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► To cite this version:

François Dépret, Adrien Polina, Juliette Amzallag, Laure Fayolle-Pivot, Maxime Coutrot, et al.. PenKid measurement at admission is associated with outcome in severely ill burn patients. *Burns*, 2020, 46, pp.1302 - 1309. 10.1016/j.burns.2020.01.002 . hal-03491618

HAL Id: hal-03491618

<https://hal.science/hal-03491618v1>

Submitted on 26 Sep 2022

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PenKid Measurement at Admission is Associated with Outcome in Severely Ill Burn Patients

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Highlights

- PenKid at admission ($\text{penKid}_{\text{admin}}$) is the first plasmatic dosage of penKid at admission
- $\text{PenKid}_{\text{admin}}$ is associated with risk of AKI and mortality in burn patients
- $\text{PenKid}_{\text{admin}}$ adds value on top of serum creatinine and SOFA to predict mortality
- $\text{PenKid}_{\text{admin}}$ did not add value to $\text{Screat}_{\text{admin}}$ to predict AKI
- Sub-AKI detected with $\text{penKid}_{\text{admin}}$ is associated with an increased risk of death

Word count of the body text: 2658 < 3,500

Abstract

Background: Proenkephalin A 119-159 (penKid) has been proposed as a sensitive biomarker of renal function. This study evaluated the association of concentrations of plasma penKid with death and risk of acute kidney injury (AKI) in severely ill burn patients.

Methods: A prospective observational study in two centers with severely ill adult burn patients was conducted. The inclusion criteria were total body surface area (TBSA) burns >15%, with burn injury occurring <72 hours before intensive care unit (ICU) admission and plasma sample taken at admission. The primary endpoint was 90-day mortality. The secondary endpoints were AKI and a combined endpoint of 90-day mortality and/or AKI. Mortality was also evaluated in the sub-group of patients with sub-clinical AKI, defined as a patient without AKI but with elevated penKid.

Results: A total of 113 consecutive patients were enrolled. The median age was 48 years (Interquartile range [IQR] 33–64), the median burn TBSA was 35% (IQR 25–53), and 90-day mortality was 31.9%. Thirty-one percent of the patients had AKI, and 41.6% of patients had the combined endpoint. There was a stepwise decrease in survival from patients without AKI, sub-AKI, and with AKI (survival rate 90.0% [95% CI 82.7–97.9], 66.7% [95% CI 48.1–92.4], and 31.4% [95% CI 19.3–51.3], respectively, $p < 0.001$). Plasma penKid concentration was significantly higher in non-survivors compared to survivors (86.9 pmol/L [IQR 53.3–166.1] versus 52.9 pmol/L [IQR 37.1–70.7]; $p = 0.0001$) and in patients with AKI compared to patients without AKI (86.4 pmol/L [IQR 56.5–153.4] versus 52.5 pmol/L [IQR 35.5–71.2]; $p < 0.001$). Penkid provided added value on top of serum creatinine (Screat) and Sepsis Related Organ Failure Assessment (SOFA) scores to predict 90-day mortality (combined c-index of 0.738 versus 0.707; $p = 0.024$ and 0.787 versus 0.752; $p < 0.001$).

Conclusions: Plasma penKid concentration at admission was associated with an increased risk of death in burn patients. PenKid has additional prognostic value on top of Sreat and SOFA to predict 90-day mortality.

Keywords: proenkephalin, burn patients, mortality, acute kidney injury, biomarkers

Abstract word count: (331 ≤ 250)

Abbreviations

PenKid: proenkephalin A 119-159

AKI: acute kidney injury

TBSA: total body surface area

SOFA: sequential organ failure assessment

PenKid_{admin}: proenkephalin A 119-159 on admission

PenKid_{Day3}: proenkephalin A 119-159 on day 3

Screat: serum creatinine

Screat_{admin}: serum creatinine on admission

KDIGO: kidney disease: improving global outcomes

BMI: body mass index

BSA: body surface area burned

ABSI: abbreviated burn severity index

UBS: unit burn standard

IQR: interquartile ranges

HR: hazard ratios

OR: odds ratios

ROC: receiver operating characteristic

Introduction

Acute kidney injury (AKI) is a frequent complication in severely ill burn patients. AKI has been associated with worse outcomes in this specific population, even in specialized burn units with mortality rates ranging from 35–70% [1–3]. Burn patients have many risk factors for AKI (e.g., systemic inflammatory response to burn injury, haemolysis, hypovolemic shock, hydroxocobalamin use, and sepsis) [4,5].

