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Associations of dipeptidyl-peptidase 3 with short-term outcome in a mixed admission ICU-cohort

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ABSTRACT

Purpose: Biomarkers independently associated with outcome of intensive care unit (ICU) patients can improve risk assessment. The cytosolic protease dipeptidyl-peptidase 3 (DPP3) is released into the circulation upon cell necrosis. We aimed to investigate the prognostic properties of cDPP3 in a mixed-admission ICU cohort.
Materials and methods: Prospective observational study in 650 adult ICU patients. cDPP3 concentrations were measured at ICU admission (day 1), and on days 2 and 3.
Results: cDPP3 concentrations on days 1 and 2, but not on day 3 were associated with 28-day mortality; HR 1.36 (95%CI 1.01–1.83, $p = 0.043$) and HR 1.49 (95%CI 1.16–1.93, $p = 0.002$) for days 1 and 2, respectively. cDPP3 was also associated with acute kidney injury (AKI), with OR's of 1.31 (95%CI 1.05–1.64, $p = 0.016$), 1.87 (95%CI 1.51–2.34, $p < 0.001$) and 1.49 (95%CI 1.16–1.92, $p = 0.002$) for measurements performed on days 1, 2, and 3, respectively. In multivariate analyses including SOFA or APACHE-II scores, cDPP3 assessed at day 2 of admission remained an independent predictor of mortality and all-stage AKI.
Conclusions: In a mixed-ICU cohort, cDPP3 concentrations after start of initial treatment were independently associated with both mortality and development of AKI. Therefore, measurement of cDPP3 can improve risk-stratification provided by established disease severity scores.

1. Introduction

In critically ill patients, multiple pathophysiological and compensatory pathways are dysregulated [1,2]. While traditional disease severity scores such as the SOFA or APACHE-II scores may provide a reasonable prediction of a patient's outcome, they do not sufficiently address or quantify the substantial heterogeneity in causative dysregulated pathways present in critical illness. Thus, assessment of biomarkers that are associated with specific dysregulations of molecular pathways might improve the risk assessment of disease severity indexes, as they address heterogeneity among critically ill patients [1,2].

Dipeptidyl peptidase 3 (DPP3) is a ubiquitous cytosolic enzyme with only low concentrations present in the plasma of healthy subjects. DPP3 is released into the circulation upon cell necrosis [3], and once released into the bloodstream, it is involved in the degradation of several important regulators of vascular tone [4,5]. High concentrations of circulating (c)DPP3 were already found to be independently associated with impaired clinical outcomes in septic shock [5,6], cardiogenic shock [3,7] and major surgery patients [8,9].

In the present study, we investigated associations of cDPP3 concentrations measured on the first three days of ICU admission with 28-day mortality in a mixed-admission cohort of critically ill patients. Furthermore, as secondary aims, we explored associations between cDPP3 and development of acute kidney injury (AKI, as a representative of organ failure), as well as correlations between cDPP3 concentrations and other established, clinically relevant biomarkers.

2. Methods

2.1. Study design and population

We performed a single-center prospective cohort study including all patients admitted to the ICU of the Radboud university medical center from September 2018 until December 2019. The study was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent. All patients or legal representatives were informed about the study details and could decline to participate. The study was conducted in accordance with the

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declaration of Helsinki, including current revisions, and Good Clinical Practice guidelines.

2.2. Outcomes

28-day mortality was the study's primary endpoint. Development of (all-stage) AKI was a secondary prognostic endpoint, as a representative of organ failure. AKI was defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [10]. Correlations of cDPP3 with other clinically relevant biomarkers represented another secondary outcome.

2.3. Clinical parameters

Upon admission to the ICU, admission category, demographics (age, sex, body mass index [BMI]), organ dysfunction scores (acute physiologic assessment and chronic health evaluation II [APACHE II] [11], sequential organ failure assessment [SOFA] [12]), need for vasopressor treatment, need for invasive mechanical ventilation, and medical history were recorded. The following routine laboratory parameters were recorded on ICU admission and on each consecutive day on the ICU until discharge or death, with a maximum of 30 days: serum creatinine, ASAT, ALAT, Alkaline Phosphatase, γGT, bilirubin, creatinine, creatinine-kinase and serum lactate. At ICU admission, these clinical biomarkers were assessed in all patients, while later measurements were performed at the discretion of the attending physician.

2.4. Biomarker measurements

Ethylenediaminetetraacetic acid (EDTA)-anticoagulated blood for determination of cDPP3 concentrations was sampled within 2 h after ICU admission (day 1), while day 2 and 3 samples were acquired during morning lab rounds. Blood samples were centrifuged at 2000*g* at 4 °C for 10 min, after which plasma was stored at −80 °C until blinded analysis using a cDPP3 luminescence immunoassay (4TEEN4 Pharmaceuticals GmbH, Berlin, Germany). The details and design principles on this assay are provided elsewhere [13].

