was developed and validated in a broad patient cohort (11). 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 measure and the true GFR and are independent of inflammation (7, 10, 11).

PenKid as a specific biomarker for glomerular filtration rate

PenKid is a reliable surrogate for the measured GFR in adults with stable and unstable renal conditions (10)

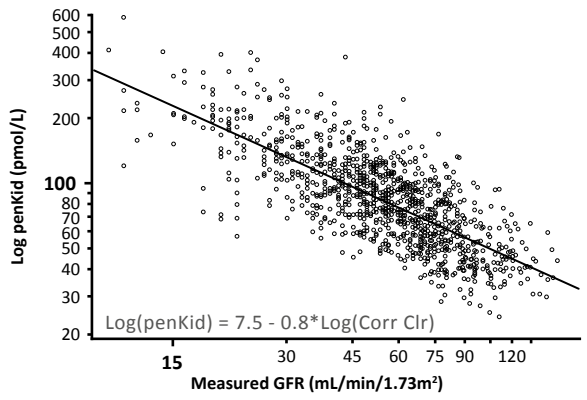


Figure 5. PenKid inversely correlates with the measured GFR (iothalamate clearance): the higher the penKid levels, the lower the mGFR. N = 1191 patients. Modified from (10).

PenKid has a high correlation with the measured GFR in neonates and children (51)

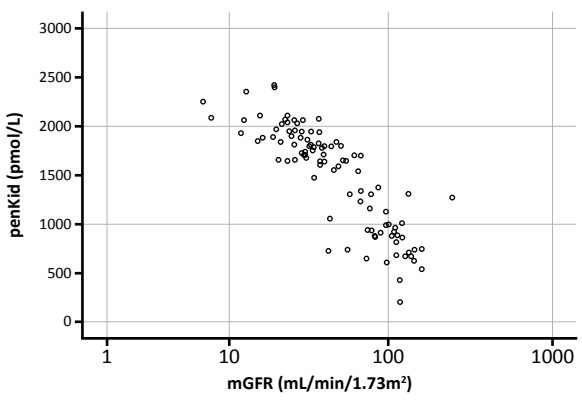


Figure 6. Correlation of penKid concentration as a function of measured GFR (mGFR, iothalamate clearance). N= 37 patients: p= - 0.88, p<0.001. Modified from (51).

PenKid eGFR formula correlates with mGFR (11)

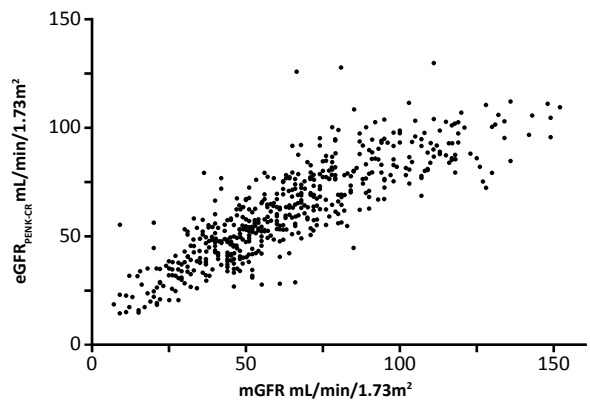


Figure 7. Correlation of mGFR and eGFR using the new penKid formula including penKid and sCr, developed from patients with corresponding assessment of GFR by iohexol or iothalamate clearance. Patient cohort: chronic kidney disease patients, healthy volunteers, sepsis and septic shock patients, kidney donors, and recipients. N=1354 patients. R-squared: 0.73 ($p < 0.001$). Modified from (11).

