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Circulating corin concentration is associated with risk of mortality and acute kidney injury in critically ill patients

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Elevated serum corin concentrations in patients with cardiac diseases have been associated with adverse cardiovascular events and progressive renal dysfunction. This study aimed to determine the role of serum corin levels in predicting the incidence of acute kidney injury (AKI) and mortality in critically ill patients admitted to intensive care units (ICUs). We screened 323 patients admitted to the ICU in our institution from May 2018 through December 2019. After excluding patients receiving renal replacement therapy, 288 subjects were enrolled. Cases were divided equally into high (n = 144) and low (n = 144) corin groups according to median serum corin levels, using 910 pg/mL as the cut-off point. Patient characteristics and comorbidities were collected from medical records. The primary outcome was AKI within 48 h after ICU admission, while the secondary outcome was all-cause of mortality within 1 year. Compared with the low corin group, patients in the high corin group had higher prevalence rates of diabetes, cirrhosis, and nephrotoxic agent exposure; higher Sequential Organ Failure Assessment scores, white blood cell counts, proteinuria, and serum N-terminal pro-brain natriuretic peptide levels; but had lower initial estimated glomerular filtration rates. Furthermore, elevated serum corin was associated with higher risks of AKI within 48h of ICU admission (43.1% vs. 18.1%, $p < 0.001$) and all-cause mortality within one year (63.9% vs. 50.0%, $p = 0.024$). High corin level showed strongly positive results as an independent predictor of AKI (OR 2.15, 95% CI 1.11–4.19, $p = 0.024$) but not for the all-cause mortality after adjusting for confounding factors in multivariate analyses. Elevated circulating corin predicted AKI in critically ill patients, but did not predict all-cause mortality within 1 year. As a key enzyme in renin–angiotensin–aldosterone system, corin expression may be regulated through a feedback loop following natriuretic peptide resistance and desensitization of natriuretic peptide receptors in different critically ill status.

Keywords Acute kidney injury, Corin, Intensive care unit, Mortality

Abbreviations

AKI	Acute kidney injury
ICUs	Intensive care units
pro-ANP	Pro-atrial natriuretic peptide
pro-BNP	Pro-brain natriuretic peptide
ANP	Atrial natriuretic peptide

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BNP	Brain natriuretic peptide
NP	Natriuretic peptide
BMI	Body mass index
APACHE	Acute Physiology and Chronic Health Evaluation
WBC	White blood cell
Hgb	Hemoglobin
Cr	Creatinine
ALT	Alanine transaminase
eGFR	Estimated glomerular filtration rate
SOFA	Sequential organ failure assessment
KDIGO	The Kidney Disease: Improving Global Outcomes
RAAS	Renin–angiotensin–aldosterone system
NPR	Natriuretic peptide receptor

Corin is a type II transmembrane serine protease expressed primarily in atrial and ventricular cardiomyocytes, and cleaves pro-atrial natriuretic peptide (pro-ANP) and pro-brain natriuretic peptide (pro-BNP) to yield mature atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), respectively. Corin is a key enzyme in the natriuretic peptide (NP) system[1,2]. ANP regulates blood pressure by maintaining fluid homeostasis[3] and suppresses cardiac fibroblast growth in cardiac hypertrophy[4]. ANP protects renal function by increasing glomerular filtration and medullary vasa recta blood flow, and by inhibiting inflammation[5–7]. Numerous corin isoforms may be detected in serum due to ectodomain shedding. Higher circulatory corin levels have been associated with improved outcomes in patients with cardiovascular diseases such as chronic heart failure (HF), acute coronary syndrome, acute myocardial infarction, and acute stroke[8–11]. Serum corin is a well-known biomarker of cardiovascular diseases and cardiac corin activity[12,13], but its role in critically-ill patients is still not fully elaborated.

Acute kidney injury (AKI) is among the most common organ failures in critically ill patients[14,15]. AKI is associated with increased mortality even without the need for dialysis[15]. The need for renal replacement therapy reduces in-hospital as well as long term survival[16]. Our previous study associated low serum corin with a higher risk of progressive renal dysfunction in patients undergoing coronary angiography[17]. Therefore, the aim of this study was to investigate the relationship between circulating corin concentration and clinical outcomes in critically ill patients. We hypothesized that serum corin could be a predictor of the risk of AKI and mortality in patients admitted to intensive care units (ICUs).

Materials and methods

Study population

A total of 323 cases admitted to ICUs in a tertiary medical center in Taiwan from May 2018 through December 2019 were screened. Thirty-five patients with end-stage renal disease and under renal replacement therapy before ICU admission were excluded. Electronic medical records of enrolled subjects were reviewed in detail to obtain patient characteristics including age, gender, body mass index (BMI), comorbidities (hypertension, diabetes mellitus, HF, cirrhosis, and malignancies); premorbid medications (including ACEi, ARB, and diuretics used continuously for more than 1 month before ICU admission), and exposure to nephrotoxic agents, defined as using nonsteroidal anti-inflammatory drugs, aminoglycosides, and platinum-based chemotherapy within 7 days before ICU admission. Contrast exposure was recorded for the administration of nonionic low-osmolality contrast medium (iopromide) during computed tomography or angiography within 48 h before ICU admission.