2.5. Statistical analyses

Continuous variables are presented as median [interquartile range (IQR)], whereas categorical variables are presented as counts and percentages. Group comparisons of continuous variables were performed using Mann-Whitney *U* tests or Kruskal-Wallis tests, depending on number of groups. Categorical data were compared using Chi-square tests. To assess cDPP3's associations with outcome, either Cox regression (for 28-day mortality) or binary logistic regression (for AKI) was performed on cDPP3 measurements performed during the first 3 days of admission, during which the majority of the cohort was still admitted to the ICU. To establish on which of these timepoints cDPP3 was most strongly associated with clinical outcomes, univariate analyses were first performed. To assess independence of biomarker predictive performance, multivariate models including clinical disease severity scores, either SOFA scores or APACHE-II scores, were also generated. To test whether cDPP3 added predictive value to these disease scores, we used the likelihood ratio chi-square test (LRT-Chi^2) for nested models. To further visualize associations of cDPP3 in univariate Cox-regression models, smoothed HR-plots were generated using the smoothHR package in R [14]. Splines-based hazard ratio (HR) curves were generated, implementing the clinically relevant cDPP3 cut-off of 40 ng/mL suggested in a previous study as the imputed covariate reference value [6]. Lastly, sensitivity, specificity and accuracy of cDPP3 cut-offs are reported as additional exploratory analyses. These analyses were restricted to timepoints where cDPP3 concentrations were found to be associated with the primary study outcome (28-day mortality) in multivariable analysis. Both DPP3's upper limit of normal (40 ng/mL) as well as the Youden Index [15] were used as cut-offs for these analyses.

To assure normal distribution, all biomarker values were log-transformed prior to analysis. Pearson correlation was used to explore the relationship between cDPP3 at days 1, 2, and 3, and peak concentrations of other clinically relevant biomarkers in the first 30 days of ICU admission. A two-sided *p*-value of <0.05 was considered to indicate statistical significance. All analyses were performed using R version 3.4.3 (https://www.r-project.org/).

3. Results

3.1. Study population

cDPP3 measurements on the first three days of ICU admission were available for 646, 620, and 364 patients, respectively. Reasons for missing samples per timepoint are described in Fig. 1. All baseline characteristics are listed in Table 1. Briefly, median [IQR] age was 65 [55–72] years, 65% of patients were male, median [IQR] APACHE-II score was 16 [13−22], while the SOFA score was 8 [5–10]. The most common reasons for admission were sepsis (11%), trauma (12%), cerebrovascular accident (CVA, 8%), cardiac surgery (32%) and non-cardiac surgery (18%).

3.2. Temporal profiles of cDPP3 following ICU admission

Concentrations of cDPP3 at ICU admission ($cDPP3_{day1}$) were higher compared to measurements performed on subsequent days; median [IQR] of 56.2 [31.8–93.1] ng/mL, vs. 25.7 [16.9–49.7] ng/mL and 30.1 [18.3–67.2] ng/mL for measurements performed on day 2 ($cDPP3_{day2}$) and day 3 ($cDPP3_{day3}$), respectively, $p < 0.001$ for both (Fig. 2). Interestingly, there was marked variation in $cDPP3_{day1}$ concentrations depending on the admission category, whereas $cDPP3_{day2}$ and $cDPP3_{day3}$ concentrations displayed less variance across the different admission categories (Fig. 2).

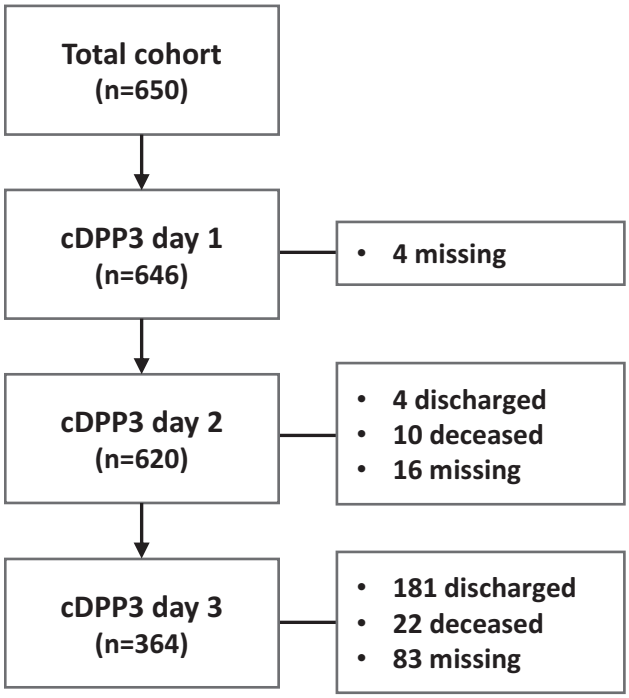

Fig. 1. Flowchart displaying patients potentially available for sampling at respective timepoints, as well as the reasons for missing samples at each timepoint. cDPP3 = circulating dipeptidyl peptidase 3.