The kidney disease: improving global outcome (KDIGO) guidelines recommend using two markers (serum creatinine [Screat] and urine output) to evaluate renal function and detect AKI [6]. Due to its large volume of distribution and decrease in inflammatory states, Screat is a late biomarker of AKI [7]. Furthermore, large amounts of fluid resuscitation may delay the rise of Screat even in patients with decreased glomerular filtration rates [7]. Proenkephalin A 119-159 (penKid) is a stable peptide derived from the same precursor as enkephalins. The gene coding for penKid is expressed in many different organs (the central nervous system, the kidney, the heart, and the muscles) [8]. Researchers have found penKid to be very well correlated with glomerular filtration rates (i.e., kidney function) [9–13], with others suggesting that it could be used as a novel plasma biomarker to detect AKI [14–19]. PenKid appears to be a more sensitive biomarker of AKI than Screat [20]. Such a biomarker could enable the detection of kidney injury in patients that is either missed or detected in late stages when using Screat [21]. The main objective of this study was to assess the association between penKid at admission (penKid_{admin}) and day 3 (penKid_{Day3}) with 90-day mortality in severely burned patients. The secondary outcomes were to evaluate the association between penKid and AKI or a combined endpoint (90-day mortality and/or AKI). Mortality was also evaluated in the sub-group of patients with sub-clinical AKI (sub-AKI), defined as patients without AKI but with elevated penKid.

Patients and methods

Study design and population

A double-center cohort study was conducted in the Burn Unit of Saint Louis Hospital (Assistance Publique Hôpitaux de Paris), Paris, France and in the Burn Unit of Edouard Herriot Hospital, Lyon, France. The study was approved by the local ethics committee (PRONOBURN study, comité de protection des personnes IV, St-Louis Hospital; Institutional Review Board 00003835, protocol 2013/17NICB). All patients admitted to the aforementioned intensive care burn units (ICBUs) between April 2014 and April 2016 and who met the inclusion criteria were included. Inclusion criteria were a total body surface area (TBSA) burn >15%, the burn injury occurring <72 hours before ICU admission, exclusion criteria were a decision to withdraw life support at admission, and absence of plasma penkid measurement at admission.

Outcome

The primary endpoint was 90-day mortality. The secondary outcomes were AKI, combined criteria of 90-day mortality and/or AKI, and the evaluation of patients with sub-clinical AKI. AKI was defined and staged according to the KDIGO guidelines [22] during the first seven days post admission. Admission Screat ($Screat_{admin}$) was used as baseline Screat. Sub-clinical AKI was defined as patients without AKI but with a $penKid_{admin}$ concentration >80 pmol/L. The cut-off of 80 pmol/L corresponds to the 99th percentile of plasma penKid levels in healthy volunteers [23].

Measurements

The following data were collected: sex, age, body mass index (BMI), TBSA, full-thickness body surface area (BSA) burned, mechanism of injury, patients' characteristics, abbreviated burn severity index (ABSI) [24], unit burn standard (UBS) [25], sequential organ

failure assessment (SOFA) score [26], 28- and 90-day mortality, AKI, and sub-AKI. Patients were resuscitated according to the ICBU resuscitation protocol [27].

Venous blood samples were collected at admission and at day 3 in tubes containing ethylene-diamine-tetra-acetic acid. After centrifugation, plasma was kept frozen at -80°C until assayed. Proenkephalin A 119-159 (penKid) was measured in duplicate using a chemiluminescence immunoassay (Sphingotec GmbH, Hennigsdorf, Germany), as described previously [28]. The lower detection limit of the immunoassay was 5.5 pmol/L. Intra-assay and inter-assay coefficients of variation were 6.4% and 9.5% at 50 pmol/L and 4.0% and 6.5% at 150 pmol/L, respectively.

