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Prognosis of critically ill patients with severe acute kidney injury and high circulating dipeptidyl peptidase 3: a *post hoc* analysis of the AKIKI 2 trial

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Christophe Vinsonneau passed away during the completion of the study, this paper is dedicated to his memory.

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Abstract

Background: Acute kidney injury (AKI) is a frequent and severe complication among critically ill patients. Circulating dipeptidyl peptidase 3 (cDPP3), an enzyme released upon cellular injury, has been implicated in hemodynamic instability and organ dysfunction. Its role in severe AKI remains poorly defined. We aimed to assess the prognostic significance of cDPP3 in critically ill patients with severe AKI.

Methods: In this *post hoc* analysis of the AKIKI 2 study, we included ICU patients with severe AKI (KDIGO stage 3) who were receiving (or had received) invasive mechanical ventilation and/or vasopressor support and had available blood samples at inclusion. Patients were stratified according to cDPP3 concentration using a predefined cutoff of 40 ng/mL. The primary outcome was 28-day mortality; secondary outcomes were organ support-free days.

Results: Among 287 included patients, 143 (49.8%) had cDPP3 concentrations above 40 ng/mL. High cDPP3 was associated with increased 28-day mortality (hazard ratio 1.95; 95% confidence interval 1.37–2.87, $p < 0.001$). Furthermore, high cDPP3 was associated with fewer days alive without vasopressors (mean difference -5.59 ; 95% CI -8.29 to -2.78 , $p < 0.001$), invasive mechanical ventilation (mean difference -6.23 ; 95% CI -8.89 to -3.36 , $p < 0.001$), or renal replacement therapy (mean difference -6.35 ; 95% CI -9.14 to -3.26 , $p < 0.001$). After adjustment for baseline markers of severity, both the associations with 28-day mortality and organ support-free days remained significant.

Conclusions: In critically ill patients with severe AKI, a high cDPP3 concentration at diagnosis is associated with increased short-term mortality and prolonged dependence on organ support

Keywords: Acute Kidney Injury, Circulating dipeptidyl peptidase 3, circulatory failure, biomarkers

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Introduction

Acute kidney injury (AKI) is a frequent and severe complication among critically ill patients. It is often triggered by complex systemic insults such as sepsis, shock, and multiorgan failure. In this context, the pathogenesis of AKI is typically multifactorial, involving a dynamic interplay between hemodynamic instability, inflammation, neurohormonal dysregulation, and intrinsic renal factors. In its most severe forms, AKI requiring renal replacement therapy (RRT) is associated with prolonged intensive care unit (ICU) stay, increased healthcare resource utilization, and a markedly elevated risk of both short- and long-term mortality [1].

In an effort to better understand the underlying mechanisms and improve risk stratification, considerable interest has emerged in the identification of novel biomarkers that reflect pathophysiological processes beyond conventional indicators of organ dysfunction. Circulating dipeptidyl peptidase 3 (cDPP3) has recently garnered attention as a biomarker of acute cellular injury and hemodynamic compromise. When released into the circulation in excess, presumably as a consequence of massive cellular injury, cDPP3 can exert deleterious hemodynamic effects through the degradation of angiotensin II, a key vasopressor peptide involved in maintaining vascular tone and organ perfusion [2,3]. At the renal level, the loss of angiotensin II-mediated vasoconstriction of the efferent arteriole reduces intraglomerular pressure and subsequently impairs glomerular filtration. This mechanism is particularly relevant in septic AKI, where early dysregulation of the renin-angiotensin-aldosterone system (RAAS) might be a key factor contributing to the initiation of renal

dysfunction [4]. However, similar pathophysiological processes may also be involved in non-septic inflammatory states. Moreover, given the pleiotropic actions of angiotensin II encompassing regulation of vascular tone, endothelial permeability, sodium homeostasis, and immune modulation, its depletion may have far-reaching consequences in the critically ill. As such, cDPP3 may represent both a marker and a potential mediator of severity in critically ill patients [3].

