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

A Nationwide Population-Based, Propensity Score-Matched, Longitudinal Follow-Up Study

Ming-Shun Hsieh, MD, Chien-Shan Chiu, MD, Chorng-Kuang How, MD, PhD, Jen-Huai Chiang, MS, Meei-Ling Sheu, PhD, Wen-Chi Chen, MD, PhD, Hsuan-Jen Lin, MD, Vivian Chia-Rong Hsieh, PhD, and Sung-Yuan Hu, MD, MS

Editor: Carlo Donadio.
Received: October 13, 2015; revised: January 31, 2016; accepted: March 17, 2016.

From the Department of Emergency Medicine (M-SH), Taipei Veterans General Hospital, Taoyuan Branch, Taoyuan; Department of Emergency Medicine (M-SH), Taipei Veterans General Hospital; Institute of Occupational Medicine and Industrial Hygiene (M-SH), National Taiwan University College of Public Health; School of Medicine (M-SH, C-SC, C-KH), National Yang-Ming University, Taipei; Department of Dermatology (C-SC), Taichung Veterans General Hospital; Institute of Biomedical Sciences (C-SC, M-LS), National Chung Hsing University; Management Office for Health Data (J-HC); College of Medicine (J-HC); Graduate Institute of Integrated Medicine (J-HC, W-CC), College of Chinese Medicine, Research Center for Chinese Medicine & Acupuncture, China Medical University; Sex Hormone Research Center (W-CC), Departments of Obstetrics and Gynecology, Urology, and Medical Research; Department of Medical Research (W-CC), Obstetrics and Gynecology, Dermatology, and Urology; Kidney Institute and Division of Nephrology (H-JL), Department of internal medicine; Department of Health Services Administration (VC-RH), China Medical University; Department of Emergency Medicine (S-YH), Taichung Veterans General Hospital; Institute of Medicine (S-YH), Chung Shan Medical University; and Department of Nursing (S-YH), College of Health, National Taichung University of Science and Technology, Taichung, Taiwan.

Correspondence: Sung-Yuan Hu, Department of Emergency Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, R.O.C (e-mail: song9168@pie.com.tw).

Vivian Chia-Rong Hsieh, Department of Health Services Administration, China Medical University, Taichung, Taiwan, R.O.C (e-mail: hsiehchiarong@gmail.com).

M-SH and C-SC contributed equally to this study.

Author contributions: these authors' individual contributions are as follows. Conception and design: M-SH, C-SC, and C-KH; data analysis and interpretation: J-HC, M-LS, W-CC, and H-JL; manuscript writing: M-SH; final approval and critical revision: S-YH and VC-RH.

Funding/support: This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037), NRPB Stroke Clinical Trial Consortium (MOST 104-2325-B-039 -005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. IRB: CMUH104-REC2-115. The funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

Potential Conflicts of Interest: none of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved with unethical publication and affirm that this study is consistent with those guidelines.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003388

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 nonadvanced CKD who underwent contrast medium-enhanced CT were identified and served as the study cohort. To avoid selection bias, we used the propensity score to match 7100 nonadvanced 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 nonadvanced 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 nonadvanced CKD patients.

(*Medicine* 95(16):e3388)

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).[1] The prevalence ranged from

2% to 30% because of different studied cohorts (underwent diagnostic or therapeutic procedures) and CIN definitions.[2,3] Patients who developed AKI after contrast medium exposure had markedly increased morbidity and mortality even after 1-year follow-up.[1,4,5]

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.[6,7] 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.[8–16] However, it was increasingly being recognized that the impaired renal function might persist even following the return of serum creatinine to the baseline level.[5,17] 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 deidentified 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 m^2) 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.[18–20] 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 cohort 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.[21–23] 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