The indication for ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score, laboratory data [white blood cell (WBC) count, hemoglobin (Hgb), serum creatinine (Cr), alanine transaminase (ALT), and glucose level] at ICU transfer, and HbA1c % within 3 months before ICU admission were obtained. BMI was calculated by dividing the weight of each patient in kilograms by the square of the height in meters. Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) was calculated using age, sex, and serum levels of blood urea nitrogen, creatinine, and albumin, according to the modified GFR estimating equations for Chinese patients[18]. Sepsis was defined according to the 2016 Surviving Sepsis Campaign guidelines, e.g., as organ dysfunction reflected by a ≥ 2-point increase in the Sequential Organ Failure Assessment (SOFA) score consequent to infection[19]. Massive bleeding was defined as either the loss of one blood volume within 24 h, a 50% blood volume loss within 3 h, or a rate of loss of 150 mL/min[20]. The study protocol was approved by the institutional review board of Taipei Veterans General Hospital. Written informed consent was obtained from all participants, and our study complied with the Declaration of Helsinki.

Laboratory investigations

Laboratory values, including corin level, were obtained from each patient within 24 h after ICU admission. Serum creatinine concentration was measured at the time of ICU admission and every day during the ICU stay. Urine dipstick analysis was performed by commercial test strip, and proteinuria was defined as a urine protein ≥ 30 mg/dL. Serum concentrations of corin were determined by the commercial enzyme-linked immunosorbent assay (R&D Systems, Inc, Minneapolis, MN); sensitivity was 7 ng/L. Intra- and interassay coefficients of variability were 4.1% and 3.9%, respectively. Enrolled patients were categorized in to two equally sized groups according to serum corin levels, as shown in Fig. 1. Subjects with serum corin levels < 910 pg/mL were assigned to the low corin group (n = 144), while those with levels ≥ 910 pg/mL were placed in the high corin group (n = 144).

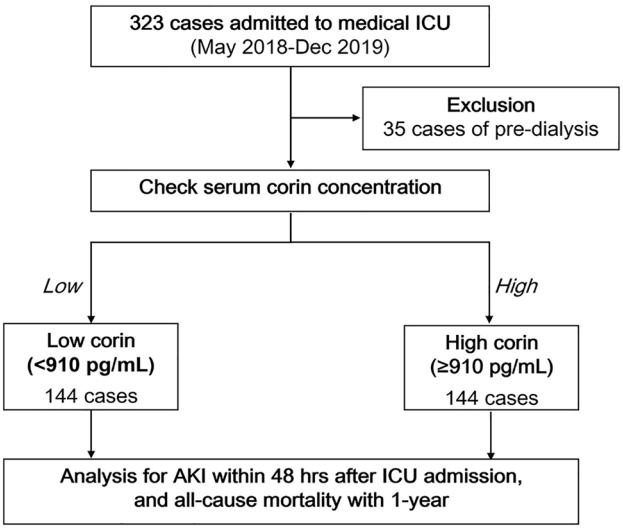

Fig. 1. Flowchart of patient enrollment and classification. *ICU* intensive care unit, *AKI* acute kidney injury.

End-points for clinical follow-up

The primary outcome was the incidence of AKI confirmed via The Kidney Disease: Improving Global Outcomes (KDIGO) guideline[21] within 48 h after ICU admission. The KDIGO guideline defines AKI as either (1) an increase in serum creatinine by ≥ 0.3 mh/dL within 48 h; (2) a ≥ 1.5-fold increase in serum creatinine over baseline, known or presumed to have occurred within the prior seven days; or (3) urine volume < 0.5 mL/kg/h for 6 h. All patients were followed for at least 1 year or until death. The secondary outcome was all-cause mortality within 1 year of enrollment.

Statistical analysis

Shapiro–Wilk test was used to test the normality distribution. Continuous variables were presented as means and standard deviations, or as medians and interquartile ranges according to the distribution of data. Continuous variables were analyzed using the Student's *t* tests or the Mann–Whitney *U* tests. Categorical variables were presented as numbers and percentages, and analyzed using the Fisher's exact tests or Chi-Squared tests. Spearman's rank correlation test was used to assess correlations between corin concentrations and other clinical factors. Kaplan–Meier survival curves and the log-rank test were used to estimate 1-year mortality. Logistic regression was performed to investigate the risk factors of AKI within 48 h after ICU admission. Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of factors associated with 1-year mortality. Confounding factors associated with AKI[22] and mortality[23] in critically-ill patients were recorded and further adjusted in the multivariate regression analysis. To reduce overfitting and optimize model performance, variables with p values < 0.1 in the univariate regression analysis were included into a forward stepwise multivariate regression model. We selected an including threshold slightly higher than the conventional level aimed at mitigating omitted-variable bias. Sensitivity analyses using different cut-off values of corin concentrations were also performed. Serum corin concentrations was either divided by the criterion value of ROC curve (> 886.3 pg/mL, ROC curve showed in Supplementary Fig. 1), or by the corin value reported in relatively robust population undergoing coronary angiography (> 1049.9 pg/mL) in the sensitivity analyses[17]. To investigate the effect of corin modified by different conditions, we performed subgroup analyses with the cohort stratified by the presence of diabetes, proteinuria, initial eGFR, HF, pneumonia, sepsis, and septic shock. Factors selected into the final multivariate regression model were also adjusted in the subgroup analysis. p values < 0.05 were considered significant. All analyses were performed using SPSS software (version 19.0; IBM Corporation, Armonk, NY, USA).

