Low serum corin levels predict end-organ damage in patients with hypertensive crisis

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ABSTRACT

Objective: The study aimed to investigate the predictive power of serum corin levels for distinguishing between hypertensive urgency (HU) and hypertensive emergency (HE) in patients with hypertensive crisis (HC) admitted to the emergency department.

Methods: A total of 120 consecutive consenting adult patients diagnosed with HC and 55 age- and sex-matched healthy controls were enrolled. Blood pressure measurements [(systolic, diastolic, and mean arterial pressure (MAP)] and the evidence of end-organ damage at the first admission were recorded. Patients with HC were classified as patients with HE or HU according to the presence or absence of acute end-organ damage. Serum corin levels were compared between the 2 groups.

Results: The mean serum corin level was significantly lower in the HC group than in the control group; it was also lower in the HE group than in the HU group (p<0.001 for all). In the HE group, clinical features associated with end-organ damage included ST-elevation myocardial infarction (n=28, 46.7%), hemorrhagic stroke (n=11, 18.3%), ischemic stroke (n=11, 18.3%), and non–ST-elevation myocardial infarction (n=10, 16.7%). The receiving operator characteristic (ROC) analysis identified a serum corin cutoff value of 45 pg/mL for distinguishing patients with HE from patients with HU with 98.3% sensitivity and 95% specificity.

Conclusion: Our findings suggest that serum corin levels play an important role in regulating blood pressure and are involved in the pathogenesis of HC. Low serum corin levels may predict end-organ damage and serve as a guide for diagnostic decision making in patients with HC.

Keywords: hypertensive crisis, hypertensive emergency, hypertensive urgency, end-organ damage, corin

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Introduction

Hypertensive crisis (HC) is the leading cause of cardiovascular mortality and morbidity worldwide (1). Although the pathogenesis of HC remains unclear, presumable contributing factors include blood volume, vascular tone, neurohormonal activation, physical inactivity, and genetic factors (2). Although the treatment of HC risk factors has lowered the incidence, HC remains a common cause of emergency department (ED) admissions worldwide (3). Patients with HC admitted to an ED are considered to present with have hypertensive urgency (HU) or hypertensive emergency (HE), subsequently dictating the treatment strategy. HC is characterized by a marked elevation in blood pressure without the evidence of end-organ damage (4, 5). On the contrary, HE is associated with severely elevated blood pressure with accompanying end-organ damage (e.g., encephalopathy, congestive heart failure, acute coronary syndrome, stroke, and aortic dissection) (4). HC has been defined as systolic blood pressure (SBP) >180 mm Hg and diastolic blood pressure (DBP) >110 mm Hg (6). However, end-organ damage is more challenging to recognize in patients with HC; additionally, clinical differential diagnosis and time-consuming tests may delay diag-
HIGHLIGHTS

- Hypertensive emergency (HE) and hypertensive urgency (HU) are distinguished based on laboratory tests or radiological methods; however, such tests are time consuming. Therefore, a novel laboratory test is required to distinguish HU from HE.
- Serum corin level was found to be an independent predictor for distinguishing patients with HE from patients with HU.
- Serum corin regulates blood pressure and may reliably predict end-organ damage in patients with hypertensive crisis.

Diagnosis. Early diagnosis of end-organ damage and treatment to decrease blood pressure significantly reduce mortality and morbidity in patients with HE (5, 6). Patients with HC who present to an ED should be assessed to rule out target organ damage, thus facilitating early differential diagnosis.7 Emergency physicians classify patients with HC as patients with HU if end-organ damage does not occur and as patients with HE if the risk of death is evident by end-organ damage. Furthermore, they identify patients who require rapid blood pressure reduction and aggressive antihypertensive therapy in acute settings to prevent the progression of end-organ damage (8). Despite the severity of HE owing to end-organ damage and the risk of death, HE is not the most frequently observed condition. In the medical practice of emergency care, HU is frequently observed (7, 8).