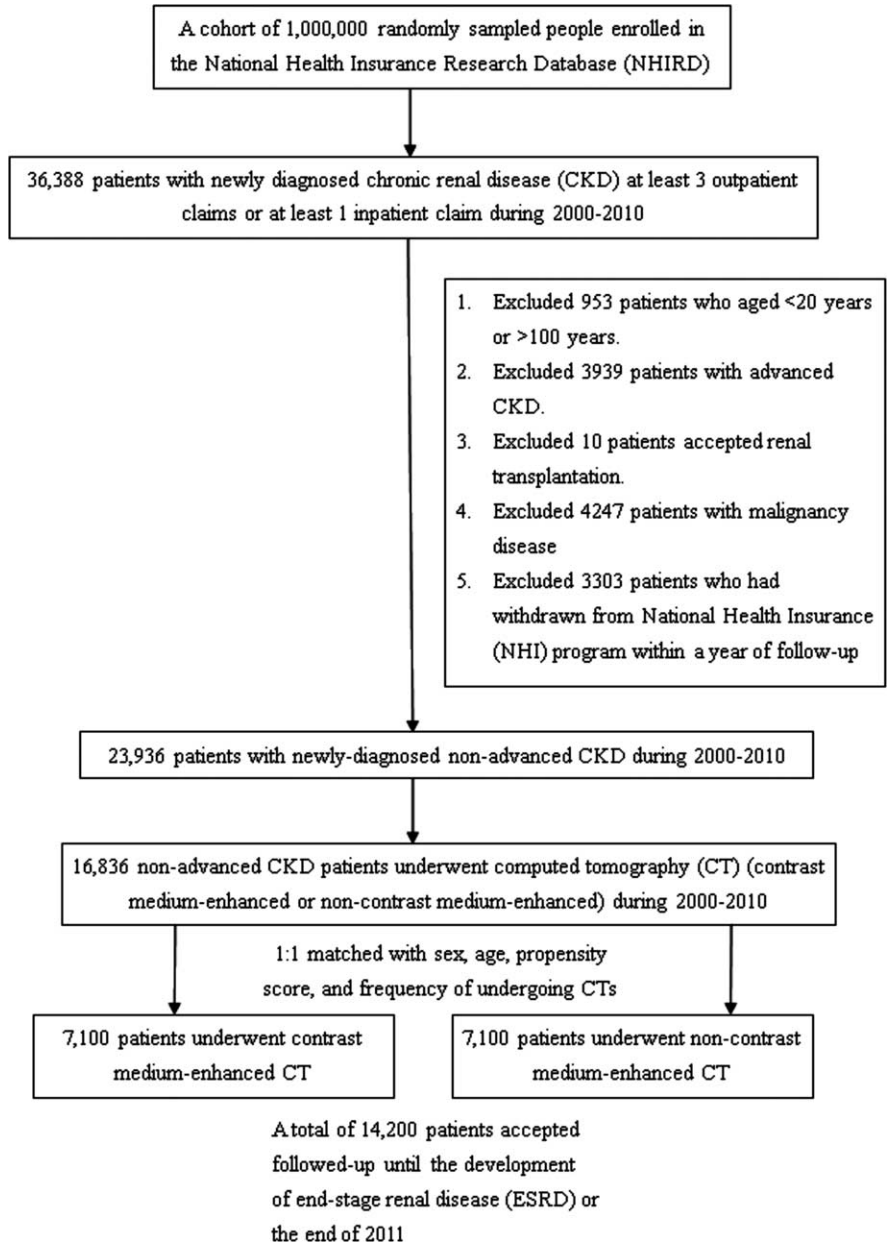

FIGURE 1. Participants selection process for the study and comparison cohorts.