The MARKISIO study, an ancillary analysis of the AKIKI 2 trial, recently explored the ability of a panel of biomarkers, including cDPP3, to predict the onset of evidence-based criteria for RRT initiation in patients with severe AKI [5,6]. While cDPP3 was independently associated with the early development of RRT criteria in multivariable analysis, its overall discriminative performance was modest (area under the receiver operating characteristic curve below 0.65). Importantly, the study was not designed to examine the hemodynamic or clinical phenotype of patients with elevated cDPP3, nor to explore its prognostic implications beyond short-term RRT indications. To date, therefore, the clinical role and prognostic significance of elevated cDPP3 in patients with severe AKI remain poorly characterized. Although elevated cDPP3 has been consistently associated with poor outcomes in various circulatory failure contexts [7-11], no study to date has specifically investigated its prognostic significance in patients suffering severe AKI.

The present study aimed to address this gap by leveraging the biobanked cohort of the AKIKI 2 study to explore the association between baseline cDPP3 concentration and clinical outcomes. We hypothesized that

elevated cDPP3 would identify a distinct population with more severe circulatory dysfunction and worse clinical trajectories.

Methods

Study design and population

This is a *post hoc* analysis of a biobanked cohort derived from the AKIKI 2 study, a multicenter randomized study comparing two RRT initiation strategies in critically ill patients with severe AKI [6]. The AKIK2 study was composed by 2 stages (observational and randomization stages). Patients who were receiving (or had received) invasive mechanical ventilation and/or vasopressor support and who had AKI stage 3 of the KDIGO classification were included in the observational stage. For the present study, we included patients from this observational stage who had available samples for cDPP3 measurement at baseline, which is the time of AKI diagnosis, according to KDIGO stage 3 criteria.

Ethical aspects

The study protocol, including the biobank collection, was approved by the competent French legal authority (Comité de Protection des Personnes Sud-Est V) for all participating centers. Patients or their surrogate gave informed consent for inclusion in the AKIKI 2 trial, including the secondary measurement of biochemical markers from the blood biobanked at inclusion. All procedures and analyses were performed in accordance with

the guidelines of the International Conference on Harmonization and Good Clinical Practice.

Data collection and follow-up

Clinical and biological data were collected prospectively at inclusion and up to day 60, including demographics, comorbidities, presumed cause of AKI, exposure to potential nephrotoxic agents, SAPS III score and organ support requirement. Vasopressor use was recorded as norepinephrine base equivalent, as previously described [12,13]. Of note, no patient received vasopressin or angiotensin II, as these agents were not used in France at the time of the AKIKI 2 study. The occurrence of supraventricular arrhythmia (atrial fibrillation or flutter) was also documented.

Biobank and cDPP3 measurement

Across centers, baseline blood was collected at inclusion for the observational stage of AKIKI-2, then, when feasible, processed on site, the plasma stored at -80°C , and subsequently shipped to the central biobank (Bichat Hospital, Paris, France). cDPP3 concentration was measured in ethylenediaminetetraacetic acid plasma using a luminescence immunoassay (4TEEN4 Pharmaceuticals GmbH, Hennigsdorf, Germany) as previously described, blinded to clinical data [14]. For reference, using this technique, median cDPP3 in a general adult population is 14 ng/mL (IQR 11–19 ng/mL) and the 97.5th percentile is 40 ng/mL [15]. The value of 40 ng/mL is the most frequently used cutoff in recent literature for cDPP3 [7,11,16]. Based on this reference value, patients were subsequently

categorized into two groups according to their baseline cDPP3 concentration: those with high cDPP3 (>40 ng/mL) and those with low cDPP3 (≤ 40 ng/mL).

Outcomes

The primary outcome was 28-day all-cause mortality, assessed from the date of inclusion. Secondary outcomes included organ support-free days (the number of vasopressor-free, ventilator-free and RRT-free days) within the first 28 days following inclusion, ICU length of stay as well as hemodynamic outcomes over the first 72 hours, including the absolute change in norepinephrine-equivalent dose from day 1 to day 3, the administration of fluid boluses, vasopressor escalation (initiation or increased dose for ≥ 1 hour), and the new onset of supraventricular arrhythmia (atrial flutter or atrial fibrillation).