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Taipei Veterans General Hospital, and our study complied with the Declaration of Helsinki.

Results

Baseline characteristics

The mean age of the study population was 67.5 years, and 197 (68.4%) of subjects were male. There were no differences between patients in low and high corin groups in age; gender; BMI; underlying diseases (hypertension, diabetes, and HF, active malignant tumor); drug exposures (ACEi/ARB, diuretics, contrast); APACHE II scores; mechanical ventilation; inotropic agent administration; or Hgb, glucose, and lactate levels. In addition, the indications for ICU admission; including pneumonia, sepsis, acute HF, or massive bleeding; were similar between the two groups. Patients with high corin levels tended to have higher prevalence rates of cirrhosis and nephrotoxic

agent exposure; and higher SOFA scores, WBC counts, proteinuria, and serum NT-pro-BNP concentrations; and were more likely to have low eGFR (Table 1).

The correlation coefficients of clinical variables to serum corin concentrations are shown in Table 2. Serum corin was positively correlated to SOFA score (r = 0.205, $p = 0.001$), WBC count (r = 0.133, $p = 0.025$), and NT-pro-BNP (r = 0.178, $p = 0.002$), and negatively correlated to eGFR (r = -0.335, $p < 0.001$). Corin level was not correlated to age (r = -0.071, $p = 0.230$); BMI (r = 0.059, $p = 0.342$); APACHE II score (r = 0.072, $p = 0.224$); mean arterial pressure (r = 0.005, $p = 0.935$); Hgb (r = -0.075, $p = 0.207$), glucose (r = 0.018, $p = 0.780$, or lactate (r = 0.059, $p = 0.324$) levels.

AKI and 1-year mortality after ICU admission

Compared to subjects with low corin levels, those with high corin levels had a higher risk of consequent AKI (18.1% vs. 43.1%, $p < 0.001$) that included an increased risk of stage 2–3 AKI (10.4% vs. 32.6%, $p < 0.001$) within 48 h of ICU admission. However, there was no difference in dialysis dependence after hospital discharge (2.1% vs. 6.3%, $p = 0.138$). Although the lengths of ICU stay and total hospitalization, ICU mortality, and in-hospital mortality were similar between the two groups, patients with high corin levels experienced a higher 1-year mortality rate (63.9% vs. 50.0%, $p = 0.024$) (Table 3). The Kaplan–Meier 1-year survival curve is shown in Fig. 2. Subjects in the high corin group had a significantly lower survival rate (log rank $p = 0.0331$). Furthermore, the onset of AKI within 48 h was associated with a significantly lower 1-year survival rate (log rank $p = 0.0065$).

Independent predictors of AKI within 48 h and 1-year mortality after ICU admission

Univariate analysis disclosed that the onset of AKI within 48 h of ICU admission was significantly associated with history of HF (OR 2.12, 95% CI 1.03–4.34, $p = 0.041$), exposure to nephrotoxic agents (OR 2.72, 95% CI