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

cohort (underwent noncontrast medium-enhanced CT), respectively. The mean ages of the contrast medium exposure and noncontrast medium exposure cohorts were 65.31 ± 15.45 and 65.99 ± 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 (±4.12) years and was 4.46 (±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 (±0.34) years and was 1.64 (±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,

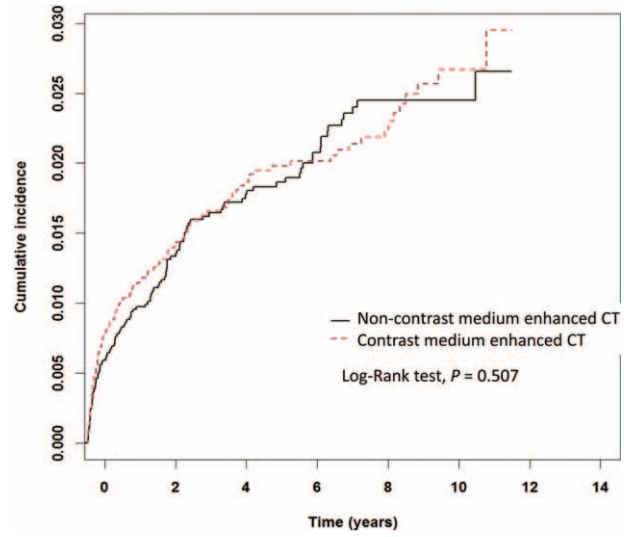

FIGURE 2. Kaplan–Meier analysis of the cumulative incidence of ESRD for the study and comparison cohorts. (*X*-axis: follow-up time in years; *Y*-axis: cumulative incidence per 1000 person-years). ESRD = end-stage renal disease.

TABLE 1. Demographic Characteristics and Comorbidities of Nonadvanced CKD Patients who Underwent Contrast Medium-Enhanced or Nonenhanced CTs

	Before Matching					Propensity Score-Matched				
	Noncontrast Medium Exposure (N = 8342)		Contrast Medium Exposure (N = 7981)			Noncontrast Medium Exposure (N = 7100)		Contrast Medium Exposure (N = 7100)		
Variable	**n**	**%**	**N**	**%**	***P* Value**	**n**	**%**	**N**	**%**	***P* Value**
Sex										
Female	3621	43.41	3340	41.85	0.044	2998	42.23	3025	42.61	0.646
Male	4721	56.59	4641	58.15		4102	57.77	4075	57.39	
Age, years										
Mean (SD)*	66.99 (15.32)		65.43 (15.63)		<0.001	65.99 (15.80)		65.31 (15.45)		0.009
20–39 years	494	5.92	636	7.97	<0.001	486	6.85	534	7.52	0.290
40–59 years	1991	23.87	2050	25.69		1872	26.37	1869	26.32	
≥60 years	5857	70.21	5295	66.35		4742	66.79	4697	66.15	
Comorbidity										
HTN	6262	75.07	5674	71.09	<0.001	5113	72.01	5033	70.89	0.137
DM	3473	41.63	3307	41.44	0.798	2830	39.86	2786	39.24	0.450
IHD	3052	36.59	2955	37.03	0.560	2539	35.76	2475	34.86	0.261
PAOD	613	7.35	722	9.05	<0.001	549	7.73	532	7.49	0.590
CHF	1279	15.33	1313	16.45	0.050	1061	14.94	988	13.92	0.081
Anemia	1253	15.02	1355	16.98	0.001	1046	14.73	1009	14.21	0.377
Outcome										
ESRD	143	1.71	146	1.83	0.577	116	1.63	121	1.7	0.743

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 standard deviation.

*Two sample *t* test.