To minimize survivorship bias, patients who died before day 3 were assigned “worst-case” values: $1.10 \mu\text{g/kg/min}$ for norepinephrine-equivalent dose variation (99th percentile of observed values in survivors), and a value of 1 for all hemodynamic binary outcomes. Similarly, patients dead by day 28 were assigned 0 organ support-free days. Thus, in the whole population (including decedents and survivors), organ support-free days is similar to “days alive without organ support”.

Statistical analyses

Patients were stratified based on baseline cDPP3 concentration using the predefined threshold of 40 ng/mL. Continuous variables were expressed as

medians [interquartile ranges] and compared using the Kruskal-Wallis test. Categorical variables were expressed as counts (percentages) and compared using Fisher's exact test or the chi-squared test, as appropriate.

The primary outcome, 28-day mortality, was analyzed using a Cox proportional hazards model. Secondary outcomes were analyzed as mean differences for organ support-free days and norepinephrine-equivalent dose variation, and as risk ratios for binary hemodynamic events.

To address potential confounding, adjusted analyses of 28-day mortality and organ support-free days were performed using a propensity score approach with inverse probability of treatment weighting, based on pre-specified baseline covariates (SAPS III score, catecholamine infusion, invasive mechanical ventilation, presence of septic shock, and time from ICU admission to AKI ≥ 7 days). Propensity score was estimated using a multivariable logistic regression, after multicollinearity was excluded through variance inflation factors. Quality of covariate balance after weighting was assessed through standardised mean difference, which remained < 0.10 . Missing covariate data were handled through multiple imputation by chained equations (10 imputations). Propensity score estimation and weighting were conducted within each imputed dataset [17].

Sensitivity analyses included modeling cDPP3 as a continuous variable after \log_{10} -transformation to assess its linear association with 28-day mortality, and restricting the analysis of organ support-free days to 28-day survivors.

All confidence intervals were generated using non-parametric bootstrapping (10,000 iterations), avoiding model misspecification. Proportional hazard assumptions were verified using scaled Schoenfeld residuals and Harrel's test. No power calculation was *a priori* performed. A p value < 0.05 was considered significant, without correction for multiple testing. All analyses were performed using R version $\geq 4.2.2$ (CRAN).

Results

Study population

Among 767 patients enrolled in the observational stage of the AKIKI 2 trial, 287 had available blood samples (**Supplemental figure 1**). The cohort was stratified into low and high cDPP3 subgroups based on the predefined cutoff of 40 ng/mL: 144 patients (50.2%) had a cDPP3 ≤ 40 ng/mL (low cDPP3 group) and 143 patients (49.8%) had a cDPP3 > 40.0 ng/mL (high cDPP3 group). Patient characteristics according to cDPP3 concentration are presented in **Table 1**. Compared to the low cDPP3 group, patients in the high cDPP3 group met criteria for inclusion in the AKIKI 2 trial sooner after ICU admission (median 1.00 [IQR, 1 to 2] vs 1.00 [IQR, 1 to 3] days, $p = 0.008$), had significantly higher SOFA (median 11, [IQR, 9 to 14] vs 10 [IQR, 8 to 12]; $p = 0.006$), heart rate (median 118 [IQR, 101 to 132] vs 103 [IQR, 85 to 122] beats per min; $p < 0.001$) and lactate concentration (median 3.4 [IQR, 2.2 to 6.6] vs 1.8 [IQR, 1.2 to 2.5] mmol/L; $p < 0.001$), were more frequently invasively ventilated (76.1% vs 62.9%; $p = 0.023$), required higher doses of vasopressors (median norepinephrine-equivalent dose 0.16 [IQR, 0.00 to 0.42] vs 0.08 [IQR, 0.00 to 0.25] $\mu\text{g}/\text{kg}/\text{min}$, $p =$

0.016) and had significantly lower prothrombin activity (median 47% [IQR, 34 to 63] vs 64% [IQR, 49 to 77], $p < 0.001$) and urine output (median 250 [IQR, 56 to 700] vs 475 [IQR, 195 to 1000] mL/24h, $p < 0.001$) at inclusion. The distribution of AKI etiologies did not differ between groups, except for rhabdomyolysis, which was more frequent in the high cDPP3 group (12.6% vs 3.5%, $p = 0.009$).