Previous studies reported that HU exhibited the highest prevalence corresponding to 71.7% and 74.7% HC cases (7, 9). An international study with 387 patients with HC revealed the confirmation of HE after further tests, including laboratory tests and imaging modalities, which were conducted in only 10.1% patients (10). However, when admitted to an ED, patients with HC should be treated considering that they are at a potential risk of death until clinical and/or radiological tests exclude the possibility of HE and confirm HU (7). Moreover, the laboratory tests and radiological methods, including computed tomography and magnetic resonance imaging, that are employed to distinguish HE from HU in patients with HC are time consuming and expensive (7, 10). Therefore, novel laboratory markers are required for distinguishing patients with HU from patients with HE who require emergency treatment and appropriate follow-up in the ED.

Corin is a type II transmembrane serine protease synthesized by cardiomyocytes (11). The enzyme regulates blood volume, blood pressure, and cardiac function through the synthesis of natriuretic peptides (12). Previous studies have revealed that corin plays a key role in the transformation of pro-atrial natriuretic peptides (proANP) and pro-brain natriuretic peptides (proBNP) to active peptides (13). El Maraghi et al. (14) found a positive correlation between BNP levels and the extent of end-organ damage in patients with HC; they concluded that BNP was a biomarker for assessing the extent of heart and brain damage in patients with HE. We hypothesized that serum soluble corin levels differed between patients with HU and patients with HE. Thus, we presumed that they could serve as a potential differentiating factor and predict target organ damage in patients with HC. To our knowledge, the significance of corin or ANP in predicting end-organ damage in patients with HC has not been investigated. Therefore, in this study, we investigated the role of serum corin levels as a predictor of end-organ damage in patients with HC who were admitted to the ED.

Methods

Study design and setting
This study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, University of Health Sciences, Haseki Training and Research Hospital (approval number 525). This prospective cross-sectional study consisted of 120 consecutive consenting adult patients diagnosed with HC (60 each in the HE and HU subgroups; age range, 27-87 years) who were admitted to the ED of our tertiary care university hospital between October 2018 and January 2019. Data including age, sex, SBP, DBP, MAP, vital signs, corin levels at the first admission, and the presence of acute end-organ damage were obtained from all participants. The control group consisted of 55 age- and sex-matched healthy normotensive volunteers without any known disease and medications.

Selection of participants
The inclusion criteria included admission to the ED with HC (SBP >180 mm Hg and DBP >100 mm Hg), age ≥18 years, and oral or written consent provided by patients or their guardians. Patients with HC who had a history of chronic hypertension were included in the HE group if they developed acute end-organ damage, including acute coronary syndrome (e.g., ST-elevation myocardial infarction or non–ST-elevation myocardial infarction), ischemic stroke, and hemorrhagic stroke (e.g., intracerebral hemorrhage or subarachnoid hemorrhage). In this study, the differential diagnosis of HE, including ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, ischemic stroke, and hemorrhagic stroke, was made based on anamnesis and physical examination, cardiac markers, and radiological examination, as appropriate. A negative or inconclusive computed tomography scan was followed by diffusion-weighted imaging based on magnetic resonance imaging for the diagnosis of stroke. Patients with HC who did not develop end-organ damage were included in the HU group. All patients included in this study had initiated monotherapy with a single drug or combination therapy, including angiotensin-converting enzyme inhibitors (ACEi), diuretics, calcium channel blockers, angiotensin receptor blockers, and beta-blockers. The exclusion criteria included age <18 years; pregnancy; refusal to provide oral or written consent; known or suspected secondary hypertension (renal artery stenosis, Cushing syndrome, Conn syndrome, aortic coarctation, glomerulonephritis, and/or polycystic kidney disease); and a history of malignancy, chronic renal impairment (serum creatinine levels, >2.5 mg/dL), thyroid dys-
function, and/or liver cirrhosis. Blood pressure was measured by trained physicians in accordance with a standard protocol (15): after the patients rested in a supine position for at least 5 minutes, a mercury manometer was used to measure blood pressure at 3-minute intervals. SBP was determined by the first Korotkoff sound as the pressure in the cuff decreased (Korotkoff phase I); DBP was determined by the absence of sound (Korotkoff phase V). All measurements were repeated thrice, and the mean values were calculated. Acute organ damage was diagnosed in accordance with international guidelines (16-19).

