Does Exposure to Computed Tomography Contrast Media Increase Risk of End-Stage Renal Disease?

Background: There are many studies on acute kidney injury (AKI) after exposure to contrast media in patients with chronic kidney disease (CKD). However, whether the risk of end-stage renal disease (ESRD) increases after exposure to contrast media in the long term, regardless of development of AKI after such exposure, has not been studied.

Material/Methods: The electronic health records of patients diagnosed with CKD and followed up from 2014 to 2018 at a tertiary university hospital were retrospectively collected. Patients were divided into patients who progressed to ESRD (ESRD group) and those who did not (non-ESRD group). Patients in the non-ESRD group were matched 1:1 to those in the ESRD group by using disease risk score generation and matching. Multivariate logistic regression analysis was performed to assess the effect of contrast media exposure on progression to ESRD.

Results: In total, 179 patients were enrolled per group; 178 (99.4%) were in CKD stage 3 or above in both groups. Average serum creatinine was 4.31±3.02 mg/dl and 3.64±2.55 mg/dl in the ESRD and non-ESRD groups, respectively (p=0.242). Other baseline characteristics were not statistically significant, except for the number of times contrast-enhanced computed tomography (CECT) was performed (0.00 [Interquartile range (IQR) 0.00–2.00] in the ESRD group and 0.00 [IQR 0.00–1.00] in the non-ESRD group [p=0.006]); in multivariate logistic regression, this number (OR=1.24, 95% CI=1.08–1.47, p=0.006) was significantly related to progression to ESRD.

Conclusions: The use of CECT increased the risk of ESRD 1.2-fold in advanced and stable CKD outpatients after 5-year follow-up.

MeSH Keywords: Contrast Media • Kidney Failure, Chronic • Renal Replacement Therapy

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Background

Contrast-enhanced computed tomography (CECT) is becoming one of the most important diagnostic modalities, and there is no doubt regarding its usefulness. CECT occasionally causes contrast-induced acute kidney injury (CI-AKI), which is defined as an acute decrease in kidney function after injection of contrast media, without other explainable etiologies [1–3]. The incidences of CI-AKI range from 2% to 15% in the general population [2,4–6]. Old age, known chronic kidney disease (CKD), diabetes, hypertension, heart failure, proteinuria, anemia, non-steroidal anti-inflammatory drug use, use of more than 100 ml of contrast media, and intraarterial injection are known risk factors for CI-AKI [2,4,7–11]. The incidence of CI-AKI in patients with CKD of varying degrees was slightly higher, ranging from 5% to 22% [1,5,12]. There are many studies on the effects of contrast media; however, most studies focused on acute kidney injury (AKI) caused by contrast media and regard AKI after contrast media exposure as a transient and reversible event.

As the prevalence of CKD is quite substantial, ranging from 11% to 13% worldwide [13], many CKD patients and physicians encounter clinical situations that force them to choose between diagnostic accuracy using CECT or preserving kidney function at the expense of accurate diagnosis. CI-AKI is by definition a type of AKI; however, irrespective of CI-AKI development, whether the risk of end-stage renal disease (ESRD) after contrast media exposure increases in CKD patients after a long period has not yet been fully studied. Thus, we aimed to investigate the long-term effect of contrast media exposure on advanced CKD patients in this study.

Material and Methods

Data source

We used a clinical research database containing basic information on patient demographics, diagnoses, drug prescriptions, and laboratory test results originating from the electronic health records (EHR) of a tertiary university-affiliated hospital in Korea (Ajou University Hospital) between January 1995 and March 2018. The EHR system includes information based on unique, de-identified patient numbers, combined with age and sex, diagnostic codes based on the International Classification of Diseases-10 (ICD-10), laboratory test results, and prescribed procedures/treatments from approximately 2.9 million patients (including 543 617 inpatients). This study was approved by the local institutional review board (MED-MDB-16-443). Patient information was anonymized and de-identified prior to analysis. Requirement for informed consent was waived due to the study’s retrospective nature.