PenKid has high specificity for renal function (7)

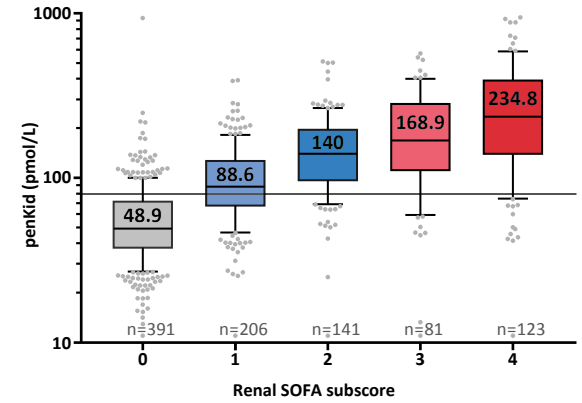
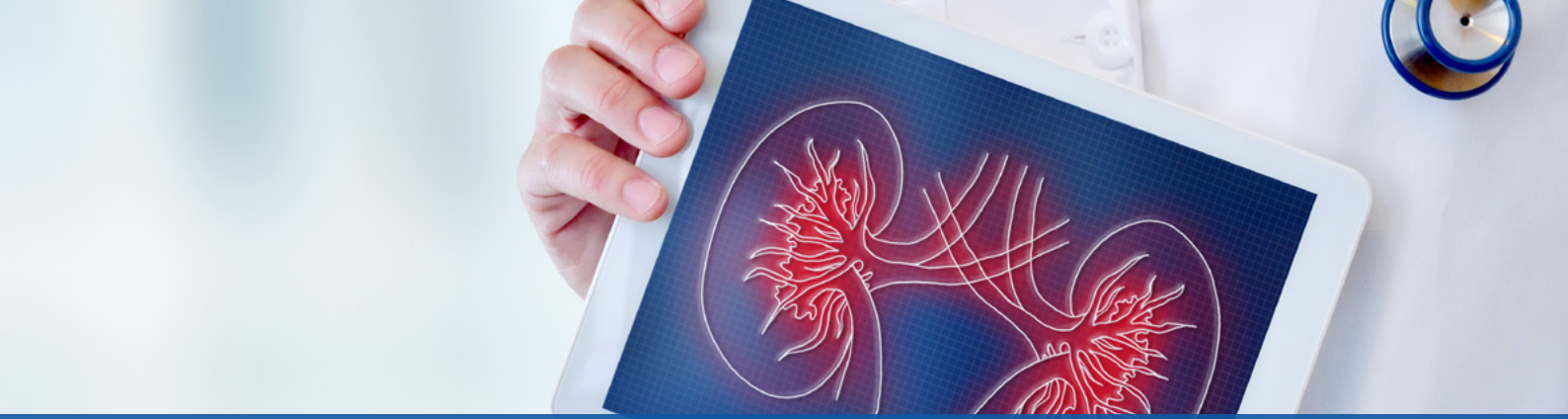


Figure 8. Association of penKid with renal SOFA score in severe septic and septic shock patients. PenKid increased only upon renal dysfunction (subscores 1 – 4), remaining within normal range even in the context of systemic inflammation, as in sepsis or septic shock (subscores 0). The line indicates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



Subclinical AKI

SCIENTIFIC EVIDENCE

Subclinical AKI (sub-AKI) is defined as a condition where there is an increase of functional or damage biomarker, without signs of AKI according to the KDIGO criteria, i.e., sCr and urine output are still within normal range. The prevalence of sub-AKI on ICU admission is still not properly explored (between 12-18% patients) (28), however, there is evidence for poor prognosis in such 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 (8, 28, 48, 53).

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

PenKid identifies sub-clinical AKI in critically ill patients (28)

