Contrast Medium Exposure During Computed Tomography and Risk of Development of End-Stage Renal Disease in Patients With Chronic Kidney Disease

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Abstract: The aim of the study was to investigate the long-term association between contrast medium exposure during computed tomography (CT) and the subsequent development of end-stage renal disease (ESRD) in patients with chronic kidney disease (CKD).

We conducted a population-based cohort study using Taiwan's National Health Insurance Research Database. A total of 7100 patients with nondiabetic CKD who underwent contrast medium-enhanced CT were identified and served as the study cohort. To avoid selection bias, we used the propensity score matching to match 7100 nondiabetic CKD patients, who underwent noncontrast medium-enhanced CT to serve as the comparison cohort. The age, sex, index year, and frequency of undergoing CTs were also matched between the study and comparison cohorts. Participants were followed until a new diagnosis of ESRD or December 31, 2011. Hazard ratios (HRs) with 95% confidence interval (95% CI) were calculated using the Cox proportional hazards regression.

Contrast medium exposure was not identified as a risk factor for developing ESRD in nondiabetic CKD patients after confounders adjustment (adjusted HR = 0.91; 95% CI, 0.66–1.26; P = 0.580). We further divided the patients who underwent CTs with contrast medium use into ≤1 exposure per year on average, >1 and ≤2 exposure per year on average, and >2 exposure per year on average. After adjusting for confounders, we identified a much higher risk for developing ESRD in the 2 groups of >1 and ≤2 exposure per year on average and >2 exposure per year on average (adjusted HR = 8.13; 95% CI, 5.57–11.87 and adjusted HR = 12.08; 95% CI, 7.39–19.75, respectively) compared with the patients who underwent CTs without contrast medium use.

This long-term follow-up study demonstrated that contrast medium exposure was not associated with an increased risk of ESRD development in nondiabetic CKD patients.

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Abbreviations: CI = confidence interval, CKD = chronic kidney disease, CT = computed tomography, DM = diabetes mellitus, ESRD = end-stage renal disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, IHD = ischemic heart disease, IR = incidence rate, LHID2000 = Longitudinal Health Insurance Database 2000, NHI = National Health Insurance, NHIA = National Health Insurance Administration, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, PAOD = peripheral arterial occlusive disease.

INTRODUCTION

Contrast-induced nephropathy (CIN) was a common cause of acute kidney injury (AKI). The prevalence ranged from...
2% to 30% because of different studied cohorts (underwent diagnostic or therapeutic procedures) and CIN definitions. Patients who developed AKI after contrast medium exposure had markedly increased morbidity and mortality even after 1-year follow-up.

With the increasing utilization of contrast medium in the intervention procedures and imaging modalities, CIN had become an important issue, particularly in chronic kidney disease (CKD) patients, who were more susceptible to CIN.

Taiwan had the highest prevalence of end-stage renal disease (ESRD) worldwide for >10 years before 2009 and remains high currently. A large Taiwanese cohort study showed that the prevalence of CKD was 11.9% in adults and was as high as 37.2% in the elderly. With the gradual increase in Taiwan’s elderly population, there has been a correspondingly steady rise in the prevalence of CKD. Furthermore, these CKD patients were prone to contrast medium exposure as they were more often required to undergo evaluation by computed tomography (CT).

CIN was generally thought to be a reversible form of AKI that happened soon after the administration of contrast medium. However, it was increasingly being recognized that the impaired renal function might persist even following the return of serum creatinine to the baseline level. This effect was particularly important in patients with CKD, among whom an occurrence of AKI might increase the risk of CKD progression, including to ESRD.

The long-term impact of contrast medium exposure for CT in CKD patients remains unknown. This study aimed to investigate the association between contrast medium exposure for CT in nonadvanced CKD patients and the development of ESRD using retrospective data of Taiwan’s National Health Insurance Research Database (NHIRD). Because patients with advanced CKD were prone to developing ESRD even after a minor disease event, this study focused on patients with nonadvanced CKD.