Table 1
Patient and clinical characteristics. Data are presented as median [interquartile range] or number (%). SOFA and APACHE-II scores were calculated during the first 24 h after ICU arrival. BMI = body mass index, COPD = chronic obstructive pulmonary disease, LOS = length of stay, AKI = acute kidney injury, RRT = renal replacement therapy, SOFA = sequential organ failure assessment, APACHE-II = acute physiology and chronic health evaluation-II, CVA = cerebrovascular accident, OHCA = out of hospital cardiac arrest. Reasons for admission were non-exclusive.

	Count (n = 650)
Demographics	
Age (years)	65 [55–72]
BMI (kg/m^2)	26.3 [23.4–30.3]
Gender, female, n (%)	230 (35.4)
COPD, n (%)	68 (10.5)
Diabetes, n (%)	100 (15.4)
Severity scores	
SOFA (points)	8 [5–10]
APACHE-II (points)	16 [13–22]
Hospital admission characteristics	
MAP (mmHg)	79 [73–89]
Norepinephrine dose (mcg/kg/min)	0.059 [0–0.142]
Mechanical ventilation, n (%)	486 (74.8)
eGFR(mL/min/1.73m^2)	79 [57–90]
ICU length of stay (days)	3 [2–7]
Hospital length of stay (days)	12 [8–23]
Serum lactate (mmol/L)	1.5 [1.1–2.2]
Reasons for admission	
Sepsis, n (%)	73 (11.3)
Trauma, n (%)	79 (12.2)
CVA, n (%)	49 (7.5)
OHCA, n (%)	31 (4.8)
Major surgery, n (%)	117 (18.1)
Cardiac surgery, n (%)	205 (31.7)

3.3. Associations between cDPP3 and clinical outcomes

Univariate Cox regression analyses revealed that both cDPP3$_{day1}$ and cDPP3$_{day2}$ were significantly associated with 28-day mortality, with HRs of 1.36 (95%CI 1.01–1.83, $p = 0.04$) and 1.49 (95%CI 1.16–1.93, $p < 0.01$) per log-unit increase of cDPP3, respectively (Fig. 3). cDPP3 concentrations on the first three days of ICU admission were all associated with all-stage AKI in binary logistic regression analyses; ORs of 1.31 (95%CI 1.01–1.83, p = 0.04), 1.87 (95%CI 1.51–2.34, p < 0.01) and 1.49 (95%CI 1.16–1.92, p < 0.01) per log-unit increase of cDDP3, respectively (Fig. 4). For both cDPP3$_{day2}$ and cDPP3$_{day3}$, significantly higher concentrations were observed in patients with more severe AKI (i.e. higher KDIGO stages, $p < 0.001$ for both timepoints, Supplementary Fig. 1). In patient subgroup analyses, cDPP3$_{day2}$ was significantly related to mortality in non-cardiac surgical patients ($n = 117$); HR 4.01, 95%CI 1.51–10.62, $p < 0.01$). No significant associations could be demonstrated in the other subgroups, which could be related to small subgroup sizes and/or low event rates; for cardiac surgery, two patients out of 205 died, HR 0.83 (95%CI 0.15–4.51, $p = 0.83$), for sepsis, 19 patients out of 73 died, HR 1.20 (95%CI 0.70–2.06, $p = 0.51$), for trauma, 14 patients out of 79 died, HR 0.89 (95%CI 0.44–1.79, $p = 0.74$), and for CVA, 12 patients out of 49 died, HR 1.43 (95%CI 0.75–2.73, $p = 0.28$), also see Supplementary Fig. 2.

3.4. Independence of associations between cDPP3 and clinical outcomes

In multivariate models adjusting for baseline disease severity (SOFA or APACHE-II scores), the relationship between cDPP3 concentrations and 28-day mortality as well as AKI were further explored. cDPP3$_{day2}$ remained significantly associated with 28-day mortality, with HRs only changing minimally following adjustment (Fig. 5A). In contrast, associations between cDPP3$_{day1}$ and 28-day mortality did not remain significant in multivariate models (Fig. 5A). cDPP3$_{day2}$ added predictive value for 28-day mortality to both SOFA (LRT-Chi^2 $p = 0.02$) and APACHE-II scores (LRT-Chi^2 $p = 0.01$).

cDPP3 concentrations measured on the first three days of ICU admission all remained associated with all-stage AKI in multivariate models (Fig. 5B), with relatively minor changes in ORs following adjustment. Similar to the unadjusted analyses, the strongest associations with AKI were found for cDPP3 $_{day2}$. Both cDPP3$_{day2}$ and cDPP3$_{day3}$ added predictive value for AKI to SOFA and APACHE-II scores (LRT-Chi^2 all $p < 0.01$). While cDPP3$_{day1}$ did add predictive value to APACHE-II scores (LRT-Chi^2 $p = 0.03$), this was not the case for SOFA scores (LRT-Chi^2 $p = 0.10$).