Study design and patient selection

This was a retrospective, single-hospital, nested, case-control study. To investigate the effect of CECT on progression to ESRD in CKD patients, we selected 3544 patients as follows: (a) Outpatients whose diagnosis included CKD or ESRD from January 2014 to December 2018; (b) patients who had at least 1 set of baseline laboratory results, including serum creatinine level within the 6-month window prior to the study period; and (c) patients who had sufficient information about the procedures and diagnoses during the study period. The following patients were excluded from the study: (a) patients who were on maintenance dialysis before the study period; (b) patients who were newly diagnosed with CKD after beginning the study period; and (c) patients who lacked critical clinical and laboratory data. The enrolled patients were divided into ESRD and non-ESRD groups. ICD-10 codes N18.1, N18.2, N18.3, N18.4, N18.5, and N18.9 were used to identify CKD patients from EHR. Likewise, ICD-10 codes N18.5C, N18.5CA, and N18.5CB were used to distinguish ESRD patients from EHR. Diagnosis of CKD patients who progressed to ESRD and started renal replacement therapy during the study period were classified into the ESRD group and patients who did not were classified into the non-ESRD group.

Variables

Demographic data, including age at the beginning of the study period and sex, were extracted from the EHR. Predisposing medical conditions reportedly associated with development of kidney injury after contrast media administration, including diabetes, hypertension, and heart failure, were also identified using the corresponding ICD-10 code. Enrolled patients with CKD were graded by their estimated glomerular filtration rate (eGFR), which is calculated by the Modification of Diet in Renal Disease Study equation. By definition, CKD stage 1 was defined as eGFR ≥90 mL/min/1.73 m², stage 2 as 60 mL/min/1.73 m² ≤eGFR <90 mL/min/1.73 m², stage 3 as 30 mL/min/1.73 m² ≤eGFR <60 mL/min/1.73 m², stage 4 as 15 mL/min/1.73 m² ≤eGFR <30 mL/min/1.73 m², and stage 5 as eGFR <15 mL/min/1.73 m². Laboratory results, including serum creatinine, blood urea nitrogen (BUN), hemoglobin, hematocrit, alanine aminotransferase (ALT), aspartate aminotransferase (AST), potassium, sodium, and total protein levels in the 6-month window prior to the study period, were also evaluated. The number of times CECT was performed during the study period before the diagnosis of ESRD in enrolled patients was counted.

Contrast media used

Two types of low-osmolality nonionic contrast agents, iohexol and iopamidol, were used while performing CECT throughout the
study: iohexol were used for routine abdomen CT (Omnihexol\textsuperscript{®}, Korean United Pharm Inc, Seoul, South Korea), CT for gastrointestinal tract bleeding (Scanlux\textsuperscript{®}, Tecmed Pharma, Midrand, Republic of South Africa), routine chest CT (Scanlux\textsuperscript{®}), pulmonary CT angiography (Omnipaque\textsuperscript{®}, GE Healthcare, Princeton, NJ), brain CT angiography and perfusion CT (Omnihexol\textsuperscript{®}), neck CT (Omnipaque\textsuperscript{®}), facial CT (Omnipaque\textsuperscript{®}), CT for aortic dissection (Omnipaque\textsuperscript{®}), and lower-extremity CT angiography (Omnihexol\textsuperscript{®}). Iopamidol was used for liver and pancreas CT (Iopamiro\textsuperscript{®}, Ilsung pharmaceuticals, Seoul, South Korea) and brain CT angiography (Pamiray\textsuperscript{®}, DK Life Science, Seoul, South Korea). In total, 140 mL of contrast agent was used in CT protocols involving intra-abdominal organs (e.g., routine abdomen, liver, pancreas, and kidney), CT for aortic dissection, and lower-extremity CT angiography. In all other protocols, 90 mL of contrast agent was used. In all cases, contrast media were administered intravenously.

The prophylaxis protocol for CI-AKI at our institution is not unified, and patients received prophylactic treatment on a case-by-case basis. Even though the protocols consistently included isotonic saline hydration and N-acetylcysteine pretreatment, the indications for this prophylaxis protocol varied among clinicians.