METHODS

Data Sources and Study Participants

Taiwan’s National Health Insurance program was promulgated on March 1, 1995, by the National Health Insurance Administration (NHIA) and covers >23.03 million residents in Taiwan (~99.2% of the population). The NHIA releases de-identified data to the National Health Research Institute (NHRI), which maintains the NHIRD. The Longitudinal Health Insurance Database 2000 (LHID2000) used in this study contains medical information of 1 million National Health Insurance beneficiaries randomly sampled from the registry of all beneficiaries for the year 2000. Claims data in the LHID2000 were retrospectively collected for the period of January 1, 1996, to December 31, 2011. The distributions of sex and age in the original claims data and the sampled data did not differ significantly. The diagnosis codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) are used in the NHIRD. The NHRI scrambles patient identification data and replaces them with surrogate numbers to ensure privacy. The data were also collected in accordance with the data regulations of the NHIA and the NHRI in order to maintain strict confidentiality. Because the NHIRD contains deidentified secondary data for research, the present study was waived from inform consent. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

The patients were defined as having CKD if they had at least 3 outpatient service claims with a diagnosis of CKD or if they had a single hospitalization in which CKD was found in 1 of the 5 spaces used to report their diagnosis when hospitalized using the ICD-9-CM (581–584, 586–588, 403, 404, 285.21). The National Health Insurance (NHI) reimbursement regulations in Taiwan allowed patients with a serum creatinine level of >6 mg/dL (approximately equivalent to eGFR <15 mL/min/1.73 m²) and a hematocrit level of <28% to receive erythropoiesis-stimulating agent (ESA) treatment for anemia. Therefore, we defined patients with advanced CKD using the above criteria: that is, the patients being treated with ESA were considered to have advanced CKD. Further, we also excluded patients who received dialysis or kidney transplantation during the study period.

Propensity score matching could reduce selection bias because it allowed the bundling of many confounding covariates that might be present in an observation study. In our study, multiple risk factors had might affect the clinical decision as to whether a patient would receive contrast medium for advanced image-enhancement or not while undergoing a CT. The propensity score indicated the possibility that contrast medium might be administered if the covariates were present. For each patient, we calculated the propensity score using the multivariate logistic regression by entering the baseline covariates, which also included important risk factors for CIN. We matched 1 comparison cohort patient (underwent noncontrast medium-enhanced CT) with each study cohort patient (underwent contrast medium-enhanced CT) according to the propensity score and obtained a dataset composed of matched patients who had a statistically identical likelihood of contrast medium exposure for CT. Also, as the propensity scores were composed of important underlying comorbidities, the propensity score matching made the study and comparison cohort patients stand on a comparable baseline condition and have equal opportunities to be affected by accidental disease events except the difference of contrast medium exposure or not.

Figure 1 illustrated the participant selection process of the study and comparison cohorts. Both the study and comparison cohort patients had undergone CTs with the only difference of contrast medium use or not. The frequencies of undergoing CTs between the study and comparison cohort patients were also further matched, that is, both the 2 cohorts patients had undergone equal times of CTs. Patients with ESRD (ICD-9-CM 585) before the first CT (with or without contrast medium-enhanced) were excluded. The ICD-9 codes for ESRD used in this study, which were from Taiwan’s NHIRD, were considered to be highly reliable, and many related studies that used these codes had been published. Patients aged <20 or >100 years were excluded in this study. In addition, patients who underwent coronary angiography or angiographic embolization during the study period (1996–2012) were excluded. All the enrollees accepted follow-up of at least 1 year. A total of 7100 patients were identified in the NHIRD and served as the study cohort (underwent contrast medium-enhanced CT). The first CKD diagnosis was defined as the index time, and the index year was defined as the calendar year of the index time. An equal number of patients undergoing noncontrast medium-enhanced CT (n = 7100) were selected from the database after matching with the study cohort patient for age, sex, propensity score, frequencies of undergoing CTs, and the index year, and served as the comparison cohort. During the study period, >90% of the contrast medium was ionic contrast medium which was paid by the national health insurance.
program. The incidence of ESRD was evaluated until December 31, 2011.

Statistical Analyses

Statistical analyses were performed using SAS 9.4 statistical package (SAS Institute Inc., Cary, NC), and the significance level was set at 0.05. Differences in demographic characteristics and comorbidities between the study and comparison cohorts were examined using chi-square and 2-sample t-tests. Hazard ratio (HR) with 95% confidence interval (95% CI) was calculated for each variable by Cox proportional hazards regression. The difference in the development of ESRD between the 2 cohorts was estimated using the Kaplan–Meier method and the log-rank test. Adjusted HRs for ESRD were obtained by Cox proportional hazards regression after adjustment for possible confounders, including age, sex, and underlying comorbidities. The adjusted underlying comorbidities were hypertension (HTN) (ICD-9-CM 401–405), diabetes mellitus (DM) (ICD-9-CM 250, 357.2, 362.01, 362.02, 366.41), ischemic heart disease (IHD) (ICD-9-CM 411–414), peripheral arterial occlusive disease (PAOD) (ICD-9-CM 440–444), congestive heart failure (CHF) (ICD-9-CM 428), and anemia (ICD-9-CM 280–285).2 Diagnoses given ahead of or in concurrence with the diagnosis of CKD were considered to be underlying comorbidities.