Statistical analysis

The measurement values are expressed as medians and interquartile ranges (IQR), or they are expressed as counts and percentages as appropriate. Group comparisons of continuous variables were performed using the Kruskal–Wallis test. Categorical data were compared using Pearson’s chi-squared test for count data. PenKid data was log-transformed. Cox proportional hazards regression was used to analyse the effect of risk factors on survival in uni- and multivariable analyses. Logistic regression was used for dichotomous endpoints. In both cases, to demonstrate independence from other variables, the added value of penKid on top of these was evaluated based on the likelihood ratio chi-square test for nested models. The concordance index (c-index or area under the curve [AUC]) was given as an effect measure for uni- and multivariable models. For multivariable models, a bootstrap-corrected version of the c-index was given. For continuous variables, hazard ratios (HR) or odds ratios (OR), as appropriate, were standardized to describe the HR/OR for a change of one IQR. Survival curves plotted by the Kaplan–Meier method were used for illustrative purposes. For dichotomous endpoints, receiver-operating-characteristic (ROC) curves were constructed for illustration. All statistical tests were two-tailed, and a two-sided p-value of 0.05 was

considered as significant. The statistical analyses were performed using R version 3.4.3 (<http://www.r-project.org>, library rms, Hmisc, ROCR) and the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Study population

From April 2014 to April 2016, 540 patients have been admitted for burn injury. 200 consecutive patients met the inclusion criteria. Of these, 12 patients declined to participate, 55 had no plasma sample at admission (four patients had missing penKid measurements at admission but had it at day 3 and were not included, 51 patients had no plasma sample at all), resulting in 113 patients who were analyzed (CONSORT diagram in supplementary material). The characteristics of the patients included in this study are summarized in Table 1. The median age was 48 (33–64) years, with a median TBSA of 35% (25–53) and a median ABSI of 8 (7–11). All of the patients had a valid penKid_{admin} measurement, and 82 patients (73%) had penKid_{Day3} (10 patients died before day 3, and 21 patients had missing measurements at day 3).

PenKid_{admin} and 90-day mortality

Thirty-six patients died at day 90 (mortality 31.9%). Median penKid_{admin} was significantly higher in non-survivors at day 90 versus survivors (86.9 pmol/L [IQR 53.3–166.1] versus 52.9 pmol/L [IQR 37.1–70.7]; $p = 0.0001$). The c-index of penKid_{admin} for 90-day mortality was 0.712 (0.622–0.802, $p < 0.0001$). PenKid_{admin} provided added value on top of Screat_{admin} and SOFA scores at admission (SOFA_{admin}) to predict 90-day mortality (combined c-index of 0.738 versus 0.707; $p = 0.024$ and 0.787 versus 0.752; $p < 0.001$). PenKid_{admin} also provided added value on top of the ABSI (combined c-index = 0.794 versus 0.755; $p < 0.001$). Furthermore, adding penKid_{Day3} to penKid_{admin} provided added value to

predict 90-day mortality (c-index increased from 0.712 to 0.728; $p = 0.010$) (see Figure 1 for illustrations of this). Of the 78 patients without AKI within the first week, 18 patients (23.1% of non-AKI, or 15.9% of all patients) had elevated penKid upon admission (defined as $\text{penKid}_{\text{admin}} > 80 \text{ pmol/L}$); they were classified as sub-AKI. These patients' survival was significantly poorer than the survival of patients without sub-AKI (i.e., with low penKid) (a 90-day survival rate of 66.7% versus 90.0%, respectively; HR 4.0 [1.3–12.3]; $p < 0.001$). There was a stepwise increase in the risk of mortality in patients without AKI, sub-clinical AKI, and with AKI ($p < 0.0001$, Figure 3). In the bivariate and multivariate analysis, $\text{penKid}_{\text{admin}}$ was associated with 90-day mortality (Table 2).