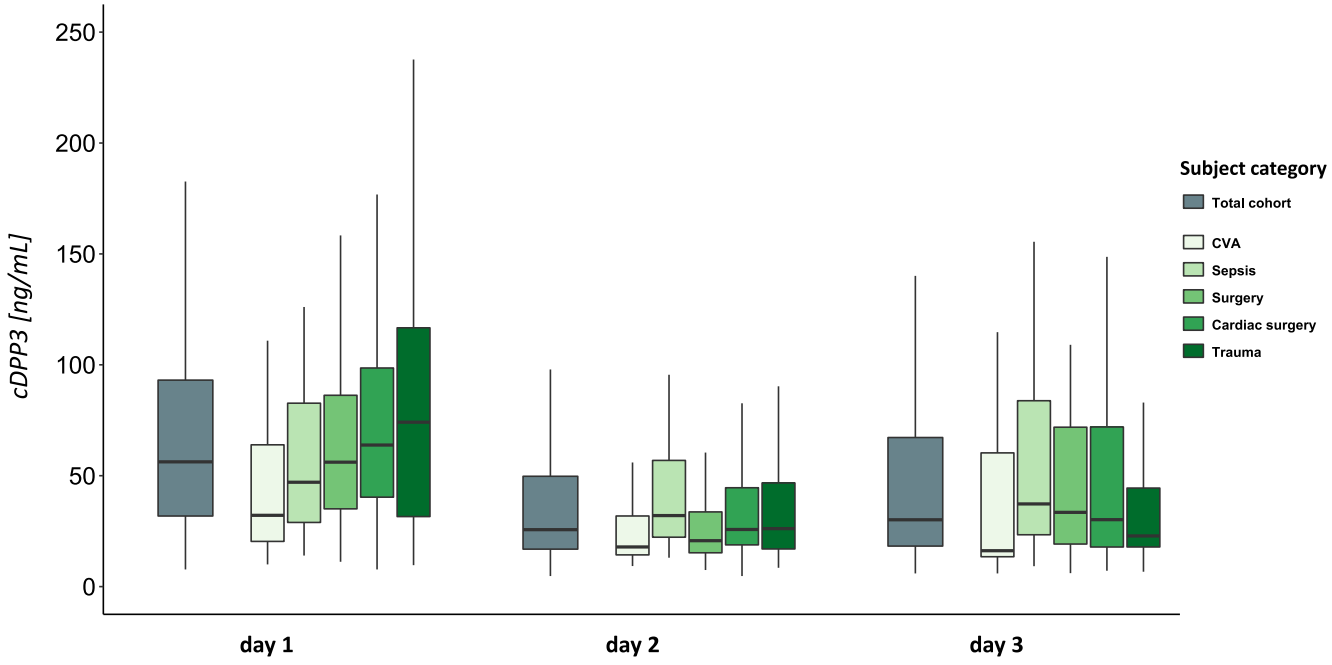

Fig. 2. Temporal profiles of cDPP3 concentrations on the first 3 days of ICU admission. Levels of the total cohort, as well as the most prevalent admission category subgroups are displayed. Median, interquartile ranges and Tukey's hinges are displayed. cDPP3 = circulating dipeptidyl peptidase 3, CVA = cerebrovascular accident.