	Overall n = 288	Low corin (< 910 pg/mL) n = 144	High corin (≥ 910 pg/mL) n = 144	*p*
Age (years)	67.5 (59.0–78.0)	68.0 (60.0–79.0)	67.0 (56.3–78.0)	0.194
Male gender	197 (68.4)	98 (68.1)	99 (68.8)	1.000
Body mass index	22.8 (20.1–25.5)	22.5 (19.8–25.3)	23.1 (20.5–26.2)	0.101
Hypertension	131 (45.5)	63 (43.8)	68 (47.2)	0.636
Diabetic mellitus	83 (28.8)	31 (21.5)	52 (36.1)	0.009
Heart failure	35 (12.2)	12 (8.3)	23 (26.0)	0.070
Cirrhosis	21 (7.3)	5 (3.5)	16 (11.1)	0.021
Malignancy (solid tumor)	113 (39.2)	63 (43.8)	50 (34.7)	0.147
ACEi/ARB exposure	62 (21.5)	25 (17.4)	37 (25.7)	0.114
Diuretic exposure	44 (15.3)	16 (11.1)	28 (19.4)	0.071
Contrast exposure	84 (29.2)	40 (27.8)	44 (30.6)	0.697
Nephrotoxic agent exposure	19 (6.6)	4 (2.8)	15 (10.4)	0.016
Indication for ICU admission				
Pneumonia	209 (72.6)	106 (73.6)	103 (71.5)	0.792
Sepsis	244 (84.7)	125 (86.8)	119 (82.6)	0.413
Acute heart failure	9 (3.1)	2 (1.4)	7 (4.9)	0.173
Massive bleeding	13 (4.5)	9 (6.3)	4 (2.8)	0.256
Disease severity				
APACHE II scores	26.0 (20.0–33.0)	26.0 (20.0–32.0)	27.0 (20.8–33.0)	0.364
SOFA scores	9.0 (7.0–12.0)	9.0 (7.0–11.0)	10.0 (8.0–12.0)	0.001
Ventilator usage	277 (96.2)	141 (97.9)	136 (94.4)	0.217
Inotrope/vasopressor usage	159 (55.2)	71 (49.3)	88 (61.1)	0.058
Mean arterial pressure (mmHg)	55.0 (47.7–64.3)	55.0 (46.4–64.0)	55.0 (48.7–64.3)	0.723
White blood cells (K)	8.7 (4.7–13.4)	8.4 (3.8–12.5)	9.4 (5.4–15.0)	0.035
Hemoglobin (mg/dL)	8.8 (7.6–10.1)	8.9 (7.8–10.6)	8.7 (7.6–9.9)	0.427
Initial eGFR (mL/min/1.73 m^2)	37.2 (19.3–74.5)	55.5 (26.8–91.2)	26.2 (14.2–50.9)	< 0.001
Proteinuria	212 (73.6)	98 (68.1)	114 (79.2)	0.045
Glucose (mg/dL)	134.0 (101.0–205.0)	135.0 (107.3–184.0)	134.0 (101.0–222.0)	0.673
Lactate (mg/dL)	12.6 (8.1–18.9)	12.6 (8.1–18.0)	13.5 (8.1–19.8)	0.176
NT-pro-BNP (pg/mL)	4666 (1628–12,595)	4185 (707–12,348)	5319 (2127–14,425)	0.012
Corin (pg/mL)	908.5 (639.1–1262.3)	640.0 (448.9–747.0)	1261.0 (1047.6–1617.5)	< 0.001

Table 1. Baseline characteristics of critically ill patients grouped by serum corin concentrations. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *APACHE* Acute Physiology and Chronic Health Evaluation, *ICI* intensive care unit, *SOFA* Sequential Organ Failure Assessment, *eGFR* estimated glomerular filtration rate, *NT-pro-BNP* N-terminal pro-brain natriuretic peptide.

	Corin	
	r	*p* value
Age (years)	−0.071	0.230
Body mass index	0.059	0.342
APACHE II score	0.072	0.224
SOFA score	0.205	0.001
Mean arterial pressure (mmHg)	0.005	0.935
White blood cells (K)	0.133	0.025
Hemoglobin (mg/dL)	−0.075	0.207
Initial eGFR (mL/min/1.73 m^2)	−0.335	< 0.001
Glucose (mg/dL)	0.018	0.780
Lactate (mg/dL)	0.059	0.324
NT-pro-BNP (pg/mL)	0.178	0.002

Table 2. Correlation coefficients of circulating corin concentrations and different variables in critically ill patients. *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *eGFR* estimated glomerular filtration rate, *NT-pro-BNP* N-terminal pro-brain natriuretic peptide.

	Overall n = 288	Low corin (< 910 pg/mL) n = 144	High corin (≥ 910 pg/mL) n = 144	*p*
AKI within 48 h after ICU admission				
AKI (total cases)	88 (30.6)	26 (18.1)	62 (43.1)	< 0.001
Stage 1	26 (9.0)	11 (7.6)	15 (10.4)	< 0.001
Stage 2–3	62 (21.5)	15 (10.4)	47 (32.6)	
Dialysis-dependence after discharge	12 (4.2)	3 (2.1)	9 (6.3)	0.138
Events during follow-up period				
Length of ICU stay (days)	9.0 (5.0–14.8)	9.0 (5.0–15.0)	9.0 (6.0–14.0)	0.955
Length of hospitalization (days)	24.0 (13.0–40.0)	26.5 (14.3–38.0)	22.0 (11.3–44.0)	0.403
Mortality, in ICU	88 (30.6)	36 (25.0)	52 (36.1)	0.055
Mortality, in hospital	149 (51.7)	69 (47.9)	80 (55.6)	0.238
Mortality, within 1 year	164 (56.9)	72 (50.0)	92 (63.9)	0.024

Table 3. Clinical outcomes of critically ill patients grouped by circulating corin concentrations. *AKI* acute kidney injury, *ICU* intensive care unit.

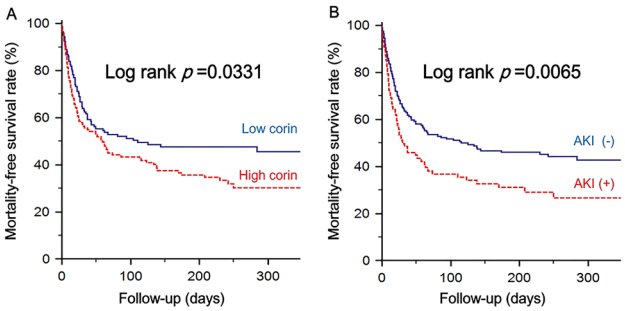

Fig. 2. Kaplan–Meier curves of 1-year survival by (**a**) serum corin concentrations and (**b**) incidence of acute kidney injury (AKI).

