

Diastolic dysfunction is associated with an increased risk of postcontrast acute kidney injury

Min-Jeong Lee, MD^a, Jin-Sun Park, MD, PhD^b, Hyuk-Hoon Kim, MD, PhD^{c,*}

Abstract

Study objective: Computed tomography (CT) is an important imaging modality in diagnosing a variety of disorders. Although systolic heart failure is a well-known risk factor for postcontrast acute kidney injury (PC-AKI), few studies have evaluated the association between diastolic dysfunction and PC-AKI. Therefore, the aim of our study was to investigate whether PC-AKI occurs more likely in patients with diastolic dysfunction.

Methods: This retrospective study was conducted by collecting the data of patients who visited an emergency medical center between January 2008 and December 2014. Patients who underwent contrast-enhanced CT (CECT) in the emergency department and had undergone echocardiography within 1 month of CECT were included. We defined PC-AKI as an elevation in the serum creatinine level of ≥ 0.5 mg/dL or $\geq 25\%$ within 72 hours after CECT.

Results: We included 327 patients, aged 18 years and older, who had a CECT scan and underwent an echocardiography within 1 month of the CECT scan at our institute over 20 years. The mean value of estimated glomerular filtration rate and E/E⁰ (early left ventricular filling velocity to early diastolic mitral annular velocity ratio) was 51.55 ± 7.66 mL·min⁻¹·1.73 m² and 11.56 ± 5.33 , respectively. A total of 32 patients (9.79%) developed PC-AKI. The prevalence of diabetes mellitus and chronic kidney disease was significantly higher in the PC-AKI group than in the non-PC-AKI group. Echocardiographic findings revealed that E/E⁰ was significantly increased in patients with PC-AKI. The logistic regression analysis showed that a higher E/E⁰ value (odds ratio [OR] 5.39, 95% confidence interval [CI] 1.51–25.23, P = .015) was a significant risk factor for PC-AKI.

Conclusion: This study demonstrated that, among the echocardiographic variables, E/E⁰ was an independent predictor of PC-AKI. This, in turn, suggests that diastolic dysfunction may be a useful parameter in PC-AKI risk stratification.

Abbreviations: CE-CT = contrast-enhanced CT, CHF = congestive heart failure, CIN = contrast-induced nephropathy, CKD = chronic kidney disease, CT = Computed tomography, DM = diabetes mellitus, ED = emergency department, EF = ejection fraction, eGFR = estimated glomerular filtration rate, LVEDD = left ventricular end-diastolic dimension, LVESD = left ventricular end-systolic dimension, LVMI = left ventricular mass index, MM = multiple myeloma, PC-AKI = postcontrast acute kidney injury, T.CO₂ = serum bicarbonate.

Keywords: diastolic dysfunction, emergency department, postcontrast acute kidney injury

1. Introduction

1.1. Background

Intravenous iodinated contrast media are routinely used to improve the diagnostic accuracy of computed tomography (CT).

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The use of CT imaging in the emergency department (ED) has increased exponentially.^[1] Contrast medium administration is reported to be the third most common cause of iatrogenic acute kidney injury,^[2,3] and has been linked to an increased risk of major adverse events, including dialysis initiation, renal failure, stroke, myocardial infarction, and death.^[2,4,5] In the ED, intravenous administration of contrast media for enhancement of CT imaging is often necessary in diagnosing acute critical conditions. Recent studies performed in the ED have reported an incidence of contrast-induced nephropathy (CIN) as high as 14%, and linked CIN to a 2-fold increased risk of major adverse events within 1 year.^[6,7] Although these reports are concerning, the causal relationship between the administration of intravenous contrast media and the development of acute kidney injury has recently been challenged.^[8,9]

The Contrast Media Safety Committee recommends that the term “postcontrast acute kidney injury” (PC-AKI) should replace the older term “CIN,” and suggests using the terms recommended by the American College of Radiology Committee on Drugs and Contrast Media when acute kidney injury occurs following contrast medium administration.^[10] The Contrast Media Safety Committee stated that PC-AKI is the best term to apply to renal function deterioration after intravascular contrast medium administration because, unlike some of the older terms, it does not imply that the contrast medium is the cause. PC-AKI is loosely defined as an increase in creatinine level or decrease in

glomerular filtration rate after contrast medium administration. The most common description is an increase in creatinine level by 25% after contrast medium administration or an absolute increase of 0.3 to 0.5 mg/dL within 3 days.