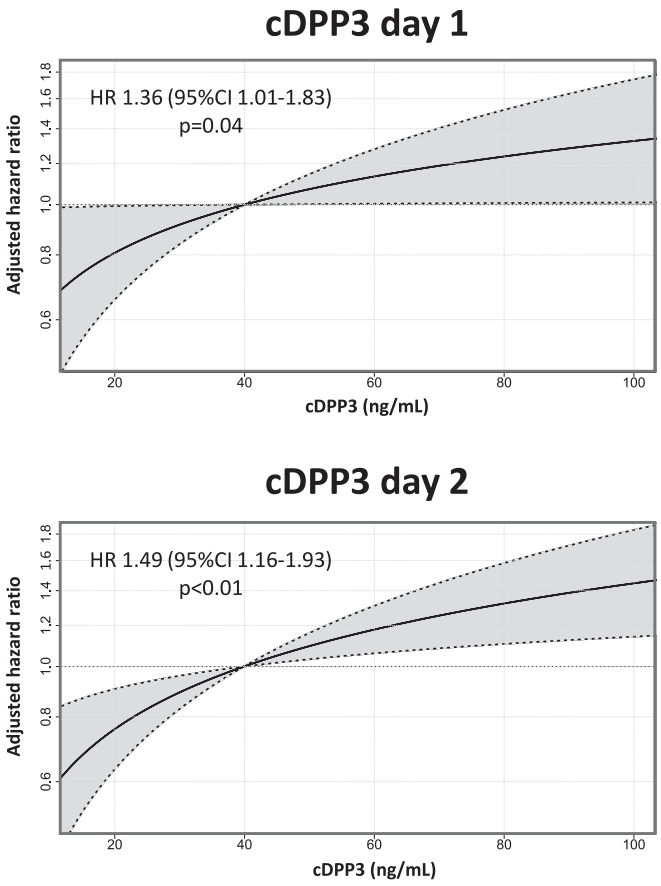

Fig. 3. Hazard ratios of 28-day mortality across cDPP3 concentrations. Solid curves represent estimates of the hazard ratios across cDPP3 concentrations relative to a reference level of 40 ng/mL. The dashed lines represent pointwise 95% confidence intervals. HR = hazard ratio, cDPP3 = circulating dipeptidyl peptidase 3.

3.5. Exploratory analyses on clinically relevant biomarker cut-offs

Only $cDPP3_{day2}$ concentrations were independently associated with the primary outcome of 28-day mortality. To provide additional data on its predictive performance, exploratory analyses using clinically relevant cDPP3 cut-offs were subsequently performed. An overview of the sensitivity, specificity and accuracy of outcome associations implementing the upper-limit of normal of 40 ng/mL as cutoff is provided in supplementary Table 1. Results for the total cohort, as well as the 5 most prevalent admission category subgroups are reported. The same test-characteristics, implementing the Youden statistic to determine the optimal cut-off, are provided in supplementary Table 2. Overall, the discriminative capacity of both investigated cDPP3 cut-offs appeared best for the surgery subgroup, while the least differentiation was observed for the trauma subgroup. Results of these analyses should be interpreted as exploratory, as subgroup stratification limited statistical power, and an independent study cohort for cut-off validation was not available.

3.6. Correlations between cDPP3 concentrations and other established clinical biomarkers

cDPP3 measurements performed during the first 3 days of ICU admission were correlated to the peak values of other clinically established biomarkers during the first 30 days of ICU admission. While all investigated biomarkers peaked within the first 4 days of ICU admission, early peak concentrations were found for cDPP3, lactate, creatinin, bilirubin and creatinin-kinase (median [IQR] of 1 [1–3], 2 [1–2], 1 [1–2], 1[1–2] and 2 [1–2] days, respectively, Fig. 6A). Peak values of ALAT, ASAT, ALP, and γGT were observed at 4 [2–9], 4 [2–9], 4 [2−11], and 4 [2−10] days, respectively (Fig. 6A). Overall, the strongest associations with cDPP3 were found for biomarkers of cellular damage, including ASAT, ALAT and LDH. When comparing correlations at different cDPP3 measurement timepoints, the strongest associations with peak concentrations of other biomarkers were found for $cDPP3_{day2}$: ASAT ($r = 0.56$, 95%CI 0.45–0.65, $p < 0.001$), ALAT ($r = 0.46$, 95%CI 0.33–0.56, $p < 0.001$), and LDH ($r = 0.58$, 95%CI 0.47–0.67, $p < 0.001$, Fig. 6B). Correlations between $cDPP3_{day3}$ and the other biomarkers were quite similar to those reported for $cDPP3_{day2}$, while associations between $cDPP3_{day1}$ and peak concentrations of other biomarkers were generally less strong (Fig. 6B).