TABLE 2. HR of ESRD Associated With Contrast Medium Exposure in Nonadvanced CKD Patients

		Crude			Adjusted		
Characteristics	**ESRD No. (n = 237**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Contrast medium Exposure for CT							
No	116	1	Reference		1	Reference	
Yes	121	0.90	(0.65–1.24)	0.513	0.91	(0.66–1.26)	0.580
Sex							
Female	120	1	Reference		1	Reference	
Male	117	0.68	(0.49–0.94)	0.019	0.77	(0.56–1.07)	0.115
Age							
20–39 years	6	1	Reference		1	Reference	
40–59 years	63	0.13	(0.03–0.51)	0.004	0.29	(0.07–1.23)	0.093
≥60 years	168	0.72	(0.5–1.03)	0.074	1.00	(0.68–1.46)	0.986
Comorbidity							
HTN							
No	40	1	Reference		1	Reference	
Yes	197	2.32	(1.51–3.57)	0.001	1.34	(0.84–2.15)	0.216
DM							
No	74	1	Reference		1	Reference	
Yes	163	4.27	(3–6.08)	<0.0001	3.6	(2.51–5.17)	<0.0001
IHD							
No	144	1	Reference		1	Reference	
Yes	93	1.62	(1.17–2.25)	0.003	0.94	(0.66–1.36)	0.755
PAOD							
No	216	1	Reference		1	Reference	
Yes	21	1.62	(0.93–2.81)	0.086	1.14	(0.65–1.99)	0.653
CHF							
No	187	1	Reference		1	Reference	
Yes	50	2.76	(1.88–4.05)	<0.0001	2.25	(1.48–3.4)	0.001
Anemia							
No	193	1	Reference		1	Reference	
Yes	44	1.16	(0.71–1.91)	0.545	0.90	(0.55–1.48)	0.674

Adjusted HR: adjusted for contrast medium exposure, age, sex, and comorbidities in Cox proportional hazards regression. CHF = congestive heart failure, CI = confidence interval, CKD = chronic kidney disease, CT = computed tomography, DM = diabetes mellitus, ESRD = end-stage renal disease, HR = hazard ratio, HTN = hypertension, IHD = ischemic heart disease, PAOD = peripheral arterial occlusive disease.

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

TABLE 3. Subgroup Analysis of IR and HR of ESRD After Contrast Medium Exposure

	Contrast Medium Exposure in Patients With Nonadvanced CKD							
	No (N = 7100)			Yes (N = 7100)			Crude HR	Adjusted HR
Variables	ESRD No.	Person-years	IR[†]	ESRD No.	Person-years	IR[*]	(95%CI)	(95%CI)
Total	116	31,632	3.67	121	32,129	3.77		
Sex[†]								
Female	60	14,200	4.23	60	14,815	4.05	0.94 (0.61–1.45)	0.94 (0.61–1.45)
Male	56	17,432	3.21	61	17,314	3.52	0.84 (0.52–1.36)	0.88 (0.54–1.41)
Age group[‡]								
20–39 years	2	2786	0.72	4	3133	1.28	0.89 (0.06–14.27)	1.59 (0.08–30.52)
40–59 years	33	10,836	3.05	30	10,379	2.89	0.81 (0.44–1.5)	0.77 (0.42–1.44)
≥60 years	81	18,010	4.5	87	18,618	4.67	0.94 (0.64–1.37)	0.95 (0.65–1.38)

Adjusted HR: adjusted for contrast medium exposure, age, sex, and comorbidities in Cox proportional hazards regression analysis.
CI = confidence interval, CKD = chronic kidney disease, ESRD = end-stage renal disease, HR = hazard ratio, IR = incidence rate.
[*]IR = incidence rate, per 1000 person-years.
[†]Adjusted for all covariates in the full model except sex.
[‡]Adjusted for all covariates in the full model except age.

ESRD development in nonadvanced CKD patients. In previous studies, however, the analyses were primarily limited to intrahospital or 1-year morbidity and mortality.[24]

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.[9,14,25] Other risk factors include DM, CHF, anemia, administration of high-dose contrast medium, use of first-generation hyperosmolality contrast medium, and application of percutaneous coronary intervention.[2,8–13,15,26–28] In fact, hemodialysis is rarely required in patients who develop CIN.[29,30] However, a growing number of studies have indicated that CIN could be a harbinger of ESRD development.[5,17] In a study by Maioli et al, it was shown that persistent kidney damage could occur after CIN which highlights the potential of CIN to accelerate CKD.[5] In the present study, we observed that a greater frequency of intensive contrast medium exposure (>1 exposure per year on average) could be an important risk factor for ESRD development in nonadvanced CKD patients compared with noncontrast medium exposure.