Congestive heart failure (CHF), especially in advanced stages of New York Heart Association class 3–4, contributes to the development of PC-AKI primarily by decreasing renal perfusion. It is related to systolic dysfunction and low stroke volume.^[11] In fact, some researchers specifically identified an ejection fraction (EF) of <30% to 40% as an independent predictor of CIN.^[12] However, the association between diastolic dysfunction and PC-AKI remains largely unknown until now.

The gold standard for estimating the diastolic function of the heart is to measure the left ventricular end-diastolic pressure with catheterization. However, it is invasive and not routinely practiced in the current clinical settings. On the other hand, E/E' (early left ventricular filling velocity to early diastolic mitral annular velocity ratio) can be assessed noninvasively with echocardiography and is known to be less influenced by heart rate, atrial activity, or EF.^[13]

A previous study demonstrated that, among the echocardiographic variables, E/E' was an independent predictor of CIN after coronary angiography.^[14] This, in turn, suggests that diastolic dysfunction may be a useful parameter in the risk stratification of patients with CIN.

However, it has been suggested that intra-arterial contrast medium administration during catheter-based angiography, with or without percutaneous coronary intervention, is associated with a higher incidence of PC-AKI than intravenous contrast medium administration.^[15,16] Catheter-based procedures may be complicated by hemodynamic instability, and by embolization of cholesterol or thrombi in the renal arteries caused by catheter manipulations.^[17] Any of these may lead to post-interventional AKI, which is often misinterpreted as CIN.^[18,19]

In this present study, we tested the hypothesis that, compared with patients who did not develop acute kidney injury, those who developed PC-AKI after contrast-enhanced CT (CECT) showed considerable diastolic dysfunction.

2. Materials and methods

2.1. Data source

This retrospective study was conducted by collecting the data of patients who visited an emergency medical center of a university-affiliated hospital in Korea (Ajou University Hospital) between January 2008 and December 2014. During the study period, our mean annual ED census was 76,657 total visits (range 44,997–91,994), with a mean annual admission rate of 25.03% (range 22.28–29.22%). We used a clinical research database containing basic information on patient demographic characteristics, diagnoses, and laboratory test results taken from the electronic health records.

This study was approved by the local institutional review board, and the need for informed consent was waived (approval no. AJIRB-MED-MDB-18-231). Patient information was anonymized and de-identified before the analysis.

2.2. Enrolled patients and study setting

In this single-hospital, retrospective case-control study, the data of patients who underwent CECT in the ED were extracted. Among the patients who underwent CECT, those who

- 1) underwent laboratory evaluations that included serum creatinine level measurements before CECT and within 72 hours after CECT, and
- 2) had undergone echocardiography within 1 month of the CECT were included.

Patients who

- 1) were 18 years old or younger,
- 2) had no hospital admission after undergoing CECT,
- 3) had any history of hemodialysis or end-stage renal disease, or
- 4) had incomplete or abnormal data for determining the development of PC-AKI were excluded.

The enrolled patients were divided into 2 groups according to the occurrence of PC-AKI. To determine the occurrence of PC-AKI, when multiple serum creatinine values were available within 72 hours, the highest serum creatinine level within 72 hours after the patient underwent CECT was extracted and compared with the baseline serum creatinine level before CECT (Roche Cobas Integra 800; Roche Diagnostics GmbH, Mannheim, Germany). Similar to other researchers, we defined PC-AKI as an elevation in the serum creatinine level of ≥ 0.5 mg/dL or $\geq 25\%$ within 72 hours after CECT.^[20–22]

2.3. Data collection

Standardized extraction of demographic, clinical, and laboratory data from the medical records was performed by an emergency physician and a nephrologist. Any discrepancy between the datasets extracted by the 2 physicians was resolved by a third physician. The physicians were blinded to the patients' serum laboratory test results. The patients' sex, age, body mass index, and medical history were obtained from the electronic health records. We extracted the laboratory results at the time of each patient's visit to the ER, to establish the patient's baseline status before undergoing CECT. Laboratory tests including the determination of serum levels of blood urea nitrogen, creatinine, and electrolytes were performed when the patient visited the ED. The comorbidities included hypertension, diabetes mellitus (DM), chronic kidney disease (CKD), heart failure, multiple myeloma (MM), and liver cirrhosis (all identified using the International Classification of Diseases, 9th Revision, Clinical Modification codes).