1.07–6.95, $p = 0.037$), higher SOFA score (OR 1.23, 95% CI 1.13–1.34, $p < 0.001$), initial eGFR (OR 0.98, 95% CI 0.98–0.99, p < 0.001), proteinuria (OR 2.38, 95% CI 1.25–4.53, $p = 0.009$), glucose (OR 1.00, 95% CI 0.99–1.00, $p = 0.025$), NT-pro-BNP (OR 1.00, 95% CI 1.00–1.00, $p = 0.045$), and high corin level (OR 3.43, 95% CI 2.00–5.88, $p < 0.001$) at ICU admission. Multivariate regression revealed that hypertension (adjusted OR, aOR 2.03, 95% CI 1.03–3.99, $p = 0.040$), exposure to nephrotoxic agents (aOR 4.49, 95% CI 1.24–16.19, $p = 0.022$), SOFA score (aOR 1.18, 95% CI 1.06–1.31, $p = 0.003$), initial eGFR (aOR 0.99, 95% CI 0.98–1.00, $p = 0.007$), glucose (aOR 0.99, 95% CI 0.99–1.00, $p = 0.006$), and high corin level (aOR 2.15, 95% CI 1.11–4.19, $p = 0.024$) were still significantly

associated with AKI within 48 h of ICU admission (Table 4). Sensitivity analyses using different cut-off values of serum corin concentration also showed similar findings. Even if we grouped patients according to the criterion value of ROC curve (Supplementary Table 1), or grouped by the corin value reported in relatively robust population (Supplementary Table 2), critically ill patients with higher corin levels were still significantly associated with greater risk of AKI.

Subgroup analysis disclosed that elevated corin levels were associated with a significantly increased risk of AKI in patients with sepsis (aOR 2.17, 95% CI 1.10–4.27, $p = 0.025$), or the absence of either HF (aOR 2.07, 95% CI 1.00–4.25, $p = 0.049$) or pneumonia (aOR 5.49, 95% CI 1.10–27.43, $p = 0.038$) after adjusting for confounding factors. Nevertheless, there was no statistical difference in interaction tests (Table 5).

Univariate analysis revealed that underlying hypertension (OR 0.6, 95% CI 0.44–0.83, $p = 0.002$), active malignancy (OR 1.68, 95% CI 1.25–2.28, $p = 0.001$), APACHE II score (OR 1.07, 95% CI 1.05–1.09, $p < 0.001$), SOFA score (OR 1.16, 95% CI 1.11–1.22, $p < 0.001$), administration of inotropic agents or vasopressors (OR 1.70, 95% CI 1.24–2.34, $p = 0.001$), mean arterial pressure (OR 0.98, 95% CI 0.97–0.99, $p < 0.001$), Hgb (OR 0.86, 95% CI 1.80–0.93, $p < 0.001$), lactate (OR 1.02, 95% CI 1.01–1.02, $p < 0.001$), confirmed AKI in ICU (OR 1.55, 95% CI 1.13–2.13, $p = 0.007$), and elevated corin (OR 1.39, 95% CI 1..02–1.90, $p = 0.035$) were significantly associated with 1-year mortality. Multivariate analysis disclosed that hypertension (aOR 0.61, 95% CI 0.42–0.89, $p = 0.009$), active malignancy (aOR 1.52, 95% CI 1.07–2.16, $p = 0.019$), APACHE II score (aOR 1.04, 95% CI 1.01–1.07, $p = 0.015$), SOFA score (aOR 1.10, 95% CI 1.08–1.17, $p = 0.005$), and lactate level (aOR 1.01, 95% CI 1.00–1.02, $p = 0.042$) were independently associated with 1-year mortality. High corin level was not an independent predictor for 1-year mortality in the multivariate analysis (Table 6).

	Univariate		Multivariate*	
	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age	1.01 (0.99–1.02)	0.556		
Male gender	0.79 (0.46–1.34)	0.380		
Body mass index	1.03 (0.97–1.08)	0.359		
Hypertension	1.58 (0.96–2.62)	0.074	2.03 (1.03–3.99)	0.040
Diabetic mellitus	1.23 (0.71–2.12)	0.456		
Heart failure	2.12 (1.03–4.34)	0.041		
Cirrhosis	0.90 (0.34–2.41)	0.838		
Malignancy (solid tumor)	0.68 (0.40–1.15)	0.149		
ACEi/ARB exposure	1.75 (0.97–3.14)	0.061		
Diuretic exposure	1.72 (0.89–3.34)	0.108		
Contrast exposure	0.74 (0.42–1.31)	0.303		
Nephrotoxic agent exposure	2.72 (1.07–6.95)	0.037	4.49 (1.24–16.19)	0.022
Indication for ICU admission				
Pneumonia	1.01 (0.58–1.78)	0.968		
Sepsis	1.06 (0.52–2.14)	0.874		
Acute heart failure	0.28 (0.03–2.24)	0.228		
Massive bleeding	0.40 (0.09–1.84)	0.239		
Disease severity				
APACHE II scores	1.06 (1.02–1.09)	0.001		
SOFA scores	1.23 (1.13–1.34)	< 0.001	1.18 (1.06–1.31)	0.003
Ventilator usage	2.03 (0.43–9.58)	0.373		
Inotrope/vasopressor usage	1.54 (0.92–2.57)	0.100		
Mean arterial pressure (mmHg)	0.98 (0.96–1.00)	0.083		
White blood cells (K)	1.02 (0.99–1.04)	0.169		
Hemoglobin (mg/dL)	0.94 (0.83–1.07)	0.330		
Initial eGFR (mL/min /1.73 m^2)	0.98 (0.98–0.99)	< 0.001	0.99 (0.98–1.00)	0.007
Proteinuria	2.38 (1.25–4.53)	0.009		
Glucose (mg/dL)	1.00 (0.99–1.00)	0.025	0.99 (0.99–1.00)	0.006
Lactate (mg/dL)	1.01 (1.00–1.02)	0.082		
NT-pro-BNP (pg/mL)	1.00 (1.00–1.00)	0.045		
High corin (≥ 910 pg/mL)	3.43 (2.00–5.88)	< 0.001	2.15 (1.11–4.19)	0.024