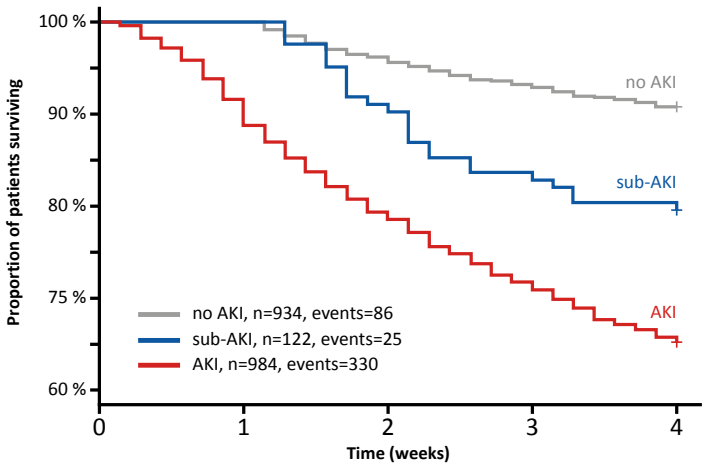


Figure 9. Survival of critically ill patients, based on presence of AKI, sub-AKI or no AKI. Sub-AKI defined based on penKid > 80 pmol/L. N=2087 patients. Modified from (28).

PenKid identifies sub-clinical AKI in burned patients (48)

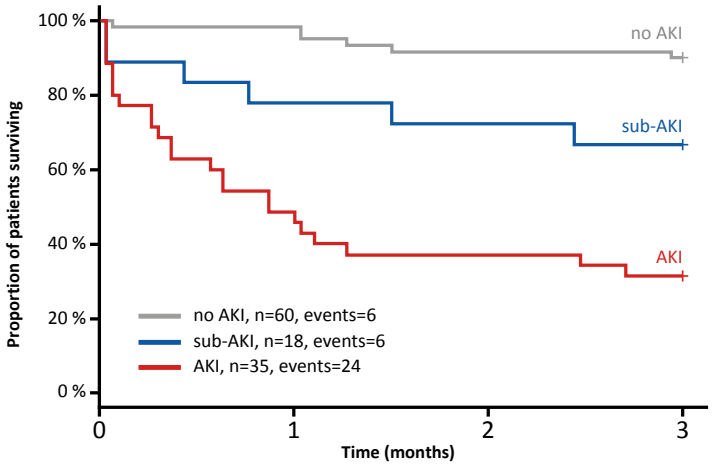


Figure 10. Survival of burned patients, based on AKI, sub-AKI or no AKI. The identification of sub-AKI allows the identification of patients who do not fall into the clinical AKI definition but still show a GFR decrease and increased risk of death. Sub-AKI defined based on penKid > 80 pmol/L. N=113 patients. Modified from (48).

Critically ill patients

SCIENTIFIC EVIDENCE

The assessment of penKid identifies patients at high risk of AKI in EDs and ICUs and delivers information on kidney function in hospitalized patients (3-7, 54, 55).

PenKid can detect AKI and its severity in sepsis patients at the ED (4)

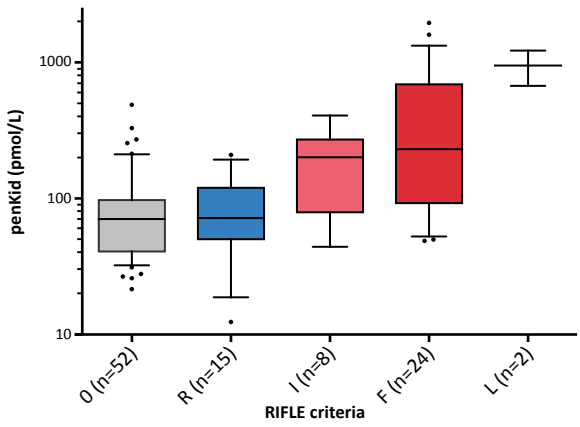


Figure 11. PenKid concentrations at ED admission in patients according to the RIFLE criteria (risk, injury, failure, loss of function and end-stage Kidney disease). Modified from (4).