In animal models, it is well accepted that CIN might be caused by acute tubular necrosis (ATN); however, the mechanism of ATN remains incompletely understood.[31–33] Two major theories have been proposed to explain the cause of ATN: (1) renal vasoconstriction mediated by nitric oxide, endothelin, and adenosine; and (2) the direct cytotoxic effect of contrast medium.[31–34] 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, acetylcysteine administration, use of iodixanol or nonionic low-osmolal agents, such as iopamidol or ioversol, and reduced dose of contrast medium.[29,35–55] 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

TABLE 4. Incidence for ESRD Among Patients who Underwent CTs With Different Frequency of Contrast Medium Exposure per Year on Average

	N	ESRD No.	Person years	IR[†]	Crude HR (95% CI)	Adjusted HR (95% CI)
Contrast medium exposure per year on average						
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.
CI = confidence interval, CT = contrast medium, ESRD = end-stage renal disease, HR = hazard ratio, IR = incidence rate.
[†]IR = incidence rate, per 1000 person-years.
[*]$P < 0.05$. [**]$P < 0.01$.
[***]$P < 0.001$.

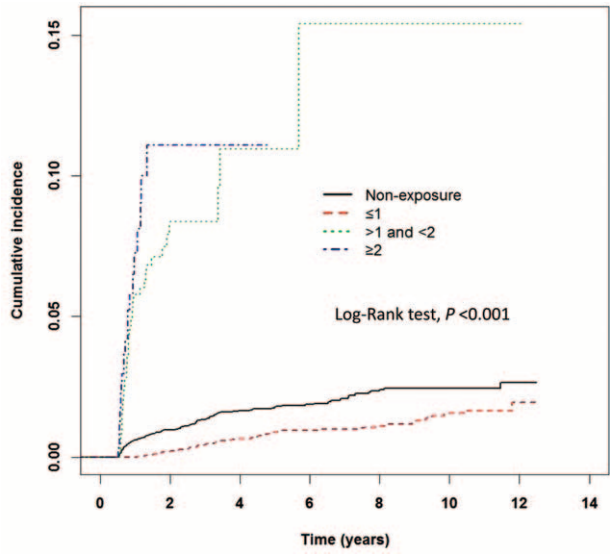

FIGURE 3. Kaplan–Meier analysis of the cumulative incidence of ESRD for the 4 groups stratified by different frequencies of contrast medium exposures per year on average. (*X*-axis: follow-up time in years; *X*-axis: cumulative incidence per 1000 person-years). ESRD = end-stage renal disease.

contrast medium administration.[56] However, the best preventive measure is to avoid the use of contrast medium. In our study, although we could not examine the effects of preventive measures, we set ESRD as the primary endpoint of most concern to CKD patients and observed that if contrast medium was not administered in an intensive frequency, there was no increased risk of ESRD development.

According to previous studies, in the majority of CIN cases, AKI was transient, and a complete or near-complete recovery to baseline creatinine occurred within 3 months.[5,29] In a study by James et al, it was found that patients who developed AKI following contrast medium exposure had an increased risk of progressive long-term kidney function loss.[57] A number of mechanisms have been proposed as possible explanations of the association between CIN and progressive kidney function loss. The most widely accepted mechanism involves the impact of underlying comorbidities, such as HTN, DM, CHF, and preexisting CKD. Patients who developed AKI following contrast medium exposure usually had multiple risk factors and these underlying comorbidities may predispose them to progression of CKD. In the present study, we used the propensity scores matching accompanied with the matching of CT frequencies to make the patients in the study and comparison cohorts comparable by standing on the same baseline of underlying conditions and they had equal opportunities to be affected by accidental disease events except the difference of contrast medium exposure or not. We observed a greater progression of CKD to ESRD after intensive contrast medium exposures for CTs. We inferred that the single random contrast medium exposure and underlying comorbidities may be not critically important risk factors for ESRD development in CKD patients.