**Disease risk score analysis**

Disease risk score generation and matching were performed using the R package MatchIt (R Foundation for Statistical Computing, Vienna, Austria). Briefly, disease risk score estimates, which represent the probability of progression to ESRD for enrolled patients, were generated using a logistic regression model derived from clinical variables. Following disease risk score generation, patients were matched by using a 1:1 optimal matching method. Matching was performed without replacement, and non-matched results were discarded. Accordingly, the patients diagnosed with ICD-code N18.1 were included at first. However, after disease scoring matching, no patients diagnosed with ICD-code N18.1 in the non-ESRD group were matched with patients diagnosed with ICD-code N18.1 in the ESRD group.

**Statistical analysis**

All variables were subjected to normality testing. Continuous variables with normal distribution were reported as mean and standard deviation (SD) using the two-tailed t test. Continuous variables with skewed distribution were reported as either median with interquartile range (IQR) using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages, using the chi-square test. Univariate analysis was performed to identify factors associated with progression to ESRD in CKD patients. Logistic regression analysis was performed to identify whether the CECT count was positively correlated with progression to ESRD. Two-sided P values <0.05 were considered statistically significant. Statistical analysis was performed using the R program software for Mac, version 3.2.2 (The R Foundation for Statistical Computing, c/o Institute of Statistical Mathematics).
Results

There were 3544 outpatients whose diagnosis included CKD or ESRD before December 31, 2017. Patients who were diagnosed with ESRD before the study period (n=211), patients who were newly diagnosed with CKD during the study period (n=1929), and patients with incomplete data (n=418) were excluded. Among the 986 patients who were diagnosed with CKD before the study period, 179 patients progressed to ESRD during the study period. Through 1:1 disease score matching, the other 179 matched patients were chosen from the non-ESRD group who did not progress to ESRD during the study period (Figure 1A). Figure 1B shows a histogram of the density of disease score distribution in the ESRD group and non-ESRD group before and after matching.

Baseline characteristics of the ESRD group and non-ESRD group are shown in Table 1. CKD stages categorized by eGFR were not different between the 2 groups. A total of 178 patients (99.4%) were in CKD stage 3 or above in both groups, and their average serum creatinine was 4.31±3.02 mg/dl and 3.64±2.55 mg/dl in the ESRD group and non-ESRD group, respectively (p=0.242). Other demographic characteristics, underlying diseases that can contribute to CKD progression, and laboratory results were compared between the groups.

Table 1. Baseline characteristics of enrolled patients.

|                              | ESRD group (%) | Non-ESRD group (%) | P-value |
|------------------------------|----------------|---------------------|---------|
| Sex                          |                |                     |         |
| Male                         | 113 (63.1)     | 105 (58.7)          | 0.448   |
| Female                       | 66 (36.9)      | 74 (41.3)           |         |
| Age (years)                  | 56.34±13.99    | 56.98±13.72         | 0.664   |
| CKD stage*                   |                |                     |         |
| 2                            | 28 (15.6)      | 27 (15.1)           |         |
| 3                            | 28 (15.6)      | 27 (15.1)           |         |
| 4                            | 84 (46.9)      | 96 (53.6)           |         |
| 5                            | 66 (36.9)      | 55 (30.7)           |         |
| Underlying disease           |                |                     |         |
| Diabetes                     | 83 (46.4)      | 68 (38.0)           | 0.134   |
| Hypertension                 | 66 (36.9)      | 51 (28.5)           | 0.115   |
| Heart failure                | 8 (4.5)        | 9 (5.0)             | 1       |
| Blood urea nitrogen (mg/dL)  | 44.86±22.17    | 40.55±21.18         | 0.06    |
| Serum creatinine (mg/dL)     | 4.31±3.02      | 3.64±2.55           | 0.242   |
| Hemoglobin (g/dL)            | 10.80±1.76     | 10.70±1.93          | 0.601   |
| Hematocrit (%)               |                |                     |         |
| Alanine aminotransferase (U/L)| 15.00 [11.00–23.50] | 15.00 [10.00–21.00] | 0.242 |
| Aspartate aminotransferase (U/L)| 18.00 [15.00–24.00] | 19.00 [16.00–25.00] | 0.06    |
| Serum potassium (mMol/L)     | 4.93±0.78      | 4.82±0.81           | 0.203   |
| Serum sodium (mMol/L)        | 139.13±3.23    | 139.51±3.51         | 0.295   |
| Total protein (g/dL)         | 6.73±0.67      | 6.86±0.83           | 0.09    |
| Number of times contrast-enhanced CT was performed (n) | 0.00 [0.00–2.00] | 0.00 [0.00–1.00] | 0.006 |
| Average amount of administered contrast media (mL) | 139.55 [0.00–205.00] | 96.26 [0.00–115.00] | 0.04 |