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

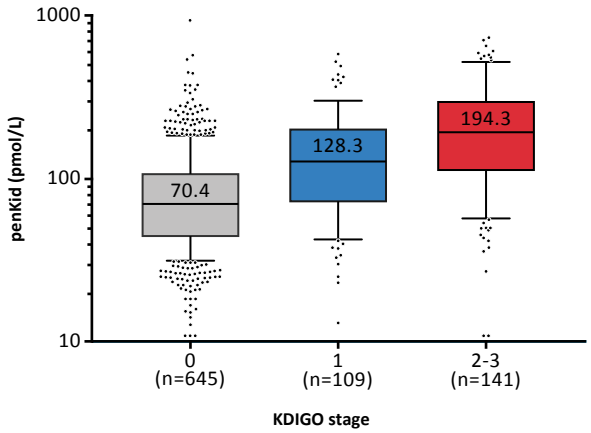


Figure 12. PenKid concentrations on day 1 about the AKI stage according to the KDIGO definition. N=656 ICU patients with severe sepsis or septic shock. Modified from (7).

High penKid levels on ED admission identify sepsis patients with poor outcome (54)

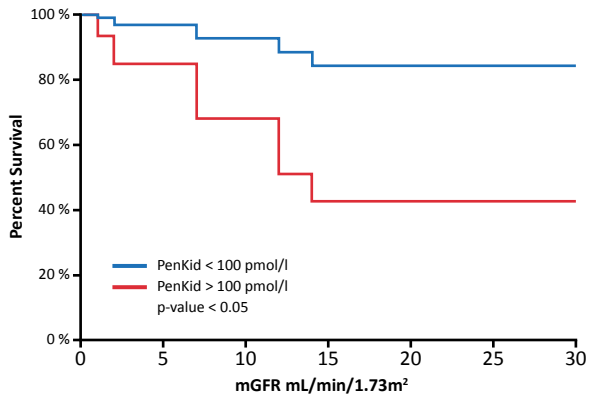


Figure 13. Survival of sepsis patients based on penKid levels on ED admission. N=153 patients. Modified from (54).

PenKid to monitor treatment success in septic patients (7)

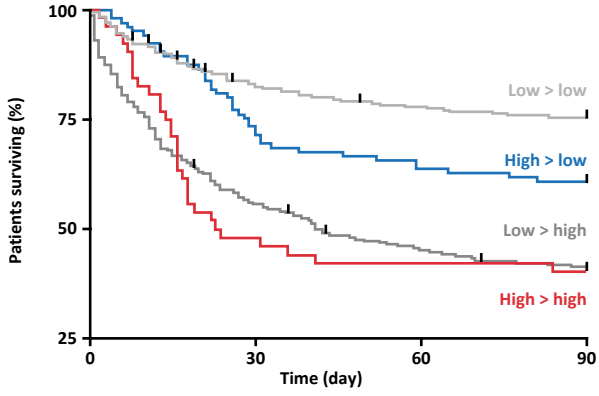


Figure 14. Kaplan-Meier survival curves up to 90 days for patients divided into four groups according to their penKid concentrations on days 1 and 7, below or above a pre-defined clinical cut-off of 100 pmol/L. While mortality risk stays high in patients with high or increasing penKid (red and orange lines), patients with low penKid show decreased risk. Modified from (7).

Renal replacement therapy

SCIENTIFIC EVIDENCE

Renal replacement therapy (RRT) is the main therapy to treat AKI complications, such as electrolyte or acid-base disbalances, uremia, or fluid overload (13). Yet, the best time to start or stop RRT remains controversial (2), and the decision to stop RRT relies on the clinical assessment of patients, measurement of creatinine clearance and 24-h urine output – both not reliable parameters (56). PenKid has shown value in identifying patients requiring RRT and aiding in their successful RRT liberation (7, 13).