McDonald et al proposed that contrast medium exposure for CT did not actually increase the risk of AKI in both groups of patients with normal and impaired renal function after single contrast medium exposure. We found a similar result to that reported by McDonald et al that a single random exposure to contrast medium for CT may not increase the risk of CKD progression to ESRD. However, there was an increased risk of CKD progression if the CKD patients were intensively exposed to contrast medium. It is reasonable to postulate that the patients who had intensive contrast medium exposure might have had multiple acute or severe disease events that required the use of contrast-enhanced imaging studies. Furthermore, these disease events might themselves predispose patients to progression of CKD. However, in contrast to previous studies, in the present study, the selection bias was particularly eliminated by using the propensity score matching between the study and comparison cohorts in order to minimize the impact of potential confounders from underlying comorbidities and accidental disease events, and thereby obtained a clearer understanding of the effects from contrast medium exposure for CT. We also excluded the patients with advanced CKD who were much more susceptible to developing ESRD, even after a minor disease event, compared with the general CKD patients. Our findings demonstrated that intensive contrast medium exposure may be associated with an increased risk of CKD progression to ESRD rather than single random exposure or nonexposure and should therefore be avoided.

The major strength of this study was the use of a large sample size from a nationwide database with a prolonged follow-up duration of >1 year. The most challenging aspect of this study was the elimination of selection bias for contrast medium use for CT in patients with different clinical conditions and severity of impaired kidney function. To overcome this selection bias, propensity score matching was used so that the 2 cohorts could be meaningfully compared. Also, the matched patients in the study and comparison cohorts had undergone equal times of CTs during the study period with the only difference of contrast medium use or not. Third, we excluded patients who underwent coronary angiography, which would have resulted in a greater risk of CIN compared with CT. Fourth, we excluded patients with advanced CKD as such patients are prone to developing ESRD and need dialysis even after a minor disease event.

The study had several limitations. First, the major limitation of our used database, NHIRD, was the lacking of clinical laboratory data, that is, the creatinine level of each patient, pre- and postcontrast medium exposure for CT. Also, some detailed information, such as the volume of used contrast medium, was not available. Although short-time kidney function change could not be evaluated, our study still provided a valuable long-term observation result. Nearly all the published articles focused on short-term kidney function change, that is, CIN, and long-term observation study was extremely rare because of complexity. Second, the enrolled patients in the study and comparison cohorts might have been in different stages of CKD. However, because of the large enrollee population, the patients with different levels of CKD severity would likely have been distributed equally. Third, preventive procedures before contrast medium exposure could not be evaluated in the present study.

CONCLUSION

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.