Primary outcome

By day 28, 115 (40.1%) patients had died. Mortality was significantly higher in the high cDPP3 group (71/143; 49.7%) compared to the low cDPP3 group (44/144; 30.6%), with a hazard ratio of 1.95 (95% confidence interval [CI], 1.37 to 2.87, $p < 0.001$ **Figure 1**). After propensity score weighting based on SAPS III score, catecholamine infusion, invasive mechanical ventilation, septic shock, and time from ICU admission to AKI ≥ 7 days, the association remained significant (weighted hazard ratio 1.83; 95% CI 1.26 to 2.76; $p = 0.002$). Covariate balance after propensity score weighting is shown in Supplemental Figure S2. When analyzed as a continuous variable, cDPP3 remained associated with 28-day mortality, with a hazard ratio of 2.81 (95%CI 1.96–4.02), per tenfold increase ($p < 0.001$).

Secondary outcomes

Compared to the low cDPP3 group, patients with elevated cDPP3 had significantly fewer organ support-free days at day 28 (**Table 2**). The mean number of vasopressor-free days was lower in the high cDPP3 group (mean

difference -5.59 ; 95% CI -8.29 to -2.78 , $p < 0.001$). Similarly, the high cDPP3 group had fewer ventilator-free days (mean difference -6.23 ; 95% CI -8.89 to -3.36 , $p < 0.001$) and fewer RRT-free days (mean difference -6.35 ; 95% CI -9.14 to -3.26 , $p < 0.001$). After propensity score weighting based on the same baseline covariates, elevated cDPP3 remained associated with fewer ventilator-free days (adjusted mean difference -5.03 ; 95% CI -7.67 to -2.42), fewer vasopressor-free days (adjusted mean difference -5.05 ; 95% CI -8.00 to -2.14), and fewer RRT-free days (adjusted mean difference -5.93 ; 95% CI -8.97 to -2.86) (Supplemental Table 1). To assess the impact of early mortality on secondary outcomes, a sensitivity analysis was conducted excluding patients who died before day 28 (**Supplemental Table 2**). In this restricted population, patients with elevated cDPP3 still had fewer ventilator-free days (mean difference -4.37 ; 95% CI -7.47 to -1.17), fewer RRT-free days (mean difference -3.31 ; 95% CI -5.89 to -0.79), and fewer vasopressor-free days (mean difference -1.6 ; 95% CI -3.17 to -0.09). No significant difference was observed in ICU length of stay between groups (median 10 days in both groups; mean difference -0.49 ; 95% CI -7.67 to 5.03). Additionally, no significant difference was observed in the change of vasopressor dose between day 1 and day 3 between both groups (median 0 [IQR -0.06 to 0.01] in patients with low cDPP3 concentration vs 0 [IQR -0.13 to 0.00] $\mu\text{g}/\text{kg}/\text{min}$, mean difference 0.02 ; 95% CI, -0.12 to 0.15 , $p = 0.805$). Similarly, short-term hemodynamic outcomes did not differ significantly between groups (**Table 3**).

Discussion

In this *post hoc* analysis of the AKIKI 2 cohort, we investigated the prognostic implications of cDPP3 concentration at the time severe AKI diagnosis. Our results demonstrate that a high cDPP3 concentration was independently associated with increased 28-day mortality in this population. Moreover, patients with elevated cDPP3 had significantly fewer vasopressor-free, ventilator-free and RRT-free days, but no significant differences were observed in short-term hemodynamic outcomes.