ESRD – end-stage renal disease; CKD – chronic kidney disease; CT – computed tomography. * CKD stage 2=60 mL/min/1.73 m² £ estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m², stage 3=30 mL/min/1.73 m² £ eGFR <60 mL/min/1.73 m², stage 4=15 mL/min/1.73 m² £eGFR <30 mL/min/1.73 m², stage 5=eGFR <15 mL/min/1.73 m².

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not significantly different between the 2 groups. CECT was performed 0.00 [IQR 0.00–2.00] times in the ESRD group and 0.00 [IQR 0.00–1.00] times in the non-ESRD group (p=0.006). The average amount of applied contrast media was 139.55 [IQR 0.00–205.00] mL in the ESRD group and 96.26 [IQR 0.00–115.00] mL in the non-ESRD group, and the difference was statistically significant (p=0.04).

Univariate and multivariate logistic regression regarding factors contributing to progression to ESRD are shown in Table 2. In univariate logistic regression, serum creatinine level (odds ratio [OR]=1.09, 95% confidence interval [CI]=1.01–1.18, p=0.03), and number of times CECT was performed (OR=1.21, 95% CI=1.06–1.40, p=0.008) were statistically significant factors for predicting progression to ESRD. After adjusting for multiple confounders, the number of times CECT was performed (OR=1.24, 95% CI=1.08–1.47, p=0.006), serum ALT (OR=1.03, 95% CI=1.00–1.05, p=0.022), and AST (OR=0.97, 95% CI=0.94–0.99, p=0.023) were significantly related to progression to ESRD in multivariate logistic regression.

To compare the 2 models including and excluding the number of times CECT was performed, DeLong’s test was performed for 2 correlated receiver operating characteristic (ROC) curves. The results are shown in Figure 2. The 2 models were significantly different (p=0.04). The area under the ROC curve (AUROC) of the model including the number of times CECT was performed was 0.6595, and it was higher than the AUROC of the model excluding the number of times CECT was performed, which was 0.0689.

### Table 2. Logistic regression for ESRD progression.

|                | Univariate OR (95% CI) | P-value | Multivariate OR (95% CI) | P-value |
|----------------|------------------------|---------|--------------------------|---------|
| Sex (Male)     | 1.21 (0.79–1.85)       | 0.39    | –                        | –       |
| Age            | 1.00 (0.98–1.01)       | 0.66    | –                        | –       |
| CKD stage*     |                        |         |                          |         |
| 3              | 1.04 (0.04–27.12)      | 0.98    | –                        | –       |
| 4              | 0.88 (0.04–22.36)      | 0.93    | –                        | –       |
| 5              | 1.20 (0.05–30.82)      | 0.90    | –                        | –       |
| Diabetes       | 1.41 (0.93–2.15)       | 0.11    | –                        | –       |
| Hypertension   | 1.47 (0.94–2.29)       | 0.09    | –                        | –       |
| Heart failure  | 0.88 (0.32–2.36)       | 0.80    | –                        | –       |
| Serum creatinine | 1.09 (1.01–1.18) | 0.03*   | –                        | –       |
| Blood urea nitrogen | 1.01 (1.00–1.02) | 0.06    | –                        | –       |
| Hemoglobin     | 1.03 (0.92–1.15)       | 0.60    | –                        | –       |
| Alanine aminotransferase | 1.00 (0.99–1.00) | 0.32    | 1.03 (1.00–1.05) | 0.022 |
| Aspartate aminotransferase | 1.00 (0.99–1.00) | 0.18    | 0.97 (0.94–0.99) | 0.023 |
| Serum potassium | 1.19 (0.91–1.55)       | 0.20    | –                        | –       |
| Serum sodium   | 0.97 (0.91–1.03)       | 0.30    | –                        | –       |
| Total protein  | 0.78 (0.59–1.04)       | 0.09    | –                        | –       |
| Number of times contrast-enhanced CT was performed | 1.21 (1.06–1.40) | 0.008* | 1.24 (1.08–1.47) | 0.006 |