2.4. Echocardiographic parameters

Echocardiography was performed with either a Vivid 7 (GE Vingmed, Horten, Norway) or an iE33 (Phillips Medical Systems, Andover, Mass) according to the recommendations of the American Society of Echocardiography (ASE). To test intra-observer and interobserver variability, the E/E' of 20 consecutive patients were measured. Left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) were measured in 2-dimensional M mode. Left ventricular systolic function was defined by the EF. The EF was calculated using the modified Simpson's method (i.e., by subtracting LVESD from LVEDD). Left ventricular mass was estimated using the Devereux-modified American Society of Echocardiography cube formula, and the left ventricular mass index (LVMI) was calculated by dividing the left ventricular mass by the body surface area.

Pulsed wave Doppler was used to check velocities in the 4-chamber apical view. Volume sampling was positioned at the tip of the mitral valve to measure early left ventricular filling velocity (E) and left atrial contraction velocity (A). Tissue Doppler was then conducted with volume sampling repositioning at the septal annulus of the mitral valve to measure the early (E') and late (A) diastolic mitral annular velocities. E/E' and E/A were calculated to represent diastolic function. The deceleration time, defined as the time between the E wave and the upper deceleration slope extrapolated to the zero line, was also determined. The variability was determined as the difference between the two sets of observations divided by the mean of the observations and expressed as a percentage. The interobserver and intraobserver variability was $5.4 \pm 4.4\%$ and $4.4 \pm 3.8\%$ for the measurement of septal E/E'.

2.5. Statistical analysis

Continuous variables are reported as either the median with the interquartile range using the Mann-Whitney *U* test or as the mean and standard deviation using the 2-tailed *t* test, for comparisons depending on a normal distribution of data. Categorical variables are presented as frequencies and percentages, using the Chi-square test for comparison. A *P* value of $<.05$ was considered statistically significant. After univariate linear regression to determine the development of PC-AKI after CECT, the echocardiographic parameters with a *P* value of $\leq .05$ were included in the multivariate regression model. A univariate analysis was performed to identify factors associated with the occurrence of PC-AKI in patients who underwent CECT. Logistic

regression analysis was performed to identify the E/E' value that could be considered positively correlated with the occurrence of PC-AKI in patients who underwent CECT. Two-sided *P* values of $<.05$ were considered statistically significant. Further, we constructed receiver operating characteristic curves to evaluate our multivariate model for predicting the development of PC-AKI. All statistical analyses were performed using the R program software for Mac, version 3.2.2 (R Development Core Team, Vienna, Austria).

3. Results

3.1. Baseline characteristics of patients with and those without PC-AKI

We included 327 patients, aged 18 years and older, who had a CECT scan and underwent an echocardiography performed within 1 month of the CT scan at our institute over 20 years.

The baseline characteristics of the study subjects are detailed in Table 1. The mean age was 63.84 ± 14.66 years, and 48.54% were men. The mean values of estimated glomerular filtration rate (eGFR) and E/E' was $51.55 \pm 7.66 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ and 11.56 ± 5.33 , respectively. A total of 32 patients (9.79%) developed PC-AKI. The prevalence of DM, CKD, and MM was significantly higher in the PC-AKI group than in the non-PC-AKI group. The laboratory findings showed that patients with PC-AKI demonstrated significantly lower serum bicarbonate levels than those without PC-AKI. However, there were no differences in eGFR between the PC-AKI group and the non-PC-AKI group. The echocardiographic findings revealed that

Table 1
Baseline characteristics of the study subjects.