RESULTS

A total of 7100 nonadvanced CKD patients and an equal number of matched patients were included in the study (underwent contrast medium-enhanced CT) and comparison

FIGURE 1. Participants selection process for the study and comparison cohorts.
cohort (underwent noncontrast medium-enhanced CT), respectively. The mean ages of the contrast medium exposure and noncontrast medium exposure cohorts were 65.31 \pm 15.45 and 65.99 \pm 15.80 years, respectively. The male to female ratio in the contrast medium exposure and noncontrast medium exposure cohorts were 1.34 and 1.36, respectively. Table 1 summarized the demographic characteristics and comorbidities of the study and comparison cohorts.

The mean follow-up duration of patients in the contrast medium exposure cohort was 4.53 (\pm 4.12) years and was 4.46 (\pm 3.99) years for patients in the noncontrast medium exposure cohort. The mean duration between the first diagnosis of CKD and ESRD for patients in the contrast medium exposure cohort was 1.57 (\pm 0.34) years and was 1.64 (\pm 0.78) years for patients in the noncontrast medium exposure cohort. During the follow-up period, the incidence rates (IRs) of ESRD in the contrast medium exposure and noncontrast medium exposure cohorts were 3.77 and 3.67 per 1000 person-years, respectively. Kaplan–Meier analysis with log-rank test did not show an increased IR of ESRD development in the study cohort compared with the comparison cohort (Figure 2).

In the univariate analysis, HTN, DM, IHD, and CHF increased the HR of ESRD development in nonadvanced CKD patients. In further multivariate analysis, DM and CHF significantly increased the adjusted HR of ESRD development (adjusted HR = 3.6; 95% CI, 2.51–5.17 and adjusted HR = 2.25; 95% CI, 1.48–3.40, respectively). However, the contrast medium exposure for CT did not show a significant correlation with ESRD development (adjusted HR = 0.91; 95% CI, 0.66–1.26; P = 0.580) (Table 2). In the subgroup analysis,

| Variable | Noncontrast Medium Exposure (N = 8342) | Contrast Medium Exposure (N = 7981) | P Value |
|----------|--------------------------------------|------------------------------------|---------|
| Sex      |                                      |                                    |         |
| Female   | 3621 43.41                          | 3340 41.85                         | 0.044   |
| Male     | 4721 56.59                          | 4641 58.15                         |         |
| Age, years |                                    |                                    |         |
| Mean (SD) | 66.99 (15.32)                        | 65.43 (15.63)                      | <0.001  |
| 20–39 years |                                    |                                    |         |
|          | 494 5.92                             | 636 7.97                          | <0.001  |
| 40–59 years |                                    |                                    |         |
|          | 1991 23.87                           | 2050 25.69                         |         |
| ≥60 years  |                                    |                                    |         |
|          | 5857 70.21                           | 5295 66.59                         |         |
| Comorbidity |                                    |                                    |         |
| HTN      | 6262 75.07                           | 5674 71.09                         | <0.001  |
| DM       | 3473 41.63                           | 3307 41.44                         | 0.798   |
| IHD      | 3052 36.59                           | 2955 37.03                         | 0.560   |
| PAOD     | 613 7.35                             | 722 9.05                          | <0.001  |
| CHF      | 1279 15.33                           | 1313 16.45                         | 0.050   |
| Anemia   | 1253 15.02                           | 1355 16.98                         | 0.001   |
| ESRD     | 143 1.71                             | 146 1.83                           | 0.577   |

Chi-square test. CHF = congestive heart failure, CKD = chronic kidney disease, CT = computed tomography, DM = diabetes mellitus, ESRD = end-stage renal disease, HTN = hypertension, IHD = ischemic heart disease, PAOD = peripheral arterial occlusive disease, SD = standard deviation.

Two sample t test.
stratified by sex and age (aged 20–39, 40–59, ≥60), we did not observe any correlation between contrast medium exposure and ESRD development in all subgroups (Table 3).

Because of varied follow-up time, the patients in the study cohort (underwent contrast medium-enhanced CT) were further divided into 3 groups: (1) underwent contrast medium-enhanced CT 1 time per year on average, (2) >1 and <2 time per year on average, (3) ≥2 time per year on average. There were 5547, 971, and 582 patients in the 3 groups, respectively. The IRs of ESRD development in the 1, >1, and <2, and ≥2 exposures per year on average groups were 1.50, 30.94, and 45.99 per 1000 person-years, respectively. The adjusted HR of groups of 1, >1, and <2, and ≥2 contrast medium exposures per year on average was 0.51 (95% CI, 0.37–0.71), 8.13 (95% CI, 5.57–11.87), and 12.08 (95% CI, 7.39–19.75) compared with the patients who underwent noncontrast medium-enhanced CT (Table 4). The Kaplan–Meier analysis revealed a higher IR for developing ESRD in both the >1 and <2 exposure per year on average and ≥2 exposures per year on average groups compared with the noncontrast medium exposure group (log-rank test, P < 0.001) (Figure 3).