A greater proportion of AKI cases attributed to rhabdomyolysis was observed in the high cDPP3 subgroup. This finding suggests that elevated cDPP3 may, at least in some circumstances, reflect massive cellular injury and cytosolic enzyme release, as observed during skeletal muscle breakdown [18,19]. In addition, although the association between elevated cDPP3 and increased risk of death or need for organ support was robust, no statistically significant differences were observed for early hemodynamic events including vasopressor dose escalation, fluid resuscitation, or arrhythmia. This may be explained by differences in baseline cardiovascular status between groups, with patients in the high cDPP3 group receiving vasopressors at higher dose. Additionally, a substantial delay between ICU admission and inclusion may have limited the ability to detect acute hemodynamic deterioration, as part of the instability may have already occurred prior to biomarker measurement. Although the association with poorer prognosis was robust to adjustment for the delay between ICU admission and inclusion, a different timing of

cDPP3 measurement (*e.g.*, at time of ICU admission, or diagnosis of shock) may better discriminate early hemodynamic trajectories.

These findings expand upon prior studies linking high cDPP3 with adverse outcomes in septic and cardiogenic shock by characterizing its relevance in the setting of severe AKI [7,10,11,15]. While the MARKISIO study had previously shown a modest association between cDPP3 and the early fulfilment of RRT initiation criteria, it did not assess clinical trajectories or longer-term outcomes [5]. Our study provides a more comprehensive description of the clinical status and prognosis associated with elevated cDPP3, suggesting that this biomarker may reflect both the severity of cellular injury and an ongoing pathophysiological process contributing to multiorgan failure. Notably, given that DPP3 has a molecular weight of approximately 83 kDa, exceeding the glomerular filtration threshold, it is unlikely to be cleared via glomerular filtration. Consequently, the rise in cDPP3 concentration observed in severe AKI is unlikely to result from reduced renal clearance alone.

This work highlights several avenues for future research. Longitudinal assessment of cDPP3 kinetics may offer additional prognostic insights and help elucidate causal mechanisms. The potential of cDPP3 as a therapeutic target warrants investigation, particularly in light of its involvement in angiotensin II degradation and circulatory failure and the proof-of-concept data that cDPP3 inhibition improves hemodynamics in an experimental model of septic shock [20]. Furthermore, incorporating cDPP3 into multimodal prognostic models could enhance risk stratification

and individualized management strategies in patients with severe AKI and may also support enrichment strategies in future clinical trials in this field.

This study has several methodological strengths. It is based on a large, multicenter, prospective cohort derived from a rigorously conducted randomized controlled trial. Biomarker measurement was centralized and performed blinded to clinical data, reducing the risk of measurement bias. Nevertheless, important limitations should be acknowledged. First, as a *post hoc* analysis of a prospective cohort, it was not initially designed to specifically assess the prognostic value of cDPP3. As such, residual confounding cannot be ruled out despite adjustment for predefined baseline severity markers. Second, cDPP3 was measured at a single time point, precluding assessment of its temporal kinetics and limiting insight into whether changes in its concentration over time correlate with clinical deterioration or recovery. In addition, because biomarker measurement was performed at the time of AKI diagnosis, often several days after ICU admission, part of the hemodynamic instability may already have resolved by the time of sampling, potentially underestimating associations with early cardiovascular events. Several potentially relevant variables, such as urinary biochemistry, had substantial missing data and could therefore not be included in the analyses. Ideally, measurements of renin and RAS peptides would have been interesting to provide mechanistic insights; however, the stringent pre-analytical conditions these labile analytes require were not ensured. Finally, reverse causation cannot be excluded: elevated cDPP3 concentration may reflect overall severity rather than play a specific role in hemodynamic instability or organ failure. Nonetheless,

the availability of anti-cDPP3 antibodies opens a potential pathophysiological and therapeutic avenue, and the present work may provide an incentive for a prospective trial of such a targeted strategy

Conclusion

High cDPP3 concentration is associated with increased short-term mortality and prolonged organ support in critically ill patients with severe AKI. These findings support the role of cDPP3 as a prognostic biomarker in this population and encourage further investigation into its biological and therapeutic significance.