Table 4. Univariate and multivariate analyses of factors associated with acute kidney injury within 48 h after intensive care unit admission. *OR* odds ratio, *CI* confidence interval, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *APACHE* Acute Physiology and Chronic Health Evaluation, *ICU* intensive care unit, *SOFA* Sequential Organ Failure Assessment, *eGFR* estimated glomerular filtration rate, *NT-pro-BNP* N-terminal pro-brain natriuretic peptide. *Adjusted for variables with $p < 0.1$ in the univariate analysis.

Subgroup (events/subjects)	High corin		High corin		p for interaction
	Crude OR (95% CI)	p	Adjusted OR (95% CI)*	p	
Diabetes mellitus					
Yes (28/83)	4.12 (1.37–12.42)	0.012	2.79 (0.76–10.21)	0.121	0.638
No (60/205)	3.22 (1.72–6.05)	< 0.001	1.75 (0.78–3.92)	0.175	
Proteinuria					
Yes (74/212)	2.64 (1.46–4.79)	0.001	1.95 (0.92–4.13)	0.080	0.906
No (14/76)	8.30 (2.08–33.19)	0.003	1.92 (0.34–10.83)	0.460	
Initial eGFR < 45					
Yes (71/161)	2.04 (1.05–3.96)	0.035	1.61 (0.72–3.58)	0.247	0.505
No (17/127)	4.47 (1.52–13.11)	0.006	3.56 (0.93–13.63)	0.064	
Heart failure					
Yes (16/35)	3.90 (0.83–18.28)	0.084	2.87 (0.35–23.82)	0.328	0.719
No (72/253)	3.23 (1.81–5.75)	< 0.001	2.07 (1.00–4.25)	0.049	
Pneumonia					
Yes (64/209)	2.63 (1.43–4.85)	0.002	1.64 (0.77–3.51)	0.200	0.112
No (24/79)	8.10 (2.43–26.97)	0.001	5.49 (1.10–27.43)	0.038	
Sepsis					
Yes (75/244)	3.16 (1.78–5.61)	< 0.001	2.17 (1.10–4.27)	0.025	0.883
No (13/44)	6.68 (1.26–35.28)	0.025	1.57 (0.02–145.27)	0.844	
Septic shock					
Yes (24/59)	4.50 (1.43–14.14)	0.010	2.27 (0.60–8.69)	0.229	0.894
No (64/229)	3.14 (1.70–5.79)	< 0.001	2.03 (0.93–4.43)	0.074	

Table 5. Stratified analysis of risk of acute kidney injury in patients grouped by the presence of diabetes, proteinuria, renal insufficiency, heart failure, pneumonia, sepsis, and septic shock. *eGFR* estimated glomerular filtration rate, *SOFA* Sequential Organ Failure Assessment. *Adjusted for hypertension, nephrotoxic agents, SOFA scores, initial eGFR, glucose.

Discussion

As a key enzyme in the renin–angiotensin–aldosterone system (RAAS), corin prevents the development of dilated cardiomyopathy by down-regulating RAAS activation, and its circulating level may serve as a valuable prognostic indicator of cardiac function. Serum corin concentrations was reported to have good prognostic value in patients with coronary artery disease[17] and HF[24]. This is the first study to measured corin in critically ill patients. This study illustrated that an elevated corin level on ICU admission is a useful biomarker to predict the onset of AKI within 48 h and may indicate an increased risk of 1-year mortality.

Corin and heart failure

Serum corin is a well-documented biomarker associated with the regulation of blood pressure and cardiac function[3,25]. Intraperitoneal administration of soluble corin in murine models of HF enhanced NP processing and activity, suppressed RAAS, and improved cardiac function and morphology[26]. Impaired corin expression and function were related to HF[26]. Patients with HF exhibited low serum corin levels[9,27]. Coincidentally, a case–control study disclosed that patients with HF were more likely to have elevated serum NT-pro-BNP and low corin levels. Furthermore, decreased corin levels were associated with higher severity of HF[25,28], and the progressive decline of corin levels has been used as a sensitive indicator of early systolic dysfunction before incipient HF[28]. A previous study associated a high circulating corin level (> 721 pg/mL) with fewer major adverse cardiac events in patients with acute myocardial infarction; however, patients in the low corin group tended to have underlying of HF and hypertension which led to low corin levels[9]. In our analysis, the prevalence of hypertension and HF were similar between the high and low corin groups (Table 1). Moreover, no interaction was found in subgroup analysis (Table 5).