	All n=327	PC-AKI n=32	No PC-AKI n=295	<i>P</i> value
Age (yr)	63.84 ± 14.66	68.27 ± 10.98	63.36 ± 14.94	.064
Sex (male)	162 (48.54%)	15 (46.88%)	147 (49.83%)	.895
BMI (kg · m ⁻²)	24.15 ± 4.24	24.82 ± 6.51	24.08 ± 3.93	.859
HTN	65 (19.88%)	7 (21.88%)	58 (19.66%)	.816
DM	52 (15.90%)	10 (31.25%)	42 (14.24%)	.020
CKD	6 (1.83%)	3 (9.38%)	3 (1.02%)	.014
HF	17 (5.20%)	4 (12.50%)	14 (4.41%)	.073
MM	6 (1.83%)	3 (9.38%)	3 (1.02%)	.014
LC	10 (3.06%)	1 (3.13%)	9 (3.05%)	1
Laboratory data				
BUN	18.17 ± 11.99	22.87 ± 16.73	17.66 ± 11.28	.115
Creatinine	1.13 ± 0.81	1.55 ± 0.68	1.09 ± 0.64	.758
Potassium	4.04 ± 0.62	4.047 ± 0.88	4.04 ± 0.58	.869
T.CO2	22.80 ± 3.84	20.75 ± 4.66	23.02 ± 3.68	<.001
eGFR	51.55 ± 7.66	51.14 ± 7.75	51.59 ± 7.66	.752
Echocardiographic parameters				
E/E'	11.56 ± 5.33	14.82 ± 7.68	11.21 ± 4.90	<.001
E/A	0.88 ± 0.45	0.95 ± 0.73	0.87 ± 0.41	.721
DT	226.56 ± 162.45	202.00 ± 63.75	229.63 ± 170.67	.498
LVEF (%)	65.25 ± 9.06	62.21 ± 10.62	65.58 ± 8.83	.120
LV mass index	100.37 ± 29.65	112.55 ± 25.39	99.05 ± 29.81	.002
LVEDD	48.17 ± 5.14	49.16 ± 5.14	48.07 ± 5.16	.275
LVESD	30.07 ± 5.41	31.50 ± 5.83	29.92 ± 5.35	.131
TR_velocity	2.65 ± 2.00	2.67 ± 0.65	2.65 ± 2.11	.261

BMI=body mass index, BUN=blood urea nitrogen, CKD=chronic kidney disease, DM=diabetes mellitus, DT=deceleration time, E/A=early left ventricular filling velocity to left atrial contraction velocity ratio, E/E'=early left ventricular filling velocity to early diastolic mitral annular velocity ratio, eGFR=estimated glomerular filtration rate, HF=heart failure, HTN=hypertension, LC=liver cirrhosis, LV=left ventricular, LVEDD=left ventricular end-diastolic dimension, LVEF=left ventricular ejection fraction, LVESD=left ventricular end-systolic dimension, MM=multiple myeloma, PC-AKI=postcontrast acute kidney injury, T.CO2=serum bicarbonate, TR velocity=tricuspid regurgitation velocity.

Table 2
Differences in variables according to diastolic dysfunction.