PenKid and kidney function

Thirty-five patients (31%) developed an AKI within the first week after admission. $\text{PenKid}_{\text{admin}}$ was significantly higher in patients with AKI compared to patients without AKI (86.4 pmol/L [IQR 56.5–153.4] versus 52.5 pmol/L [IQR 35.5–71.2]; $p < 0.0001$). The c-index for $\text{penKid}_{\text{admin}}$ to predict AKI was 0.744 (0.648–0.840), with a standardized OR of 3.8 (2.0–7.2). $\text{PenKid}_{\text{admin}}$ did not add value to $\text{Screat}_{\text{admin}}$ (used in the definition of AKI) to predict AKI (combined c-index for $\text{Screat}_{\text{admin}}$ and $\text{PenKid}_{\text{admin}}$ was 0.857 vs 0.845 for serum creatinine, $p = 0.186$).

PenKid and combined criteria (90-day mortality and/or AKI)

Of the 36 deaths, 24 experienced AKI, and 12 died without AKI. In addition to the 36 deaths within 90 days, 11 patients experienced AKI but survived, creating a cumulative number of patients who experienced either of the endpoints to 47 (41.6%). The median $\text{penKid}_{\text{admin}}$ was significantly higher in patients with a combined endpoint compared to patients without a combined endpoint (86.4 pmol/L [IQR 54.5–153.4] versus 51.6 pmol/L [IQR 33.9–63.4]; $p < 0.0001$). The c-index for predicting the combined endpoint was 0.766

(0.678–0.854, $p < 0.0001$). Furthermore, penKid_{admin} added value on top of Screat_{admin} and SOFA_{admin} (combined c-index: 0.824 versus 0.792; $p = 0.008$ and combined c-index = 0.866 versus 0.795; $p < 0.001$) for the combined endpoint. Figure 2 illustrates that both patients with AKI and/or deaths within 90 days had elevated penKid_{admin}.

Discussion

This prospective observational study showed that penKid_{admin} was strongly associated with 90-day mortality and the occurrence of AKI in severely burned patients. Furthermore, adding penKid_{admin} to Screat_{admin}, SOFA_{admin}, or ABSI outperformed Screat_{admin}, SOFA_{admin}, and ABSI alone in their association with 90-day mortality and with 90-day mortality and/or AKI within seven days. Serial measurements of penKid improved the prediction of outcome compared to penKid_{admin} alone. PenKid allowed classification between patients with AKI, sub-AKI patients, and non-sub-AKI patients in terms of mortality. In septic patients, penKid_{admin} has been found to be associated with worse outcomes (i.e., major acute kidney events, AKI and worsening renal function) if measured in a timely manner [18].

The actual definition of AKI is based on urine output and/or Screat [6]. Both biomarkers have limitations, particularly in severely burned patients. Indeed, the large amount of fluid received by severe burn patients in the first 48 hours increases the Screat volume of distribution and decreases the ability to detect AKI early on [27]. A biomarker that relies on the detection of AKI in the presence of oliguria or increased Screat would be useless, but biomarkers such as penKid could find a place in the early detection of patients who were not detected by classical biomarkers for sub-AKI-

In the present study, the reasons why penKid_{admin} did not significantly add value to Screat_{admin} to predict AKI might be several. First, we compared penKid to the biomarkers defining AKI in its current definition making unlikely to perform better (i.e. penkid is unlikely to be more

specific than Screat). Second, penkid might meet the same limits than Screat regarding its kinetic and progressive increased after glomerular filtration rate has dropped. Importantly, penKid was high in a substantial number of patients who did not meet the current definition for AKI. Those patients defined as sub-clinical AKI had higher mortality risks compared to patients with low penKid (i.e. non-sub-clinical AKI patients). Altogether, these findings strongly suggest that penKid allows for the identification of patients who do not fall into the current definition but still show a glomerular filtration rate (GFR) decrease and an increased risk of death. Penkid might identify some episodes of AKI before Screat has raised (i.e. with higher sensitivity). This latter hypothesis would ideally need confirmation using real time measurement of glomerular filtration rate. Even when Screat elimination is impaired due to low GFR, Screat can remain within the normal range for many reasons (e.g., decrease of creatinine production in an inflammatory state or in patients with low muscle mass, increase of volume of distribution) [7,29]. Screat might therefore have limited value to detect mild drops in GFR [30]. Altogether, Screat might not lack sensitivity to detect some episodes of AKI in critically ill burn patients. If confirmed in larger studies, the present results could allow practitioners to refine the definition of AKI by using penKid for earlier detection of AKI and AKI episodes not detected by Screat. This earlier detection could enable earlier therapeutic intervention that could improve outcome. However, this hypothesis has to be proven in a randomized controlled trial (RCT) comparing a resuscitation strategy based on penKid results with a resuscitation strategy based on the usual standard of care. Furthermore, whether an early intervention targeting a decrease in penkid_{admin} after admission could improve renal and global outcome needs to be evaluated in burn patients [31].