**DISCUSSION**

To the best of our knowledge, this is the first nationwide cohort study to investigate the association between contrast medium exposure for CT and subsequent development of ESRD in nonadvanced CKD patients. Our study demonstrated that contrast medium exposure for CT was not associated with an increased risk of ESRD development in nonadvanced CKD patients. However, in the patients with a greater frequency of intensive contrast medium exposure (>1 contrast medium exposure per year on average), there was an increased risk of ESRD development in nonadvanced CKD patients compared with those underwent noncontrast medium-enhanced CT. In the present study, the follow-up time was prolonged for >1 year to determine the effect of contrast medium exposure on the risk of...
In a study by Maioli et al, it was shown that CIN could be a harbinger of ESRD development. Other studies have indicated that CIN could be a harbinger of ESRD development in nonadvanced CKD patients. In previous studies, however, the analyses were primarily limited to in-hospital or 1-year morbidity and mortality.

CIN is defined as the impairment of renal function after contrast medium exposure with either a 25% increase in the serum creatinine level from baseline or a 0.5 mg/dL (44 μmol/L) increase in absolute value within 48 to 72 hours of intravenous contrast medium administration. In a typical course, the serum creatinine level begins to increase at 48 to 72 hours postcontrast medium exposure, peaks at 3 to 5 days, and returns to baseline within 3 to 5 days thereafter. Compared with patients with normal kidney function who are generally thought to be not at risk for CIN, patients with pre-existing CKD are much likely to develop this complication. Moreover, the risk increases with greater severity of underlying CKD.

In animal models, it is well accepted that CIN might be associated with acute kidney injury (AKI) or non-AKI, and its incident rate is proportional to the severity of the condition. In contrast, in human studies, the association between CIN and AKI is not clear. The incidence of CIN is usually higher in patients with CKD compared with noncontrast medium exposure. A variety of preventive measures have been suggested to reduce the risk of CIN according to its possible pathogenesis, including intravenous volume administration with isotonic saline, isotonic sodium bicarbonate, acetylecysteine administration, use of ioxaglate or nonionic low-osmolal agents, such as iopamidol or ioversol, and reduced dose of contrast medium. Other preventive measures include avoiding volume depletion, stopping nonsteroid anti-inflammatory drugs use, and withdrawal of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers before contrast medium administration.

### Table 3

| Variables | No (N = 7100) | Yes (N = 7100) | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-----------|--------------|---------------|------------------|---------------------|
| Total Sex |              |               |                  |                     |
| Female    | 60           | 40            | 1.50 (0.99–2.27) | 1.01 (0.62–1.65)   |
| Male      | 56           | 61            | 1.50 (1.00–2.25) | 1.00 (0.62–1.65)   |
| Age group |              |               |                  |                     |
| 20–39 years | 2            | 4             | 1.50 (0.99–2.27) | 1.01 (0.62–1.65)   |
| 40–59 years | 33           | 30            | 1.50 (1.00–2.25) | 1.00 (0.62–1.65)   |
| ≥60 years | 81           | 87            | 1.50 (0.99–2.27) | 1.01 (0.62–1.65)   |

### Table 4

| Contrast medium exposure per year on average | N | ESRD No. | Person years | IR | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---------------------------------------------|---|----------|--------------|----|-------------------|---------------------|
| Nonexposure                                 | 7100 | 116 | 38,732 | 2.99 | 1 (reference) | 1 (reference) |
| ≤1                                          | 5547 | 56 | 37,372 | 1.50 | 0.51 (0.37–0.70)* | 0.51 (0.37–0.71)* |
| >1 and <2                                   | 971 | 42 | 1357 | 30.94 | 8.73 (6.03–12.65)** | 8.13 (5.57–11.87)** |
| ≥2                                          | 582 | 23 | 500 | 45.99 | 14.24 (8.23–22.9)** | 12.08 (7.39–19.75)** |

Adjusted HR: adjusted for contrast medium exposure, age, sex, and comorbidities in Cox proportional hazards regression analysis.

*P < 0.05. **P < 0.01.

Adjusted for all covariates in the full model except sex.

Adjusted for all covariates in the full model except age.
Contrast medium exposure for CT was not associated with an increased risk of ESRD development in nonadvanced CKD patients. But when intensive contrast medium exposure for CT was mandatory, alternative imaging modality without contrast medium use should be considered.
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