REFERENCES

1. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis.* 2002;39:930–936.
2. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol.* 2004;44:1393–1399.
3. McCullough PA, Adam A, Becker CR, et al. Epidemiology and prognostic implications of contrast-induced nephropathy. *Am J Cardiol.* 2006;98:5K–13K.
4. Rao QA, Newhouse JH. Risk of nephropathy after intravenous administration of contrast material: a critical literature analysis. *Radiology.* 2006;239:392–397.
5. Maioli M, Toso A, Leoncini M, et al. Persistent renal damage after contrast-induced acute kidney injury: incidence, evolution, risk factors, and prognosis. *Circulation.* 2012;125:3099–3107.
6. Wen CP, Cheng TY, Tsai MK, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet.* 2008;371:2173–2182.
7. Wu PC, Wu VC, Tarng DC. Chronic kidney disease in Taiwan's aging population: something far more than a distant ship's smoke on the horizon. *J Formos Med Assoc.* 2014;113:890–891.
8. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med.* 1989;320:143–149.
9. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. *Kidney Int.* 1995;47:254–261.
10. Davidson CJ, Hlatky M, Morris KG, et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. *Ann Intern Med.* 1989;110:119–124.
11. Schwab SJ, Hlatky MA, Pieper KS, et al. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. *N Engl J Med.* 1989;320:149–153.
12. Cigarroa RG, Lange RA, Williams RH, et al. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med.* 1989;86:649–652.
13. Lautin EM, Freeman NJ, Schoenfeld AH, et al. Radiocontrast-associated renal dysfunction: a comparison of lower-osmolality and conventional high-osmolality contrast media. *Am J Roentgenol.* 1991;157:59–65.
14. Rudnick MR, Berns JS, Cohen RM, et al. Nephrotoxic risks of renal angiography: contrast media-associated nephrotoxicity and atheroembolism—a critical review. *Am J Kidney Dis.* 1994;24:713–727.
15. Barrett BJ. Contrast nephrotoxicity. *J Am Soc Nephrol.* 1994;5:125–137.
16. Weisbord SD, Palevsky PM. Radiocontrast-induced acute renal failure. *J Intensive Care Med.* 2005;20:63–75.
17. Wi J, Ko YG, Kim JS, et al. Impact of contrast-induced acute kidney injury with transient or persistent renal dysfunction on long-term outcomes of patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Heart.* 2011;97:1753–1757.
18. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011;46:399–424.
19. Qin R, Titler MG, Shever LL, et al. Estimating effects of nursing intervention via propensity score analysis. *Nurs Res.* 2008;57:444–452.
20. Austin PC. Assessing balance in measured baseline covariates when using many-to-one matching on the propensity-score. *Pharmacoepidemiology Drug Saf.* 2008;17:1218–1225.
21. Lin SY, Lin WM, Lin CL, et al. The relationship between secondary hyperparathyroidism and thyroid cancer in end stage renal disease: a population based cohort study. *Eur J Intern Med.* 2014;25:276–280.
22. Wang IK, Lin CL, Lin PC, et al. Effectiveness of influenza vaccination in patients with end-stage renal disease receiving hemodialysis: a population-based study. *PLoS One.* 2013;8:e58317.
23. Su FH, Su CT, Chang SN, et al. Association of hepatitis C virus infection with risk of ESRD: a population-based study. *Am J Kidney Dis.* 2012;60:553–560.
24. Dangas G, Iakovou I, Nikolsky E, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol.* 2005;95:13–19.
25. Solomon RJ, Mehran R, Natarajan MK, et al. Contrast-induced nephropathy and long-term adverse events: cause and effect? *Clin J Am Soc Nephrol.* 2009;4:1162–1169.
26. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation.* 2002;105:2259–2264.
27. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med.* 1997;103:368–375.
28. Nikolsky E, Mehran R, Lasic Z, et al. Low hematocrit predicts contrast-induced nephropathy after percutaneous coronary interventions. *Kidney Int.* 2005;67:706–713.
29. Brar SS, Shen AY, Jorgensen MB, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *JAMA.* 2008;300:1038–1046.
30. McDonald RJ, McDonald JS, Carter RE, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. *Radiology.* 2014;273:714–725.
31. Detrenis S, Meschi M, Musini S, et al. Lights and shadows on the pathogenesis of contrast-induced nephropathy: state of the art. *Nephrol Dial Transplant.* 2005;20:1542–1550.
32. Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney Int.* 2005;68:14–22.
33. Heyman SN, Rosenberger C, Rosen S. Regional alterations in renal haemodynamics and oxygenation: a role in contrast medium-induced nephropathy. *Nephrol Dial Transplant.* 2005;20(Suppl 1):i6–11.
34. Katholi RE, Taylor GJ, McCann WP, et al. Nephrotoxicity from contrast media: attenuation with theophylline. *Radiology.* 1995;195:17–22.
35. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med.* 2003;348:491–499.
36. Rudnick MR, Davidson C, Laskey W, et al. Nephrotoxicity of iodixanol versus ioversol in patients with chronic kidney disease: the Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) Trial. *Am Heart J.* 2008;156:776–782.
37. Solomon RJ, Natarajan MK, Doucet S, et al. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation.* 2007;115:3189–3196.
38. Laskey W, Aspelin P, Davidson C, et al. Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. *Am Heart J.* 2009;158:822–828e823.