	E/E' ≤ 8 n=82	8 < E/E' < 15 n=192	E/E' > 15 n=53	P value
Age (yr)	53.31 ± 13.91	65.33 ± 13.61	73.17 ± 11.14	<.001
Sex (male)	55 (67.07%)	90 (46.86%)	17 (32.08%)	<.001
BMI (kg·m ⁻²)	23.20 ± 3.72	24.58 ± 4.83	24.06 ± 4.31	.052
HTN	12 (14.63%)	45 (23.44%)	8 (15.09%)	.157
DM	9 (10.98%)	33 (17.19%)	10 (18.87%)	.355
CKD	3 (3.66%)	2 (1.04%)	1 (1.89%)	.298
HF	1 (1.22%)	6 (3.13%)	10 (18.87%)	<.001
MM	1 (1.22%)	3 (1.56%)	1 (1.89%)	.510
LC	2 (2.44%)	4 (2.08%)	4 (7.55%)	.139
PC-AKI	3 (3.66%)	20 (10.42%)	9 (16.98%)	.035
Laboratory data				
BUN	15.58 ± 9.64	17.96 ± 11.39	22.92 ± 15.70	.006
Creatinine	1.09 ± 0.78	1.12 ± 0.78	1.25 ± 0.97	.006
Potassium	4.03 ± 0.49	4.02 ± 0.60	4.09 ± 0.83	.997
T.CO2	22.93 ± 3.89	22.92 ± 3.39	22.19 ± 5.11	.259
eGFR	54.26 ± 7.23	51.14 ± 7.65	48.55 ± 7.20	<.001
Echocardiographic parameters				
E/E'	6.97 ± 1.09	11.08 ± 1.83	20.40 ± 7.10	<.001
E/A	0.96 ± 0.41	0.82 ± 0.41	0.97 ± 0.62	.001
DT	203.86 ± 58.48	242.32 ± 206.18	208.73 ± 81.09	.009
LVEF (%)	66.00 ± 6.82	65.44 ± 8.66	63.41 ± 12.73	.955
LV mass index	85.31 ± 21.96	100.97 ± 27.67	121.46 ± 33.68	<.001
LVEDD	46.62 ± 4.65	48.29 ± 4.83	50.17 ± 6.31	.002
LVESD	28.88 ± 3.94	29.95 ± 5.04	32.34 ± 7.98	.028
TR_velocity	2.34 ± 0.43	2.76 ± 2.61	2.81 ± 0.53	<.001

BMI = body mass index, BUN = blood urea nitrogen, CKD = chronic kidney disease, DM = diabetes mellitus, DT = deceleration time, E/A = early left ventricular filling velocity to left atrial contraction velocity ratio, E/E' = early left ventricular filling velocity to early diastolic mitral annular velocity ratio, eGFR = estimated glomerular filtration rate, HF = heart failure, HTN = hypertension, LC = liver cirrhosis, LV = left ventricular, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic dimension, MM = multiple myeloma, PC-AKI = postcontrast acute kidney injury, T.CO2 = serum bicarbonate, TR velocity = tricuspid regurgitation velocity.

E/E' and LVMI were significantly increased in patients with PC-AKI (Table 1).

When patients were classified into 3 groups based on E/E' values of 8 and 15, PC-AKI occurred in 9 (16.98%) patients in the highest tertile, compared with 20 (10.42%) in the middle tertile and 3 (3.66%) in the lowest tertile ($P = .03$). In addition, patients in the highest tertile were older and had lower eGFR levels (Table 2). Among the echocardiographic parameters, LVMI, LVEDD, and LVESD were significantly increased in patients in the highest tertile (Table 2).

3.2. Risk factors for the development of PC-AKI

The logistic regression analysis showed that a higher E/E' value (odds ratio [OR] 5.39, 95% confidence interval [CI] 1.51–25.23, $P = .015$) was a significant risk factor for PC-AKI (Table 3). After adjustment for DM, CKD, MM, and serum bicarbonate (T.CO2), E/E' remained as an independent risk factor (OR 1.09, 95% CI 1.02–1.16, $P = .009$, as a continuous variable). The validity of the multivariate model was verified by the Hosmer and Lemeshow test ($P = .712 > .05$).

Table 3
Univariate and multivariate logistic regression analysis for postcontrast acute kidney injury.

Variables	Univariate Odds ratio (95% CI)	P value	Multivariate Odds ratio (95% CI)	P value
DM	2.74 (1.16–6.07)	.016	2.37 (0.92–5.72)	.062
CKD	10.07 (1.79–56.60)	.006	6.53 (0.72–48.47)	.071
MM	10.07 (1.79–56.60)	.006	10.57 (1.66–66.03)	.009**
T.CO2	0.87 (0.79–0.95)	.002	0.91 (0.82–1.00)	.062
E/E'	1.088 (1.03–1.15)	.002	1.09 (1.02–1.16)	.009**
E/E' ≤ 8	-	-	-	-
8 < E/E' < 15	3.06 (1.01–13.26)	.078	-	-
E/E' > 15	5.39 (1.51–25.23)	.015	-	-

CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, E/E' = early left ventricular filling velocity to early diastolic mitral annular velocity ratio, MM = multiple myeloma, T.CO2 = total carbon dioxide.