Corin and renal function

Serum corin mitigates progressive renal dysfunction by increasing glomerular filtration and medullary vasa recta blood flow, and by inhibiting inflammation[17]. Our previous studies indicated that a low serum corin level (cutoff level < 1049.9 pg/mL) is a strong independent risk factor for progressive renal dysfunction but not for contrast-induced nephropathy developing within 48 h of coronary angiography[17]. In this study, high corin levels in patients with acute critical illness exhibited a highly negative correlation to initial eGFR and was associated with AKI within 48 h. On the other hand, similar to the expression of corin in chronic HF, low renal corin levels promoted sodium retention in rat models of nephrotic syndrome and glomerulonephritis[29]. Due to the different clinical contexts and corin levels mentioned above, corin may enhance the conversion of pro-ANP to ANP during acute illness in response to oxidative stress and renal inflammation, but not in late-phase or chronic disease[30,31]. ANP resistance may be caused by desensitization of natriuretic peptide receptor-A after chronic ANP

	Univariate		Multivariate*	
	Crude HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
Age	1.00 (0.99–1.00)	0.281		
Male gender	1.17 (0.84–1.63)	0.345		
Body mass index	0.97 (0.93–1.01)	0.098		
Hypertension	0.60 (0.44–0.83)	0.002	0.61 (0.42–0.89)	0.009
Diabetic mellitus	0.66 (0.46–0.94)	0.021		
Heart failure	0.74 (0.45–1.23)	0.249		
Cirrhosis	1.04 (0.57–1.92)	0.895		
Malignancy (solid tumor)	1.68 (1.23–2.28)	0.001	1.52 (1.07–2.16)	0.019
ACEi/ARB exposure	0.81 (0.55–1.20)	0.291		
Diuretics exposure	1.26 (0.84–1.89)	0.267		
Contrast exposure	0.97 (0.69–1.36)	0.856		
Nephrotoxic agents exposure	0.86 (0.47–1.59)	0.638		
Etiologies of ICU admission				
Pneumonia	0.91 (0.65–1.29)	0.597		
Sepsis	1.08 (0.70–1.68)	0.729		
Acute heart failure	0.31 (0.08–1.23)	0.096		
Massive bleeding	0.69 (0.30–1.55)	0.366		
Disease severity				
APACHE II scores	1.07 (1.05–1.09)	< 0.001	1.04 (1.01–1.07)	0.015
SOFA scores	1.16 (1.11–1.22)	< 0.001	1.10 (1.03–1.17)	0.005
Ventilator usage	2.09 (0.78–5.64)	0.146		
Inotrope/vasopressor usage	1.70 (1.24–2.34)	0.001		
Mean arterial pressure (mmHg)	0.98 (0.97–0.99)	< 0.001		
White blood cells (K)	0.98 (0.96–1.00)	0.087		
Hemoglobin (mg/dL)	0.86 (0.80–0.93)	< 0.001		
Initial eGFR (mL/min /1.73 m^2)	1.00 (1.00–1.00)	0.659		
Proteinuria	1.02 (0.72–1.44)	0.903		
Glucose (mg/dL)	1.00 (1.00–1.00)	0.104		
Lactate (mg/dL)	1.02 (1.01–1.02)	< 0.001	1.01 (1.00–1.02)	0.042
AKI during ICU admission	1.55 (1.13–2.13)	0.007		
NT-pro-BNP (pg/mL)	1.00 (1.00–1.00)	0.760		
High corin (≥ 910 pg/mL)	1.39 (1.02–1.90)	0.035		

Table 6. Univariate and multivariate analyses of factors associated with all-cause mortality within 1 year among critically ill patients. *HR* hazard ratio, *CI* confidence interval, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *APACHE* Acute Physiology and Chronic Health Evaluation, *ICU* intensive care unit, *SOFA* Sequential Organ Failure Assessment, *eGFR* estimated glomerular filtration rate, *NT-pro-BNP* N-terminal pro-brain natriuretic peptide. *Adjusted for variables with $p < 0.1$ in the univariate analysis.

stimulation[32]. We propose that elevated circulating corin levels indicate NP resistance and natriuretic peptide receptor (NPR) desensitization. High serum corin level could be recognized as an antecedent indicator of ANP synthesis only during acute illness. Therefore, treatment with human ANP has no benefit in reducing neither the requirement for dialysis nor death in critically ill patients who developed AKI during ICU stays[33]. Patients with effective NP utilization during acute illness reveal lower serum NT-pro-BNP levels and thus exhibit with lower corin levels (low corin group). Conversely, high serum corin and NT-pro-BNP were found in patients with ineffective NP utilization (high corin group). This positive correlation between corin and NT-pro-BNP levels would be compatible with the results shown in Table 2. Nevertheless, once NP resistance is established in chronic illness, high ANP/BNP levels might act through a negative feedback loop to inhibit corin synthesis, leading to a low circulating level. Consequently, the reversal of corin levels from high to low may thus be compatible with the transformation from acute to chronic disease (Fig. 3), as a reduced corin level has been recognized as a predictor for early cardiac dysfunction and development of HF[28].