PenKid is higher in patients requiring RRT (7)

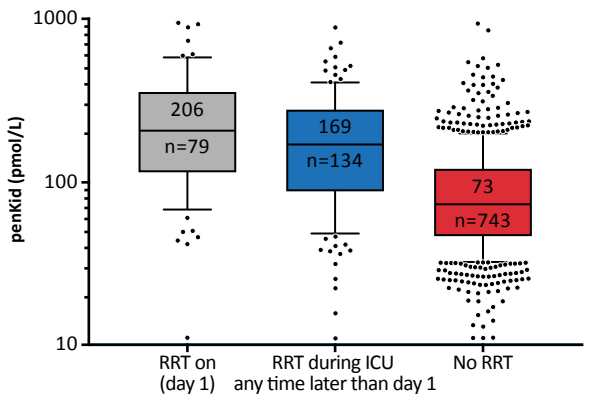


Figure 15. PenKid is higher in severe sepsis or septic shock patients requiring immediate RRT on day 1 or any time later. ALBIOS study. N=656 patients, p<0.0001. Modified from (7).

PenKid is higher in patients after liver transplantation receiving RRT (8)

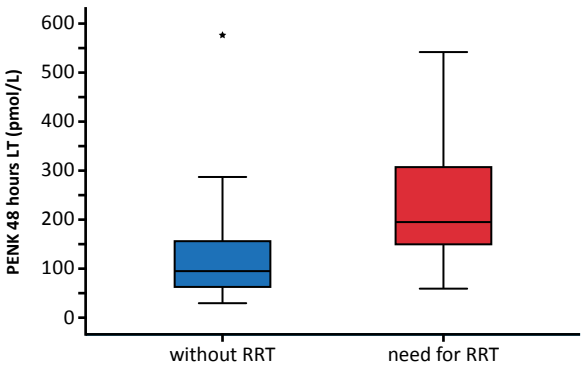


Figure 16. Higher penKid levels indicate the need for RRT in patients after 48h liver transplantation. Modified from (8).

PenKid is associated with the successful liberation* from RRT (13)

PenKid assessement in patients during the third day of RRT

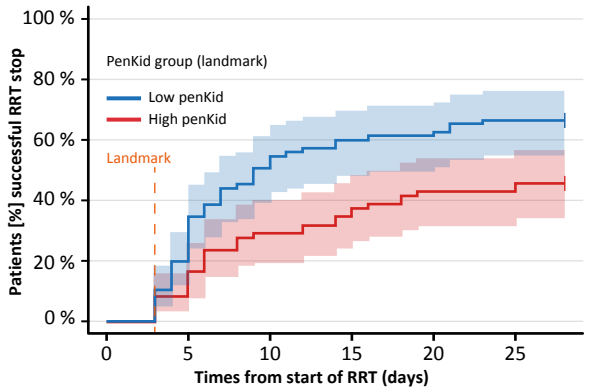


Figure 17. Proportion of patients who successfully discontinued RRT within 28 days. Landmark: start point on day 3 which includes all patients still receiving RRT. sHR 1.78 (95% CI 1.17 – 2.71); p = 0.007 (Gray-k-sample). Modified from (13).