A limitation of the present study is its relatively low number of patients. However, the results are consistent with those observed in different clinical settings and in bigger populations, and they represent a rather large sample size of severe burn patients [18]. Second, penKid_{admin} has

neither been compared to the gold standard method for glomerular filtration rate (i.e., inulin clearance) nor to alternative biomarkers of kidney injury in burns (i.e., cystatin C, insulin-like growth-factor binding protein 7 and tissue inhibitor of metalloproteinase 2). In this line, the lack of comparator biomarker for mortality is also a limitation.

Conclusion

PenKid_{admin} concentration was associated with risk of mortality and AKI in burn patients. It added value on top of creatinine and SOFA to predict 90-day mortality. Sub-AKI detected with penKid was associated with an increased risk of death. However, penKid did not add value over Screat for predicting AKI, as currently defined.

Conflict of interest statement

FD has no conflict of interest.

AP has no conflict of interest.

JA has no conflict of interest.

MCo has no conflict of interest.

MCh has no conflict of interest.

JS and OH are employed by Sphingotec GmbH, a company that holds patent rights in and commercializes the penKid assay.

MJ has no conflict of interest.

AF has no conflict of interest.

HO has no conflict of interest.

AC has no conflict of interest.

SS has no conflict of interest.

MB has no conflict of interest.

LG has no conflict of interest.

AM has received speaker's honoraria and fees from Novartis, Orion, and Servier. AM is also a member of the advisory board and/or steering committees of Cardioentis, Adrenomed, Sphingotec, Sanofi, Roche, Abbott, and Bristol-Myers Squibb.

JT is employed by Biomerieux.

ML has received research grants from the French Ministry of Health, lecture fees from Baxter and Fresenius, and research support from Sphingotec.

Authors' contributions

FD collected data, contributed to the interpretation of the data, and helped draft the manuscript.

AP collected data, contributed to the interpretation of the data, and helped draft the manuscript.

JA collected data, contributed to the interpretation of the data, and helped draft the manuscript.

LFP collected data, contributed to the interpretation of the data, and helped draft the manuscript.

MCo collected data, contributed to the interpretation of the data, and helped draft the manuscript.

MCh collected data, contributed to the interpretation of the data, and helped draft the manuscript.

JS performed penKid measurements, contributed to the interpretation of the data, and helped draft the manuscript.

OH performed analysis, contributed to the interpretation of the data, and helped draft the manuscript.

MJ collected data, contributed to the interpretation of the data, and helped draft the manuscript.

AF collected data, contributed to the interpretation of the data, and helped draft the manuscript.

HO collected data, contributed to the interpretation of the data, and helped draft the manuscript.

AC collected data, contributed to the interpretation of the data, and helped draft the manuscript.

SS collected data, contributed to the interpretation of the data, and helped draft the manuscript.

MB collected data, contributed to the interpretation of the data, and helped draft the manuscript.

LG collected data, contributed to the interpretation of the data, and helped draft the manuscript.

AM conceived the study, contributed to the interpretation of the data, and helped draft the manuscript.

JT collected data, contributed to the interpretation of the data, and helped draft the manuscript.

ML conceived the study, contributed to the interpretation of the data, and helped draft the manuscript.

All of the authors read and approved the final manuscript.

Acknowledgments

The authors would like to thank the clinical research assistants and Elisabeth Cerrato from the joint research unit HCL/bioMérieux for their technical assistance with the samples.

Funding

This study was supported by a grant from the “Association des Gueules cassées” awarded to ML. Measurement of penKid was funded by Sphingotec.