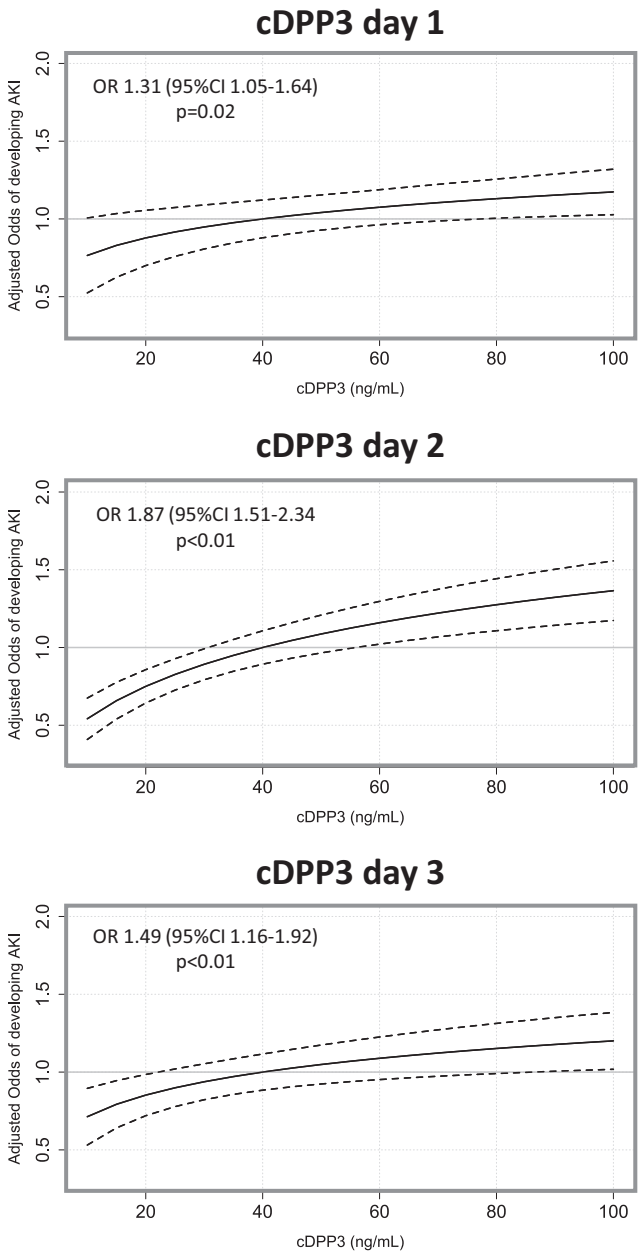

Fig. 4. Odds ratios of all-stage AKI across cDPP3 concentrations. Solid curves represent estimates of the odds ratios across cDPP3 concentrations relative to a reference level of 40 ng/mL. The dashed lines represent pointwise 95% confidence intervals. OR = odds ratio, AKI = acute kidney injury, cDPP3 = circulating dipeptidyl peptidase 3.

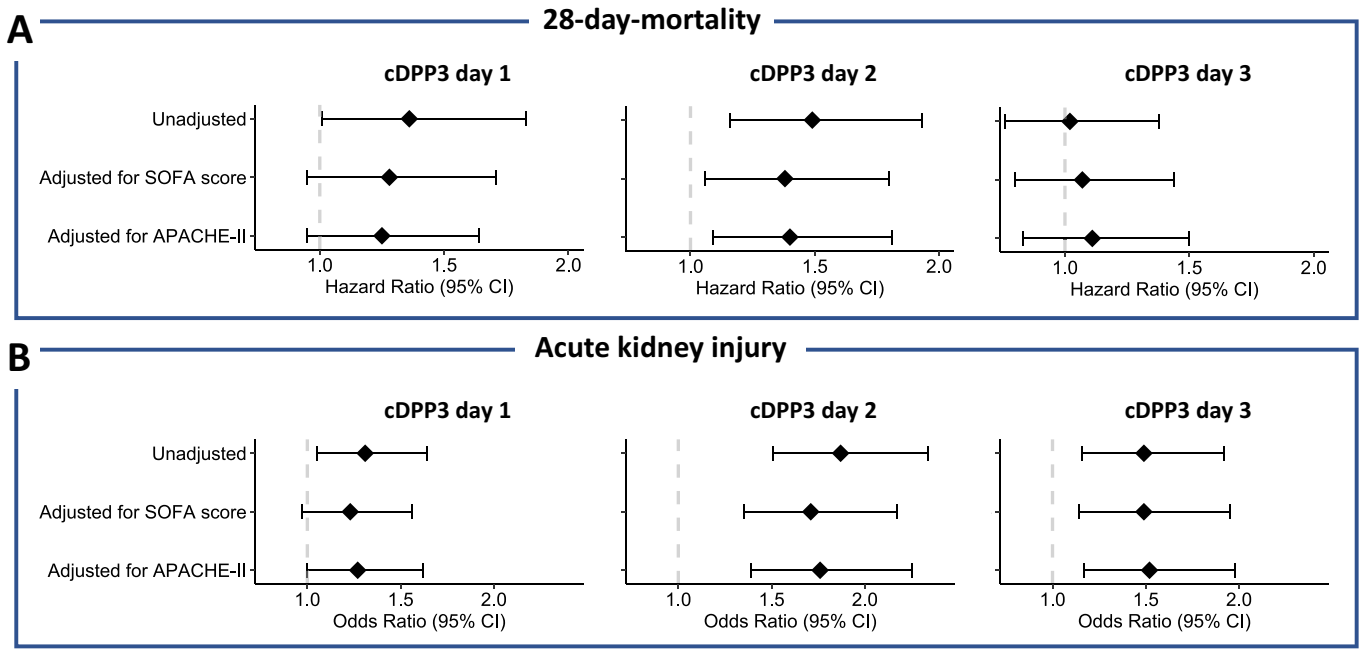

Fig. 5. HR/OR of cDPP3 measurements for 28-day mortality (panel A) and AKI (panel B) in unadjuted and adjusted regression models. Multivariate models included either admission SOFA or admission APACHE-II scores. For 28-day mortality, results of Cox-regression analyses using time-event data are displayed. For AKI, results of binary logistic regression are displayed. cDPP3 = circulating dipeptidyl peptidase 3, AKI = acute kidney injury.