The patients received antihypertensive therapy after presenting to the ED in accordance with the current 2017 American College of Cardiology/American Heart Association guidelines (20).

Blood sampling
Venous blood samples (5 mL) were drawn from the antecubital vein at admission in the absence of medications (i.e., oral or parenteral antihypertensive drugs), serum infusions, or diagnostic imaging techniques (computed tomography angiography of the brain) that could affect serum corin levels. Blood samples were collected in heparinized tubes and immediately stored at 4°C. Plasma was separated by centrifugation at 3000 revolutions per minute for 10 minutes and was stored at -80°C until further use. All serum samples were brought to room temperature before analysis. Serum corin levels were measured using a Quantikine enzyme-linked immunosorbent assay for human corin (KTE62815; Abbkine Inc., Wuhan, China). Absorbances were detected using a Biotek ELX800 (Biotek; Winooski, VT, USA) microplate reader that operates at a wavelength of 450 nm. All samples were assayed in duplicates. Intra and interassay coefficients of variation were less than 2.7% and 6.3%, respectively. Serum corin levels were expressed as pg/mL.

Statistical analyses
Before data were collected, a statistical power analysis was performed for estimating the required sample size. The analysis revealed that at least 120 participants and 55 healthy controls would be required to detect significant differences in serum corin levels between patients with HU and patients with HE, with a power of 95% and an alpha error of 5%. All statistical tests were performed using Statistical Product and Service Solutions statistical software for Windows (version 26.0; IBM Corporation, Armonk, NY, USA). Numerical data (corin, SBP, DBP, and MAP levels) were expressed as means ± standard deviations or as a minimum, maximum, and median; categorical variables (sex and age) were expressed as numbers (n) and percentages (%). Intergroup comparisons (controls vs. patients) and intragroup comparisons (HE vs. HU subgroups) were performed using Pearson chi-squared test for nonparametric data (sex) and Mann-Whitney U test for parametric variables (e.g., age and corin, SBP, DBP, and MAP levels). Normality tests were performed using Kolmogorov-Smirnov test. Spearman rank correlation test was used to assess the correlation between corin levels and blood pressure measurements (SBP, DBP, and MAP levels). Predictive factors were determined using ROC analysis with the forward method for determining corin cutoff values. The predictors, including serum levels of corin; SBP, DBP, and MAP levels; age; and sex, that can be significant to the HE and HU groups were modeled using binary logistics regression analysis. Confidence intervals were estimated at 95% level, and p values <0.05 were considered to indicate statistical significance.

Results
The mean age of 120 patients with HC was 59.90±11.80 years (range, 27-87 years), and 80 (66.7%) of them were women. Of the 120 patients, 73 (60.8%) patients had initiated 2-drug combination or single-pill combination therapy, and 47 (39.2%) patients had initiated monotherapy with a single drug. The mean age of 55 healthy controls was 58.90±7.60 years (range, 45-73 years), and 37 (67.3%) of them were women. Age and sex did not significantly differ between patients and healthy controls (p=0.937 for both). However, the mean serum corin level was significantly lower in patients than in healthy controls (57.50±43.50 pg/mL vs. 140.40±64.80 pg/mL, respectively; p<0.001) (Table 1, Fig. 1). Furthermore, stratification using serum corin concentrations (<25, 26-75, 76-99, and ≥100 pg/mL) revealed that corin levels were significantly lower in patients than in healthy controls (p<0.001; Table 1). ROC analysis identified a corin cutoff value of 76 pg/mL for distinguishing patients from healthy controls with 65% sensitivity, 96.4% specificity, a positive predictive value of 97.5%, and a negative predictive value of 55.8% [area under the curve (AUC), 0.807; 95% confidence interval (CI), 0.743-0.871; Fig. 2]. Furthermore, HC and control groups differed significantly concerning the mean SBP levels (196.25±21.90 mm Hg vs. 123.54±6.70 mm Hg, respectively), mean DBP levels (111.30±18.00 mm Hg vs. 75.18±7.60 mm Hg, respectively), and MAP levels (139.60±16.50 mm Hg vs. 91.30±5.90 mm Hg, respectively; p<0.001 for all comparisons; Table 1).