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Tables

Table 1: Patient characteristics

	Total	90-day survivors	90-day non-survivors	
Patient characteristics	N = 113	N = 77	N = 36	p-value
Sex				
Male (n %)	73 (64.6)	53 (68.8)	20 (55.6)	0.2445
Age (year range)	48 (33–64)	42 (29–58)	56 (46–77)	0.0014
Medical history				
Cardiopathy (n %)	3 (2.7)	2 (2.6)	1 (2.8)	1.0000
COPD (n %)	4 (3.5)	3 (3.9)	1 (2.8)	1.0000
CKD (n %)	5 (4.4)	1 (1.3)	4 (11.1)	0.0612
Chronic HBP (n %)	27 (23.9)	14 (18.2)	13 (36.1)	0.0649
Psychiatric (n %)	35 (31)	23 (29.9)	12 (33.3)	0.8787
Burn characteristics				
TBSA (%)	35 (25–53)	31 (24–45)	57 (31–70)	<0.0001
Deep burn BSA (%)	21 (10–40)	18 (8–30)	42 (17–60)	<0.0001
Inhalation injury (n %)	55 (48.7)	29 (37.7)	26 (72.2)	0.0013
Characteristics during hospitalization				
Mechanical ventilation (n %)	84 (74.3)	54 (70.1)	30 (83.3)	0.2055
Screat (μmol/l)	72.5 (57.5–92.75)	70 (55.8–81.2)	90.5 (67.8–130.8)	0.0004
Lactate (mmol/l)	3.45 (1.9–5.52)	2.6 (1.7–4.4)	5.2 (3.5–7.9)	<0.0001
Bilirubin (mmol/l)	14.1 (9.38–21.6)	12.9 (9.0–19.3)	18.0 (10.9–24.8)	0.1094
Platelet (G/l)	250 (189–315)	236 (189–280)	279 (194–368)	0.0279
Length of hospitalization (days)	90 (38–90)	90 (90–90)	18 (2–31)	<0.0001
RRT (n %)	24 (21.2)	5 (6.5)	19 (52.8)	<0.0001
Severity scores				
SOFA	4 (1–7)	2 (0–4)	6.5 (4–9)	<0.0001

ABSI	8 (7–11)	8 (6–9)	11 (9–13)	<0.0001
SAPS2	33 (23–49)	28 (20–42)	47 (33–61)	<0.0001
UBS	100 (54–165)	84 (46–128)	184 (89–246)	<0.0001

COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; HBP: high blood pressure; TBSA: total burn surface area; ECMO: extracorporeal membrane oxygenation; Screat: plasmatic creatinine at admission; RRT: renal replacement therapy; SOFA score: simplified organ failure assessment; ABSI: abbreviated burn severity index; UBS: unit burn standard; SAPS 2: the simplified acute physiology score 2

Table 2: Univariate and multivariate analysis of factors associated with 90-day mortality

	Univariable			
	c-index	HR (95% CI)	p-value	
penKid_{admin}	0.712	3.1 (2.0–5.0)	<0.00001	
Screat	0.707	2.8 (1.9–4.3)	<0.00001	
SOFA score	0.752	3.9 (2.4–6.4)	<0.00001	
ABSI	0.755	3.3 (2.2–5.1)	<0.00001	
Age, TBSA, inhalation injury				
• Age	0.67	2.9 (1.7–4.9)	0.00012	
• TBSA	0.696	2.5 (1.7–3.7)	0.00001	
• Inhalation injury	0.646	3.4 (1.6–7.0)	0.00052	
	Bivariable and multivariable			
	c-index	Added chi ² penKid	p-value penKid	HR _{adj} (95% CI)
penKid_{admin} + Screat	0.738	5.11	0.02374	1.9 (1.1–3.4)
penKid_{admin} + SOFA score	0.787	14.94	0.00011	2.1 (1.1–4.1)
penKid_{admin} + ABSI	0.794	16.4	0.00005	3.3 (2.2–5.1)
penKid_{admin} + Age, TBSA, inhalation injury	0.839	19.8	<0.0001	3.2 (1.9–5.5)

PenKid_{admin}: proenkephalin dosage at admission; Screat: serum creatinine at admission;

SOFA score: simplified organ failure assessment; ABSI: abbreviated burn severity index;

TBSA: total burn surface area

Figure legends

Figure 1: The left panel represents the survival Kaplan–Meier curve depending on penKid_{admin} quartiles (the legend gives quartile ranges for penKid in pmol/L). The right panel represents an illustration of the added value of penKid_{day 3} using a cutoff point of 80 pmol/L at admission and day 3. Patients without penKid data from day 3 were left in the subgroup they were assigned to on day 1. HH: patients above 80 pmol/L on admission and at day 3; HL: patients above 80 pmol/L on admission and below 80 pmol/L at day 3; LL: patients below 80 pmol/L on admission and on day 3. One patient, who survived until day 81, was below 80 pmol/L on admission and above 80 pmol/L on day 3 (omitted from the figure due to low sample size).