A

Biomarker	Median [IQR] admission day of peak levels
cDPP3	1 [1-3] days
ASAT	4 [2-9] days
ALAT	4 [2-9] days
ALP	4 [2-11] days
yGT	4 [2-10] days
Bilirubin	1 [1-2] days
Creatinin	1 [1-2] days
Creatinin Kinase	2 [1-2] days
LDH	4 [2-8] days
Lactate	2 [1-2] days

B

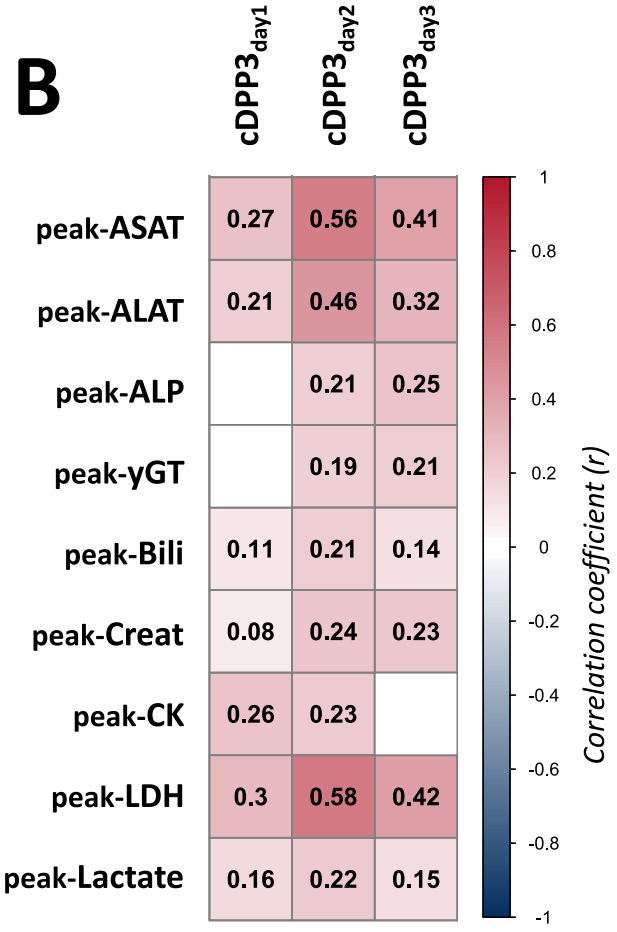

Fig. 6. Correlations of cDPP3 concentrations with other clinically relevant biomarkers. Significant correlations ($p < 0.05$) are displayed in colors ranging from r-coefficients from − 1 to 1. Non-significant correlations are displayed as white panels. Panel A displays the median [IQR] day at which peak concentrations of biomarkers were observed. Panel B displays correlations of cDPP3 assessed at days 1, 2 and 3 of admission versus peak concentrations of other biomarkers (measurements up until day 30 of ICU admission were included). Results of Pearson correlations on log-transformed data are displayed. cDPP3 = circulating dipeptidyl peptidase 3, ASAT = aspartate-transaminase, ALAT = alanine-transaminase, ALP = alkaline-phosphatase, yGT = gamma-glutamyl-transferase, Bili = bilirubin, Creat = creatinine, CK = creatinine-kinase, LDH = lactate-dehydrogenase.

4. Discussion

In this prospective cohort study of a mixed-admission ICU cohort, we found that cDPP3 concentrations measured at ICU admission and on the following day were significantly associated with 28-day mortality, while concentrations at the first three days of ICU admission were all associated with the development of AKI. After correction for disease severity, cDPP3 measured on the second day of ICU admission remained independently associated with both 28-day mortality and all-stage AKI. This implies that assessing cDPP3 further improves the outcome prediction provided by traditional disease severity indexes.