Age and sex did not significantly differ between the HU and HE subgroups (p=0.222 and p=0.053, respectively; Table 2). However, the mean serum corin level was significantly lower in the HE group than in the HU group (22.10±9.70 vs. 93.00±34.10 pg/mL, respectively; p<0.001; Table 2, Fig. 2). Similarly, stratification using serum corin concentrations (<25, 26-75, 76-99, and ≥100 pg/mL) revealed that corin levels were significantly lower in the HE group than in the HU group (p<0.001; Table 2). Clinical features associated with end-organ damage in patients with HE included ST-elevation myocardial infarction (n=28, 46.7%), ischemic stroke (n=11, 18.3%), non-ST-elevation myocardial infarction (n=10, 16.7%), and hemorrhagic stroke (n=11, 18.3%). Of the patients, 72.5% (n=87) patients exhibited comorbidities including diabetes mellitus (31.1%, n=27), cardiovascular disease such as coronary artery disease (21.8%, n=19), chronic kidney failure (13.8%, n=12), chronic heart failure (17.2%, n=15), and chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (16.1%, n=14).

ROC analysis identified a corin cutoff value of 45 pg/mL for distinguishing patients with HE from patients with HU; the cutoff exhibited 98.3% sensitivity, 95% specificity, a positive predictive
value of 95.2%, and a negative predictive value of 88.3% (AUC, 0.967; 95% CI, 0.929-1.000) (Fig. 3). Furthermore, the mean SBP level was significantly higher in the HE group than in the HU group (199.10±18.10 mm Hg vs. 193.40±25.10 mm Hg, respectively; p=0.022). Neither the mean DBP level nor the MAP level differed between the HE and HU subgroups (p=0.121 and p=0.813, respectively) (Table 2). The binary logistics regression analysis demonstrated that serum corin level remained an independent predictor for distinguishing patients with HE from patients with HU. According to binary logistics regression analysis, corin was the most important predictor for distinguishing patients with HE from patients with HU with an odds ratio of 1.216 (95% CI, 1.098-1.346; p<0.001; Table 3).

Serum corin levels were significantly negative and weakly correlated with SBP, DBP, and MAP levels in patients with HC (Spearman correlation coefficients, rho=-0.387, rho=-0.517, and rho=-0.478, respectively; p<0.001, all correlations) (Fig. 4).

**Discussion**

To our knowledge, this study is the first clinical study to investigate the role of serum corin levels in predicting end-organ damage in hypertensive crisis.
damage in patients with HC. The key findings are as follows: (1) the HC group had a higher percentage of women than men, and acute coronary syndrome was the most common cause of target organ damage in patients with HE; (2) serum corin levels were significantly lower in patients than in healthy controls, and a corin cutoff value of 76 pg/mL exhibited 65% sensitivity and 96.4% specificity for distinguishing patients from healthy controls; and (3) the mean serum corin level was significantly lower in patients with HE (target organ damage) than in patients with HU (no target organ damage), and a corin cutoff value of 45 pg/mL exhibited 98.3% sensitivity and 95% specificity for predicting target organ damage. HC is a common complaint in EDs because it is a complication of undiagnosed hypertension or treatment-resistant hypertension (8, 21). HE is defined as severe hypertension accompanied by acute end-organ damage (e.g., cardiac ischemia, nephropathy, retinopathy, and encephalopathy); HU is defined by

Figure 2. Specificity and sensitivity of serum corin cut-off for distinguishing patients with hypertensive crisis from controls using receiver operating characteristic curves (area under the curve, 0.807; 95% confidence interval 0.743–0.871)