Figure 2: Illustration of combined endpoint: boxplot of the four groups (from left to right) survivors without AKI, survivors with AKI, deaths without AKI, deaths with AKI (the median penKids for the four groups are 51.6, 81.5, 80.6, and 88.9 pmol/L, respectively; $p < 0.001$). PenKid is elevated in all groups with AKI and/or deaths compared to survivors without AKI (all post-hoc $p \leq 0.01$).

Figure 3: Survival Kaplan–Meier curve of patients with no AKI, sub-AKI, and with AKI ($p < 0.001$).

Supplementary data:

Flow chart

Figure 1

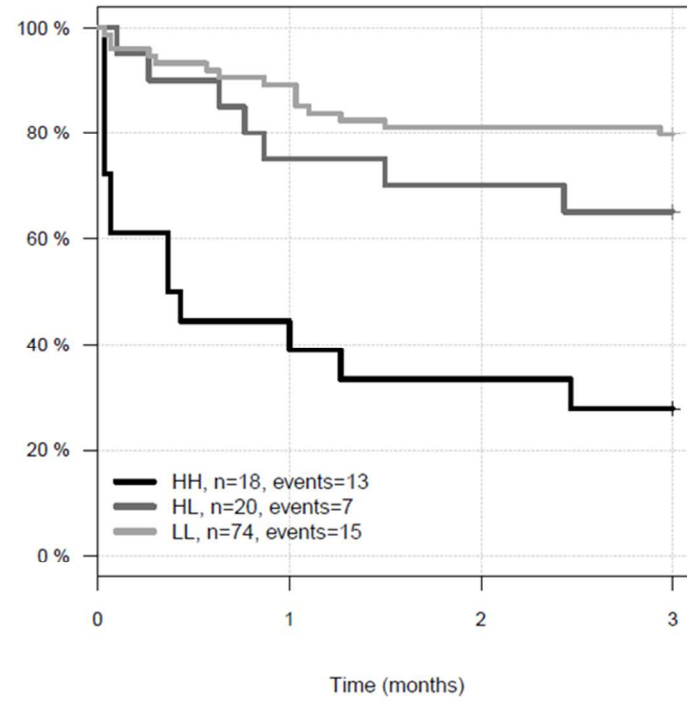
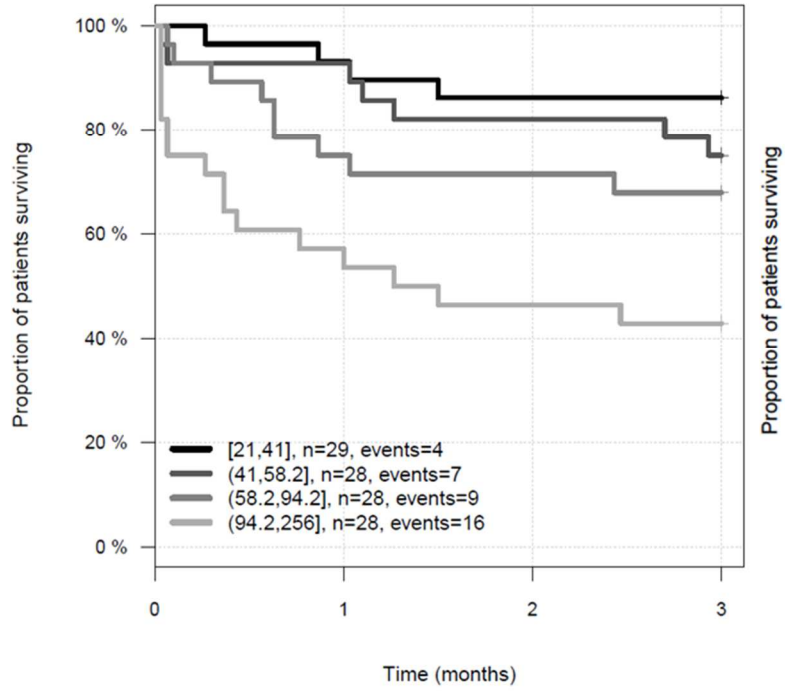