39. Reed M, Meier P, Tamhane UU, et al. The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. *Cardiovasc Interv.* 2009;2:645–654.
40. Kushner FG, Hand M, Smith SC Jr et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2009;54:2205–2241.
41. Weisbord SD, Palevsky PM. Prevention of contrast-induced nephropathy with volume expansion. *Clin J Am Soc Nephrol.* 2008;3: 273–280.
42. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med.* 2002;162:329–336.
43. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA.* 2004;291:2328–2334.
44. Briguori C, Airoldi F, D'Andrea D, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation.* 2007;115:1211–1217.
45. Recio-Mayoral A, Chaparro M, Prado B, et al. The reno-protective effect of hydration with sodium bicarbonate plus N-acetylcysteine in patients undergoing emergency percutaneous coronary intervention: the RENO Study. *J Am Coll Cardio.* 2007;49:1283–1288.
46. Ozcan EE, Guneri S, Akdeniz B, et al. Sodium bicarbonate, *N*-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial. *Am Heart J.* 2007;154: 539–544.
47. Hoste EA, De Waele JJ, Gevaert SA, et al. Sodium bicarbonate for prevention of contrast-induced acute kidney injury: a systematic review and meta-analysis. *Nephrol Dial Transplant.* 2010;25: 747–758.
48. Maioli M, Toso A, Leoncini M, et al. Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *J Am Coll Cardiol.* 2008;52:599–604.
49. Alonso A, Lau J, Jaber BL, et al. Prevention of radiocontrast nephropathy with *N*-acetylcysteine in patients with chronic kidney disease: a meta-analysis of randomized, controlled trials. *Am J Kidney Dis.* 2004;43:1–9.
50. Vasheghani-Farahani A, Sadigh G, Kassaian SE, et al. Sodium bicarbonate plus isotonic saline versus saline for prevention of contrast-induced nephropathy in patients undergoing coronary angiography: a randomized controlled trial. *Am J Kidney Dis.* 2009;54:610–618.
51. Brar SS, Hiremath S, Dangas G, et al. Sodium bicarbonate for the prevention of contrast induced-acute kidney injury: a systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2009;4: 1584–1592.
52. Joannidis M, Schmid M, Wiedermann CJ. Prevention of contrast media-induced nephropathy by isotonic sodium bicarbonate: a meta-analysis. *Wien Klin Wochenschr.* 2008;120:742–748.
53. Zoungas S, Ninomiya T, Huxley R, et al. Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. *Ann Intern Med.* 2009;151:631–638.
54. Klima T, Christ A, Marana I, et al. Sodium chloride vs. sodium bicarbonate for the prevention of contrast medium-induced nephropathy: a randomized controlled trial. *Eur Heart J.* 2012;33:2071–2079.
55. Trivedi HS, Moore H, Nasr S, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. *Nephron Clin Pract.* 2003;93:C29–34.
56. Rim MY, Ro H, Kang WC, et al. The effect of rennin–angiotensin–aldosterone system blockade on contrast-induced acute kidney injury: a propensity-matched study. *Am J Kidney Dis.* 2012;60:576–582.
57. James MT, Ghali WA, Tonelli M, et al. Acute kidney injury following coronary angiography is associated with a long-term decline in kidney function. *Kidney Int.* 2010;78:803–809.