** P value < .05.

3.3. Receiver operating characteristic analysis of E/E' for the development of PC-AKI

To estimate the predictive accuracy of the echocardiographic parameter E/E' for the development of PC-AKI, receiver operating characteristic analysis was performed. The area under the curve for E/E' was 0.75 (95% CI 0.68–0.82, $P < .001$) (Fig. 1).

4. Discussion

This is the first study to show the relationship between PC-AKI and diastolic dysfunction after CECT in the ED. This study

showed that patients with PC-AKI exhibited higher E/E' and LVMI on echocardiography. Increased E/E', which is a well-known marker of increased left ventricular end-diastolic pressure, can be assessed noninvasively with echocardiography in real clinical settings.

In addition, the highest tertile of E/E' was associated with a significantly increased risk of PC-AKI, beyond the well-known risk factors such as DM, MM, and CKD. This indicates that diastolic dysfunction may be a useful parameter for predicting the development of PC-AKI after a CECT scan.

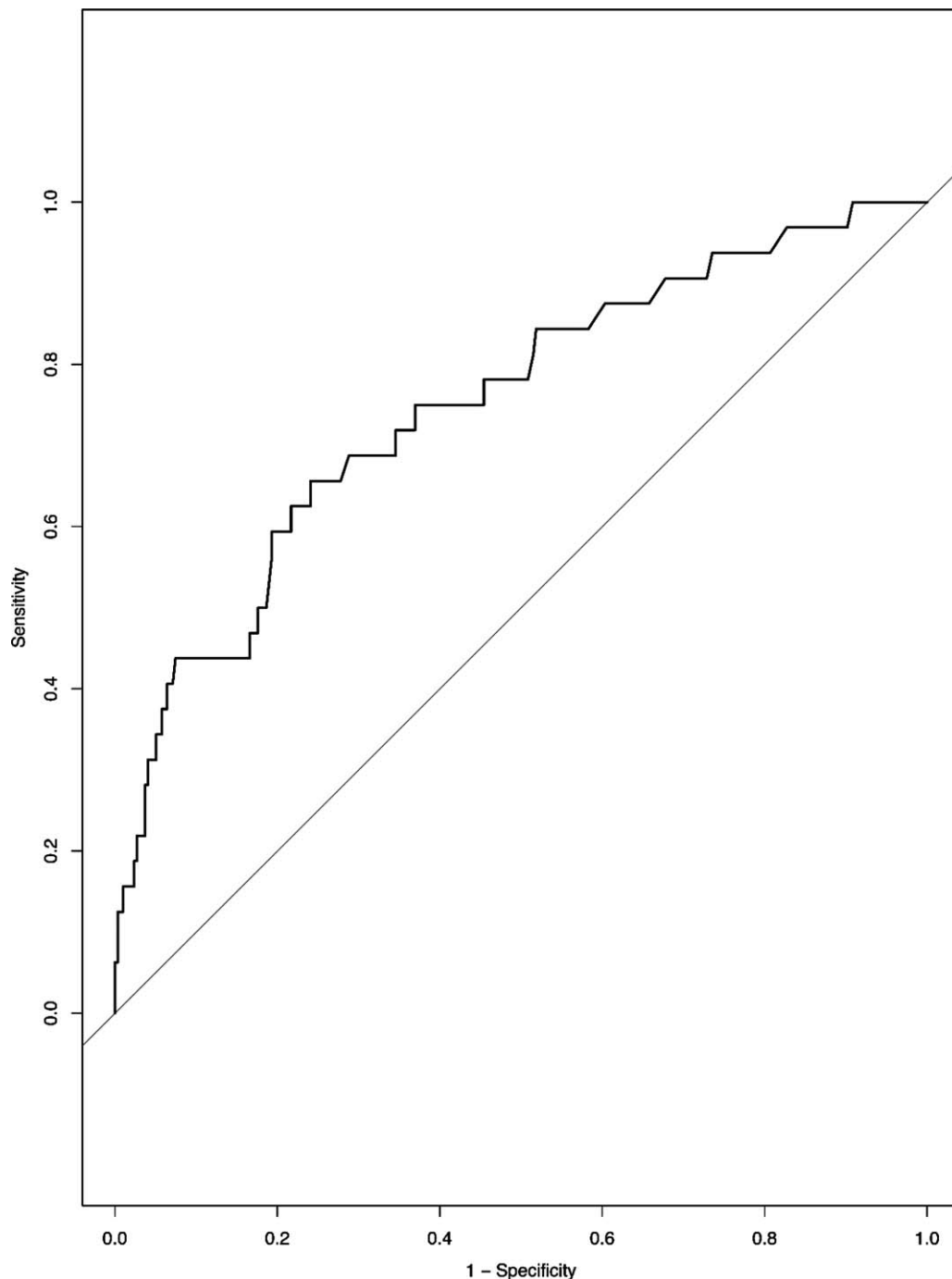


Figure 1. Receiver operating characteristic curve for the development of postcontrast acute kidney injury according to the echocardiographic variable E/E' (early left ventricular filling velocity to early diastolic mitral annular velocity ratio). The area under the curve of E/E' was 0.75.

The commonly reported risk factors for PC-AKI include renal insufficiency, DM, advanced age, heart failure, periprocedural volume depletion or hypotension, and high volume of contrast media.^[23,24] In our study, DM, CKD, MM, and low T.CO₂ were risk factors of PC-AKI development.

Although CHF is a well-proven risk factor for CIN, only low EF has previously been studied among various components of heart failure such as diastolic dysfunction, ventricular hypertrophy, and volume overload.^[11,12,25] This has likely been because a decreased effective circulatory volume is considered the primary event in the development of CIN in patients with CHF.^[26,27]

Moreover, most studies demonstrated that EF only affects the CIN rates in patients with severe CHF of New York Heart Association class 3–4 or with an EF of <30% to 40%. Given that CIN occurs in higher rates in patients with lower severity of CHF, the hemodynamic compromise status in milder stages of heart failure may not be properly represented by EF.^[12]