The fact that the predictive properties of cDPP3 varied depending on the measurement timepoint may be explained by the mechanisms underpinning DPP3 release and its kinetics. During critical illness, high cDPP3 concentrations are putatively caused by cellular injury/death as a consequence of profound microcirculatory perturbances [3,5]. Correspondingly, we observed the highest cDPP3 concentrations at ICU admission, when organ supportive therapies were only just initiated. While these early measurements were associated with mortality, they appeared to mainly reflect baseline disease severity, as associations of day 1 measurements with mortality were no longer present in models corrected for baseline disease severity. Moreover, the large variation in admission cDPP3 levels across different admission categories implies that factors such as surgery may act as an additional competing mechanism of cDPP3 release at ICU admission. As this competing release mechanism is unrelated to tissue-hypoperfusion, it might provide an additional explanation on why admission cDPP3 levels were not independently associated with outcome. Because cDPP3 has a half-life of only 20–70 min [13,16], high concentrations on admission should quickly normalize if a patient's clinical condition improves. In contrast, if cDPP3 concentrations remain high, this suggests that tissue perfusion disturbances persist, indicating an increased risk for development of organ failure and detrimental outcomes. Supporting this hypothesis, the large variation in admission DPP3 levels depending on the reason for admission were not observed at later timepoints, suggesting tissue hypoperfusion represents the main driver of high cDPP3 levels in the post-acute phase of ICU admission. Correspondingly, cDPP3 concentrations at day 2 of ICU admission demonstrated strong and disease-severity independent associations with both 28-day mortality and AKI. Similar to our findings, cDPP3 measurements performed 12–24 h after admission were also most strongly associated with outcomes in cohorts of cardiogenic shock and aortic aneurysm repair, while measurements performed later on during admission had less predictive value [3,8]. Nevertheless, it needs to be acknowledged that cDPP3 measured on day 3 of admission was still associated with mortality in these previous studies [3,8], while it was not in the current study. This might be due to notably higher disease severity (reflected by higher mortality rates and more use of organ supportive treatments) than in our current cohort, as this was identified as an important driver of persistently high cDPP3 concentrations [9].

Interestingly, associations between cDPP3 concentrations and AKI were stronger than those between cDPP3 concentrations and 28-day mortality in our cohort. On one hand, these results might be explained by the molecular pathophysiological mechanisms associated with DPP3 release. Systemic angiotensin-II responses are essential to maintain glomerular filtration, especially during periods of attenuated renal perfusion [17]. As circulating DPP3 is able to rapidly degrade angiotensin-II in vivo [18,19], high cDPP3 concentrations might be causally related to the development of impaired kidney function. However, these stronger associations could also be explained by the higher event-rates for AKI compared to mortality in our cohort (35% incidence of all-stage AKI vs. 13% 28-day mortality). Importantly, as DPP3 clearance is mediated by the liver and not the kidneys, elevated concentrations are not the consequence of impaired renal function.

In accordance with previous work [20], cDPP3 correlated most strongly with ALAT and ASAT, biomarkers of liver cell damage as well as with LDH, a more general marker of cellular lysis. Nevertheless, as ASAT is present (and therefore released upon injury) in many other cell types besides those residing in the liver, it is considered a less specific marker of liver injury than ALAT [21]. As correlations of cDPP3 with ASAT were stronger than those with ALAT in all analyses, our data do not necessarily support a liver-specific origin of cDPP3. The finding that early cDPP3 concentrations strongly correlated with peak concentrations of other cellular damage biomarkers that were observed two days later suggest that cDPP3 is as an earlier marker of cellular injury during the early phase of critical illness.

Our findings have several clinically relevant implications. First, if cDPP3 concentrations assessed after initial treatment are high, this is associated with a higher risk of detrimental outcome than predicted by disease severity scores alone. Consequently, patients could be reexamined for causes of continued microcirculatory perturbances, such as hypovolemia or cardiac function disturbances. Second, related to the aforementioned potential causal relationship between cDPP3 and AKI, cDPP3-blocking antibodies, aimed at improving vascular responsiveness in shock, are currently in preclinical stages of development [16,22]. Based on the narrower time-window of cDPP3-outcome associations found in our mixed cohort compared to earlier studies of septic -and cardiogenic shock, we believe this therapy may be particularly beneficial for patients with a high disease severity. As we found consistent associations between cDPP3 concentrations and the development of AKI, cDPP3-blocking antibodies also show promise as a potential therapy aimed at mitigating critical illness-associated AKI.

Our study has several limitations. While >600 patients were included in the cohort, some admission category groups were relatively small, resulting in limited statistical power to assess differences in outcome associations among the various admission categories. Moreover, the observational nature of this study implies that the proposed causal relation between cDPP3 and outcome (i.e. AKI) remain largely speculative. Lastly, we were unable to perform a direct comparison of cDPP3 with other candidate biomarkers such as procalcitonin, as all plasma available from the biobank was already used up for measurement of cDPP3 and PCT was not routinely measured in these patients.

5. Conclusion

In a mixed-ICU cohort, assessment of cDPP3 after start of initial treatment is independently associated with both mortality and AKI, improving the risk-stratification provided by disease severity scores. Whether DPP3-targeted therapies are able to improve outcome in critical illness should be investigated in future studies.

Author contributions

MK and PP conceptualized the study. DvL drafted the manuscript. RB acquired and processed the samples. DvL, RB and MK performed data quality control and assurance, transformation. DvL performed data analyses. All authors critically revised the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Assistance with the article

None declared.

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study. 4TEEN4 had no role in the design of the study, its execution, analyses, interpretation of the data, as well as the decision to submit results.

Declaration of Competing Interest

Peter Pickkers received travel and consultancy reimbursement from 4TEEN4 Pharmaceuticals, the company that produces the cDPP3 bioassay described in this manuscript. All other authors have no financial or other disclosures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154383.

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