Figure 3. Specificity and sensitivity of serum corin cut-off for distinguishing patients with hypertensive emergency from those with hypertensive urgency using receiver operating characteristic curves (area under the curve, 0.967; 95% confidence interval 0.929–1.000)

Figure 4. Correlations between corin level and blood pressure measurements in patients with hypertensive crisis
SBP - systolic blood pressure; DBP - diastolic blood pressure; MAP - mean arterial pressure

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a marked increase in blood pressure without acute end-organ damage. Treatment for HC depends on the extent of end-organ damage and the underlying cause of the condition (8, 20); therefore, distinguishing between HE and HU is crucial because patients with HE require immediate treatment with intravenous medications to prevent further end-organ damage. On the contrary, patients with HU can be treated with oral medications, which reduce blood pressure gradually over 24-48 hours (21). Although clinical presentation, electrocardiography, posterioranterior chest radiography, cranial–thoracic–abdominal computed tomography, blood urea nitrogen levels, and serum creatinine levels are useful for detecting end-organ damage, biomarkers that allow rapid differential diagnosis of HU and HE are urgently required. Various biomarkers have been reported to serve as early markers of several cardiovascular and cerebrovascular diseases (e.g., heart failure, acute coronary syndrome, hypertension, and hemorrhagic stroke) (22-25). Corin is a type II transmembrane serine protease principally synthesized by atrial cardiomyocytes and ventricular cardiomyocytes. Natriuretic peptides are important in regulating the salt and body fluid balance. In cells, these peptides serve as the precursors that are converted to active forms by proteolytic processing. Corin converts proANP to active ANP in a sequence-specific manner (13). The binding of ANP and BNP to their receptors stimulates intracellular cyclic guanosine monophosphate production, which results in natriuresis, diuresis, and vasodilatation (13). For years, radioimmunoassay and enzyme-linked immunosorbent assay have been used to measure ANP and BNP in a variety of clinical and experimental settings (26, 27). The antibodies used in such assays may not distinguish processed from unprocessed natriuretic peptides. For example, antibodies that bind to ANP may also recognize proANP. Consequently, it is not clear which molecular forms, whether ANP, proANP, or both, are measured in such assays (26).

Corin regulates the salt and water balance, blood pressure, and cardiac function (19, 26); it has been proposed as a potential biomarker for the diagnosis and prognosis of various diseases (22, 23, 25, 28). For example, Dong et al. (22) reported that serum corin could be safely used as a biomarker for diagnosing heart failure. Zhou et al. (13) found that corin was a predictor of major adverse cardiac events in patients with acute myocardial infarction, independent of established conventional risk factors. In a pilot study that included 116 patients with hemorrhagic stroke and 2498 healthy controls, Peng et al. (25) found that serum soluble corin levels reduced in patients with stroke when compared with healthy controls; they concluded that serum soluble corin might

### Table 2. Patient characteristics in hypertensive emergency and hypertensive urgency subgroups

| Characteristic | Hypertensive emergency (n=60) | Hypertensive urgency (n=60) | P-value* |
|---------------|-----------------------------|---------------------------|---------|
|               | Mean ± SD / n-%             | Median (25%-75%)          | Mean ± SD / n-%             | Median (25%-75%)          |         |
| Age           | 58.8±11.2 / 58.0 (51.25-64.50) | 61.0±12.5 / 60.0 (53.0-70.7) | 0.222 |
| Sex           |                              |                           |         |
| Male          | 15 / 25                      | 25 / 41                     | 0.053  |
| Female        | 45 / 75                      | 35 / 58.3                   |         |
| Corin (pg/mL) | ≤25 / 22.1±9.7               | 22.1 (13.8-29.5)           | 93.0±34.1 / 90.1 (71.9-97.7) | <0.001 |
|               | 26-75 / 21.7                | 19 / 16                     |         |
|               | 76-99 / 0.0                 | 29 / 48.3                   |         |
|               | ≥100 / 0.0                  | 0 / 14                      |         |
| SBP (mm Hg)   | 199.1±18.1 / 190.0 (180-210) | 193.4±25.1 / 199.5 (187.2-210.0) | 0.022  |
| DBP (mm Hg)   | 113.7±17.5 / 113.0 (100.0-127.5) | 109.0±18.3 / 110.0 (96.2-120.0) | 0.121  |
| MAP (mm Hg)   | 140.2±17.6 / 135.5 (126.6-153.3) | 139.0±15.4 / 136.6 (126.8-147.7) | 0.813  |

*Intragroup comparisons (hypertensive emergency vs. hypertensive urgency groups) were performed using chi-squared and Mann-Whitney U tests, as appropriate.