Corin as biomarker of disease severity and mortality

Cardiac dysfunction is a common and potentially lethal complication of sepsis. Therefore, predictors of heart function after acute illness become significant prognostic factors of outcomes of patients under intensive care. Although the mechanism of pro-ANP release during sepsis needs further study, pro-ANP on the day of admission has been proven as a valuable prognostic marker for risk assessment that is similar to the APACHE II score and

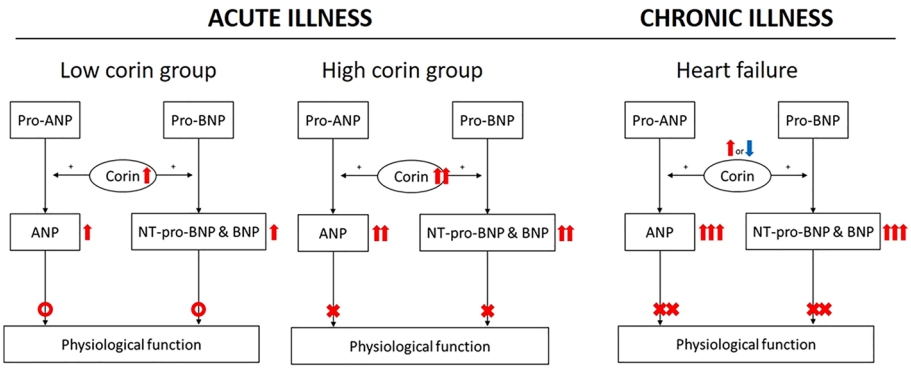

Fig. 3. Circulating corin levels in acute and chronic illness.

performs better than C-reactive protein and procalcitonin levels[34,35]. The pro-ANP value is significantly lower in sepsis survivors than nonsurvivors[34]. The proteolytic cleavage of pro-ANP by corin to yield ANP may play a pivotal role and may indicate NPR desensitization (Fig. 3).

On the other hand, elevated NT-pro-BNP and BNP levels caused by volume retention, HF, and poor renal clearance were meaningful predictors of mortality in chronic renal disease despite the lack of an established connection between the two predictors and increased mortality[30]. Elevated NT-pro-BNP (value ≥ 3270 pg/mL) is a well-known biomarker of left ventricular dysfunction[36]; furthermore, tachycardia occurring with concurrently increased NT-pro-BNP tended to predict poor outcomes in septic ICU patients[37]. To summarize, increased NT-pro-BNP, as a cleavage product of pro-BNP generated through the proteolytic activity of corin, could indicate deteriorating cardiac function in sepsis patients. We observed that patients in the high corin group also had higher NT-pro-BNP levels (5319 vs. 4185 pg/mL; $p = 0.012$) (Table 1). An investigation of the potential utility of the combination of neprilysin, a zinc-dependent metalloprotease that degrades active NPs, and corin to stratify patients with chronic HF revealed that the group with both neprilysin and corin elevations experienced higher mortality due to cardiovascular death and HF[24]. Because NT-pro-BNP and BNP have been used as diagnostic biomarkers for HF and are associated with increased in-hospital mortality[38], corin may be reasonably considered as a novel indicator for predicting outcomes of acute critical illness (Fig. 3). The results of previous studies[24,38] were similar to our finding that high corin levels correlated to an increased risk of AKI within 48 h of acute status and to a higher 1-year mortality via a gradual loss of NP-mediated suppression of the RAAS.

Limitations

This single-center study was limited by its relatively small case numbers. Because this study did not include healthy controls, it lacked a comparison of serum corin levels between patient and normal populations. Underlying diseases such as diabetes, hypertension, renal insufficiency, and HF may have influenced corin levels. Our adjusted analyses may have missed unidentified confounding factors. The etiologic relationship between elevated corin levels and AKI should be confirmed in further prospective or interventional studies.

Conclusions

Among critically ill patients, a high circulating corin level may be a valuable predictor of AKI within 48 h of ICU admission. Although the corin level was not an independent predictor of 1-year mortality, it was to a certain degree correlated with all-cause death within 1 year. In our opinion, increased corin levels indicate NP resistance and NPR desensitization. This study provides indirect evidence of corin's involvement in the pathophysiology of AKI.

Data availability

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

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Author contributions

PHH & RHC conceived of the presented idea. JYG & RHC analyzed and interpreted the patient data. CEC & JYG drafted and wrote the manuscript. CEC, JYG, RHC, CHW, CSK, JHW & PHH contributed to the interpretation of the results. Both PHH & RHC contributed to the final version of the manuscript. PHH supervised the project. All authors read and approved the final manuscript. Written informed consent was obtained from all participants.

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Competing interests
The authors declare no competing interests.

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