OR – odds ratio; CI – confidence interval; CT – computed tomography; CKD – chronic kidney disease. * CKD stage 3=30 mL/min/1.73 m$^2$ < eGFR <60 mL/min/1.73 m$^2$, stage 4=15 mL/min/1.73 m$^2$ < eGFR <30 mL/min/1.73 m$^2$, stage 5=eGFR <15 mL/min/1.73 m$^2$. Adjustment for multiple confounders included sex, age, chronic kidney disease stage, past history of diabetes, hypertension, heart failure, serum creatinine, blood urea nitrogen, hemoglobin, alanine aminotransferase, aspartate aminotransferase, serum potassium level, serum sodium level, serum total protein level, and number of times contrast-enhanced CT was performed. Hosmer-Lemeshow X-squared=5.84, df=8, p-value=0.67, indicating a good model fit. Hosmer-Lemeshow test (binary model).
There are several studies supporting this hypothesis that also are consistent with this study. Hsieh et al. investigated the risk of ESRD after CECT in non-advanced CKD patients, and concluded that more than 1 contrast media exposure per year is statistically related to the development of ESRD [8]. Although CKD stages were not included in propensity score matching, repeated exposure to contrast media did influence progression to ESRD in this nationwide study. There are other studies, from Canada, that analyzed the risk of ESRD in patients who underwent coronary angiography [10,12]. They showed sustained kidney injury in patients who had CI-AKI after the procedure and reported that the risk of ESRD is also increased in patients who have had CI-AKI. In these studies, baseline eGFR distribution of CI-AKI and non-CI-AKI groups was different. On the contrary, McDonald et al. suggested that risk of CI-AKI and emergent dialysis is not increased by CECT in advanced CKD patients [18]. They matched 32 clinical variables in this well-designed study, but patients were followed up only for 1 month.

AST and ALT were associated with progression to ESRD in multivariate logistic regression. It is known that both liver enzymes tend to be lower in CKD patients than in the general population, and researchers suggest that a lower upper margin of liver enzyme level should be applied to CKD patients [19,20]. However, the prognostic implication of liver enzymes in progression to ESRD is unknown to date. Although the result turned out to be statistically significant, the clinical importance seemed unclear because of the opposing tendencies of the 2 liver enzymes.

The present study has some distinct strengths. First, major risk factors for progression to ESRD were included in the disease risk score matching. Consequently, the possibility of selection bias was decreased. Second, we only included outpatients and excluded patients who were admitted to the hospital during the study period. In other words, only clinically stable patients were enrolled, and the enrolled patients did not experience any serious illness that might accelerate the decline of their kidney function.

Conversely, there are several limitations to this study. First, this study was conducted in a single tertiary medical center and included only Koreans. Therefore, the number of enrolled patients was relatively small, and the results of this study might not be generalizable across all racial groups. Second, although disease risk score matching was used, there is a possibility of undetected confounding factors. Furthermore, several variables known as risk factors for progression to ESRD, such as glomerulonephritis or nephrotoxic drug usage, were not included in the disease risk score matching. Third, we did not analyze whether preventive measures such as intravenous hydration were performed. Fourth, we did not separate the patients who underwent CT without contrast media from those who did not undergo CT at all. Fifth, as we did not analyze post-CECT
creatinine levels or post-CECT eGFR, the exact incidence of AKI after CECT is unknown. However, based on the study conducted by Winther et al., we assumed that there will be no statistically significant relationship between AKI after contrast media exposure and the need for permanent renal replacement therapy in advanced CKD patients [21].

Conclusions

The risk of ESRD was increased 1.2-fold by using contrast media in advanced, yet stable, CKD outpatients after 5-year follow-up. The number of times CECT was performed, rather than baseline kidney function, affects the progression to ESRD. However, with its limitations, the results presented in this study are not conclusive and should be further validated in an independent cohort before they can be applied to real clinical practice. Finally, studies with a larger number of patients and more matched variables are required in the future.

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Conflict of interest

None.

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