### Table 3. Independent predictors for distinguishing patients with hypertensive emergency from patients with hypertensive urgency identified using binary logistics regression analysis

| Characteristic | Univariate adjusted model | Multivariate unadjusted model | P-value | P-value |
|---------------|---------------------------|-------------------------------|---------|---------|
|               | OR (95% CI)               | OR (95% CI)                  |         |         |
| Age           | 1.016 (0.985-1.048)       | —                             | 0.309   | —       |
| Sex           | 0.467 (0.214-1.016)       | —                             | 0.055   | —       |
| SBP           | 1.012 (0.995-1.030)       | —                             | 0.157   | —       |
| DBP           | 0.985 (0.965-1.006)       | —                             | 0.158   | —       |
| MAP           | 0.996 (0.974-1.018)       | —                             | 0.692   | —       |
| Corin (pg/mL) | 1.216 (1.098-1.346)       | 1.216 (1.098-1.346)          | <0.001  | <0.001  |

CI - confidence interval; DBP - diastolic blood pressure; MAP - mean arterial pressure; OR - odds ratio; SBP - systolic blood pressure; SD - standard deviation.
patients with HC; therefore, it is a promising new biomarker for blood pressure and may reliably predict end-organ damage in patients with HE or indirectly acts through the conversion of natriuretic peptides is unknown. The manifestations of hypertensive end-organ damage, such as encephalopathy, congestive heart failure with preserved ejection fraction, aortic dissection, and subarachnoid hemorrhage, were not included in the study. The significance of serum levels of corin is unclear in such cases. Such complications should be considered in future studies that involve patients with HE of various causes. Corin is a newly identified protease, and its exact physiological functions are not yet fully understood; therefore, its significance in determining end-organ damage and prognosis in patients with HE is limited. The relationship between corin and end-organ damage warrants further investigation.

The pathophysiology of the corin pathway associated with the activation of ANP and BNP remains to be elucidated (26). Although previous studies in animal models and humans have demonstrated that corin, which plays a key role in the transformation of the natriuretic peptides, is critically involved in the regulation of salt-water balance, blood pressure, and cardiac function; the findings of clinical and experimental reports that assess corin and natriuretic peptide concentrations in hypertensive subjects remain controversial (13, 14, 26, 33, 35). Some studies have found decreased plasma natriuretic peptide and corin concentrations in response to elevated blood pressure, (13, 26, 33) whereas other studies have found increased plasma natriuretic peptide and corin concentrations (14, 35). Peng et al. (35) reported that serum corin levels were significantly lower in patients with HC (Spearman correlation coefficients, rho=-0.387, rho=-0.517, and rho=-0.478, respectively; p<0.001 for all), suggesting that corin deficiency is associated with the regulation of salt and water balance and blood pressure. These findings suggest that serum corin levels may serve as rapid biomarkers for diagnosing HC.

In conclusion, our findings suggest that serum corin plays a significant role in the regulation of blood pressure and the pathogenesis of HC. Decreased serum corin levels may reflect a severely disturbed salt and body fluid balance in patients with HE during HC, which results in inadequate natriuresis, diuresis, and vasodilatation leading to an increased risk of end-organ damage. Thus, low serum corin levels may predict end-organ damage and serve as a guide for diagnostic decision making in patients with HC. Furthermore, corin concentrations may facilitate the classification of HC as HE or HU. Serum corin levels may be useful for determining prognosis and assessing end-organ damage in patients with HC. Further investigation is warranted regarding the predictive and diagnostic value of corin.

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