Abbreviations

AKI: acute kidney injury

RRT: renal replacement therapy

ICU: intensive care unit

(c)DPP3: (circulating) dipeptidyl peptidase 3

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Author contributions

KC, AP, JB, DD and SG were responsible for the design, analysis, and writing of the manuscript. KC, AP, AM, FA and SG were responsible for the organization of the samples collection and the measurements of biomarkers GL, LML, DTB, BL, SB, JB, GC, NC, SB, CV, JMF, DT, GL, SN,

JM, KK, JR, JDR and JPQ were responsible for recruitment and clinical care of the patients. All authors reviewed and approved the final version of the manuscript.

Statements and declaration

The AKIKI 2 trial was promoted by the Assistance Publique - Hôpitaux de Paris and funded by a grant of the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2016; AOM16278). Circulating dipeptidyl peptidase 3 concentration was measured free of charge by 4TEEN4 Pharmaceuticals GmbH, Hennigsdorf, Germany. The Cardiovascular Markers in Stress Conditions Research Group is supported by a research grant from 4TEEN4 Pharmaceuticals GmbH.

Availability of data and material

Restrictions apply to the availability of these data and so are not publicly available. However, data are available from the authors upon reasonable request under the supervision of AP-HP, Hôpital Bichat-Claude Bernard, Département d'Épidémiologie, Biostatistique et Recherche Clinique, F-75018 Paris, France.

Ethics approval and consent to participate

The study protocol, including the biobank collection, was approved by the competent French legal authority (Comité de Protection des Personnes de Sud-Est V) for all participating centers. Patients (or their surrogates) who

were included were informed about the study both verbally and with a written document in accordance with French law.

Consent for publication

Not applicable.

Competing interests

The AKIKI 2 trial was promoted by the Assistance Publique—Hôpitaux de Paris and funded by a grant of the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2016; AOM16278). Circulating DPP3 concentration was measured free of charge by 4TEEN4 Pharmaceuticals GmbH, Hennigsdorf, Germany. The Cardiovascular Markers in Stress Conditions Research Group is supported by a research grant from 4TEEN4 Pharmaceuticals GmbH, which allowed salary support for A. Picod. A. Mebazaa received fees as a member of advisory board from Spingotec. The other authors declare no competing interest regarding the submitted work.

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Figures and tables

Table 1. Patients' characteristics. cDPP3^{LOW} and cDPP3^{HIGH} subgroups refer to patients with cDPP3 \leq 40 ng/mL and $>$ 40 ng/mL, respectively. Septic shock was defined as sepsis induced hypotension despite fluid resuscitation of at least 30 mL/kg intravenous fluid administered within the period spanning the 4 h before and 4 h after initiation of vasopressor therapy. * 5 most frequent reasons for ICU admission, other less frequent reasons are not displayed. \$ Multiples causes per patient could apply. cDPP3: circulating dipeptidyl peptidase 3; ICU: intensive care unit; RAAS: renin-angiotensin-aldosterone system; ACEi: angiotensin-converting enzyme inhibitors; ARB: Angiotensin II, type 1 receptor blockers; AKI: acute kidney injury. MAP: Mean arterial pressure, NED: norepinephrine-equivalent dose

	Available N	cDPP3 ^{LOW} N=144	cDPP3 ^{HIGH} N=143	p
Demographics				
Age	287	68.0 (57.8- 75.0)	67.0 (60.0- 77.0)	0.778
Sex	287			0.593
Female		50 (34.7%)	55 (38.5%)	
Male		94 (65.3%)	88 (61.5%)	
Delay between ICU admission and inclusion, days	287	1.00 [1.00- 3.00]	1.00 [1.00- 2.00]	0.008
Comorbidities				
Hypertension	287	79 (54.9%)	78 (54.6%)	1.00
Diabetes	287	46 (31.9%)	42 (29.4%)	0.730
Heart failure	287	9 (6.3%)	5 (3.5%)	0.419
Cancer	287	22 (15.3%)	15 (10.5%)	0.555
Hemopathy	287	12 (8.3%)	9 (6.3%)	0.662
Immunosuppression	287	9 (6.3%)	6 (4.2%)	0.605