Pump failure and decreased renal perfusion may aggravate the impairment of renal function by mainly activating the renin-angiotensinogen-aldosterone system. The pathophysiological mechanisms in systolic heart failure including renal ischemia and increased oxidative stress play an important role in the development of PC-AKI.^[28] Initially, left ventricular hypertrophy occurs to compensate for the stiffness of the left ventricle, by increasing stroke volume. However, pathologic proliferation, fibrotic deposition, and calcification of the ventricle become evident, and left ventricular compliance eventually decreases.^[29] The same vicious cycle in hemodynamics is considered to be the chief mechanism behind a higher E/E' causing PC-AKI. Further, there is accumulating evidence demonstrating the relationship between diastolic dysfunction and increased inflammation, neurohumoral activation, and impaired renal hemodynamics despite the presence of preserved left ventricular EF.^[30–33]

This study has several limitations. First, it was a single-center study. Further large-scale, randomized controlled multicenter trials are needed to confirm and assess the clinical applicability of our findings. Second, there may be a selection bias because patients who visited the ED and underwent both CECT and echocardiography may be high-risk patients. Therefore, our results may overestimate the incidence of PC-AKI in the general ED. However, it is indisputable that diastolic dysfunction is an independent risk factor for the development of PC-AKI because our study confirmed that the PC-AKI risk increased according to E/E' among our patients. Third, we could not provide information about contrast volume, type of contrast media, and other nephrotoxic drugs used before and after CECT scan. Fourth, studies were observational in nature, the influence of residual confounders could not be completely excluded.

In conclusion, we demonstrated that, among the echocardiographic parameters, E/E' can be a useful predictor for the development of PC-AKI after a CECT scan. It should be noted that the occurrence of PC-AKI after CECT is higher in the presence of diastolic dysfunction. Nephroprotective point-of-care clinical decision support has the potential to improve outcomes in ED patients with diastolic dysfunction.

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