Patients with increased penKid levels might benefit from early initiation of RRT

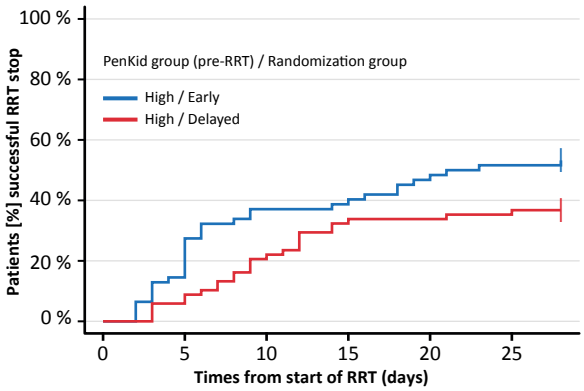
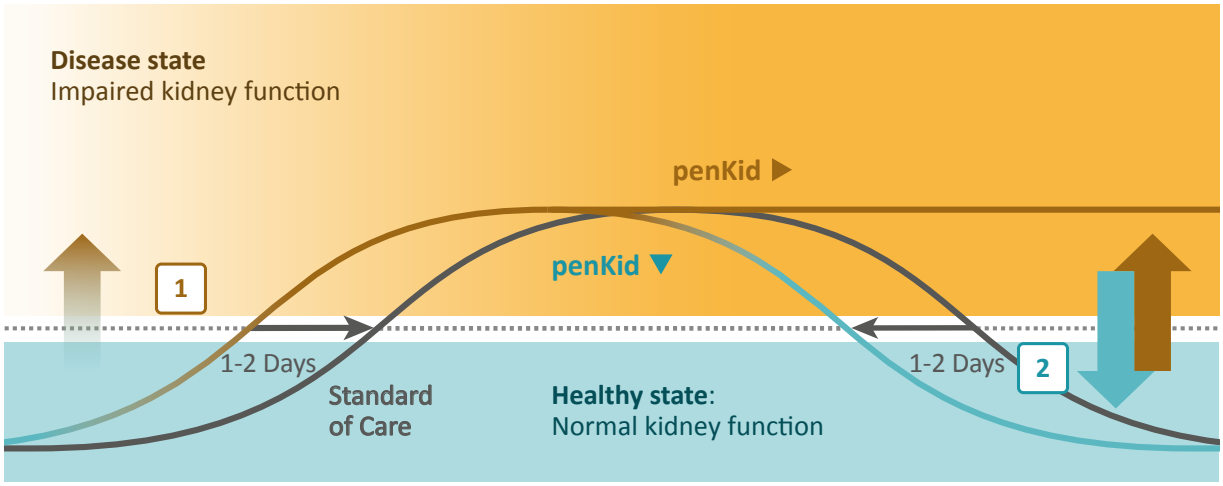


Figure 18. PenKid levels in patients randomized to start RRT early (8 hours after KDIGO AKI stage 2 diagnosis) or delayed (12 hours after KDIGO stage 3 diagnosis). PenKid levels (> 89 pmoL/L) up to 48 hours before RRT indicated that patients in the earlier group were more successfully liberated from RRT than the delayed group. N= 210 patients. Modified from (13).

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

Summary

- PenKid is an innovative biomarker for the early diagnosis of AKI in critically ill patients.
- Publications show that penKid correlates with true GFR and enables early assessment of worsening and improving kidney function.
- PenKid has been measured in over 80,000 patients.
- Scientific evidence shows that penKid blood level is not influenced by inflammation.



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.

Literature on penKid as a new functional kidney biomarker

Clinical settings already evaluated:

- Acute myocardial infarction (41)
- Burns (48)
- Cardiac arrest (57)
- Cardiac surgery (9, 14, 43, 58)
- Cardiogenic shock (59)
- Chronic kidney disease (60, 61)
- Contrast-induced nephrotoxicity (12)
- Heart failure (36-40, 42, 62-64)
- ICU (50, 65-67)
- Renal and liver transplantation (8, 44)
- RRT (7, 13, 47)
- Sepsis (4-7, 24, 28, 46, 52, 68, 69)

Other potential applications where penKid might benefit:

- Guidance of nephrotoxic drug administration.
- ICU discharge decisions.
- Management of patients attending catheterization intervention.
- Triaging.

Abbreviations

ADQI:	Acute Disease Quality Initiative
AHF:	Acute heart failure
AKI:	Acute kidney injury
CHF:	Chronic heart failure
ED:	Emergency department
EDTA:	Ethylenediaminetetraacetic acid
GFR:	Glomerular filtration rate
HFpEF:	Heart failure with preserved ejection fraction
ICU:	Intensive care unit
KDIGO:	Kidney disease: improving global outcomes
MAKE:	Major adverse kidney events
mGFR:	measured glomerular filtration rate
NPV:	Negative predictive value
PenKid:	Proenkephalin A 119-159
PPV:	Positive predictive value
RIFLE:	Risk, injury, failure, loss and end-stage kidney disease
ROC:	receiver operating characteristic
RRT:	Renal replacement therapy
RTR:	Renal transplants recipients
Sub-AKI:	Subclinical acute kidney injury
sCr:	Serum creatinine
SOFA:	Sequential Organ Failure Assessment

References

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