Organ transplantation	287	3 (2.1%)	3 (2.1%)	1.00
Prior use of RAAS inhibitors				
ACEi	286	33 (22.9%)	29 (20.4%)	0.713
ARB	286	21 (14.5%)	27 (19.0%)	0.399
Main reasons for ICU admission*				
Cardiac arrest	287	4 (2.8%)	5 (3.5%)	0.750
Septic shock	287	79 (54.9%)	78 (54.6%)	1.00
Cardiogenic shock	287	4 (2.8%)	11 (7.7%)	0.108
Hemorrhagic shock	287	9 (6.3%)	11 (7.7%)	0.804
Anaphylactic shock	287	8 (5.6%)	5 (3.5%)	0.579
Cause of AKI[§]				
Shock	287	112 (77.8%)	119 (83.2%)	0.311
Sepsis	287	92 (63.9%)	97 (67.8%)	0.562
Rhabdomyolysis	287	5 (3.5%)	18 (12.6%)	0.009
Nephrotoxic agent	287	21 (14.6%)	15 (10.5%)	0.385
Clinical and biological characteristics				
SOFA	258	10 [8-12]	11 [9-14]	0.006
SAPS-3	254	69 [60-80]	71 [63-81]	0.433
Vasopressor	286	110 (79.9%)	113 (79.02%)	0.775
Vasopressor dose, NED	280	0.08 [0.00-0.25]	0.16 [0.00-0.42]	0.016
Invasive mechanical ventilation	285	90 (62.9%)	108 (76.1%)	0.023
MAP, mmHg	282	63 [57-69]	63 [57-72]	0.992
Heart rate, bpm	284	103 [85-122]	118 [101-132]	<0.001
PaO ₂ /FiO ₂	248	226 [145-322]	205 [137-263]	0.078
pH	260	7.32 [7.23-7.37]	7.29 [7.22-7.36]	0.122
Lactate, mmol/L	253	1.8 [1.2-2.5]	3.4 [2.2-6.6]	<0.001

Platelets, $\cdot 10^9/L$	249	170 [76-255]	130 [80-189]	0.072
Prothrombin time, %	208	64 [49-77]	47 [34-63]	<0.001
Creatinine, $\mu\text{mol/L}$	275	324 [247-402]	306 [241-391]	0.587
Urea (mmol/L)	275	23.5 [17.3-32.0]	23.0 [16.0-29.0]	0.186
Diuresis (mL)	275	475 [195-1000]	250 [56-700]	<0.001
Potassium (mmol/L)	275	4.4 [3.9-5.0]	4.7 [4.0-5.1]	0.170

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Table 2. Organ support-free days. cDPP3^{LOW} and cDPP3^{HIGH} subgroups refer to patients with cDPP3 \leq 40 ng/mL and $>$ 40 ng/mL, respectively. RRT: Renal replacement therapy.

Variable	cDPP3^{LOW}	cDPP3^{HIGH}	Mean difference	p
Ventilator-free days	18 [0-28]	0 [0-21]	-6.23 (-8.89; -3.36)	<0.001
Vasopressor-free days	25 [0-27]	2 [0-26]	-5.59 (-8.29; -2.78)	<0.001
RRT-free days	27 [0-28]	1 [0-28]	-6.35 (-9.14; -3.26)	<0.001

Table 3. Hemodynamic events. cDPP3^{LOW} and cDPP3^{HIGH} subgroups refer to patients with cDPP3 \leq 40 ng/mL and $>$ 40 ng/mL, respectively.

Variable	cDPP3^{LOW}	cDPP3^{HIGH}	Risk ratio	p
Vasopressor escalation	37/91 (40.7%)	48/98 (49.0%)	1.20 [0.88; 1.73]	0.246
Fluid bolus	38/91 (41.8%)	51/98 (52.0%)	1.25 [0.91; 1.74]	0.152
Supraventricular arrhythmia	18/91 (19.8%)	29/98 (29.6%)	1.50 [0.84; 2.76]	0.132

Figure 1. Day-28 mortality according to cDPP3. cDPP3^{LOW} and cDPP3^{HIGH} subgroups refer to patients with cDPP3 \leq 40 ng/mL and $>$ 40 ng/mL, respectively. cDPP3: circulating dipeptidyl peptidase 3.