Figure 2

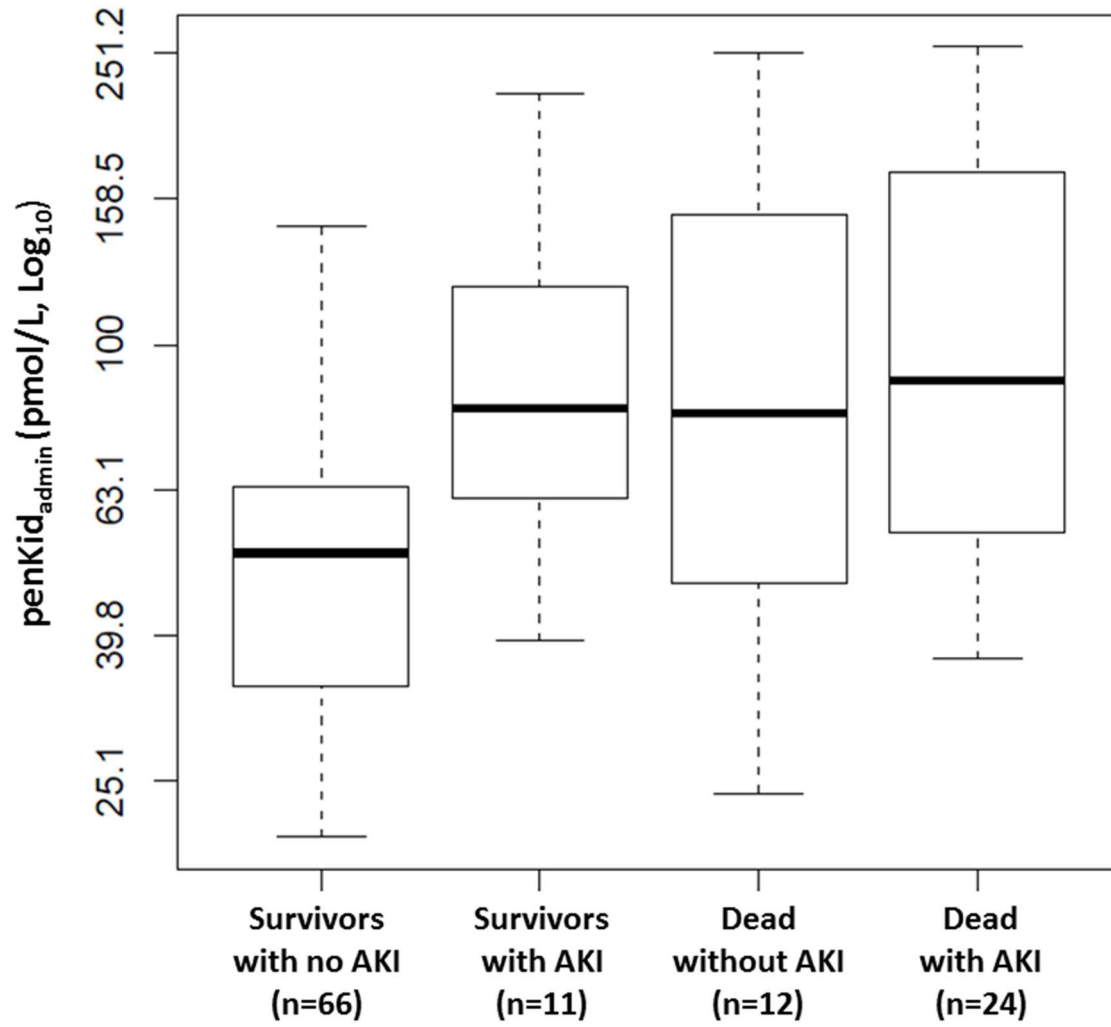


Figure 3

