

Association between Contrast Media Volume and 1-Year Clinical Outcomes in Patients Undergoing Coronary Angiography

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Abstract

Background: The excess volume of contrast media (CM) is a marker of a more severe coronary culprit lesion and longer intervention duration in patients undergoing cardiac procedures. However, it is unclear whether the contrast volume is directly correlated with worse clinical outcomes. The aim of this study was to investigate the association between contrast dose and the incidence of 1-year major adverse cardiac and cerebrovascular events (MACCE) and all-cause bleeding events in patients undergoing cardiac catheterization and coronary angiography (CAG).

Methods: We prospectively enrolled 10,961 consecutive patients diagnosed with coronary heart disease expecting CAG from 2012 to 2013. The study population was pursued with a follow-up duration of 1 year. The predictive value of contrast volume, divided into quartiles, for the risk of MACCE and all-cause bleeding events was assessed using logistic regression analysis.

Results: The cumulative incidence of 1-year MACCE was 8.65%, which was directly associated with increasing contrast volume. In particular, MACCE was observed in 7.16%, 7.89%, 9.31%, and 11.73% of cases in the contrast volume quartile Q1 (≤ 100 ml), Q2 (101–140 ml), Q3 (141–200 ml), and Q4 (>200 ml), respectively ($P < 0.001$). Moreover, the incidence of 1-year all-cause bleeding events was noted in 4.70%, 5.93%, 7.28%, and 8.21% of patients in Q1, Q2, Q3, and Q4, respectively ($P < 0.001$). The survival analysis showed that the 1-year MACCE rate was higher in patients using greater CM volume during the CAG. CM volume used >140 ml was associated with the occurrence of 1-year MACCE, and the incidence was dramatically elevated in patients exceeding a contrast volume of 200 ml ($P = 0.007$).

Conclusion: Our data suggested that higher contrast volume was significantly correlated with an increased risk of MACCE and all-cause bleeding events in patients undergoing cardiac catheterization.

Trial Registration: ClinicalTrials.gov, NCT01735305; <https://clinicaltrials.gov/ct2/show/NCT01735305?id=NCT01735305&rank=1>.

Key words: Bleeding; Cerebrovascular Event; Contrast Media; Coronary Artery Disease

INTRODUCTION

Nowadays, cardiac intervention procedure has become an important tool for the treatment of cardiovascular disease (CVD). The risk of occurrence of a major complication (death, myocardial infarction [MI], and major embolization) during diagnostic cardiac catheterization has become very rare. However, high-risk subgroups have been concluded in many large-scale studies. Aged above 60 years, female, and those with complex lesions, such as severe disease of the left main coronary artery, have been identified as high-risk factors.^[1-3] After cardiac catheterization,

mortality is especially high in those with pre-existing renal insufficiency, diabetes mellitus, congestive heart

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failure, hypertension, and so on. The prior study revealed that contrast media (CM) volume was one of the strongest predictors of mortality in patients undergoing cardiac catheterization, and it was irrespective of contrast-induced acute kidney injury (CI-AKI) development. It is known that contrast agents have hyper-osmotic compounds, and they contact endothelial cells. Use of CM directly acts on the endothelium and inhibits nitric oxide (NO) production and also causes changes in intracellular pH, mitochondrial dysfunction, and apoptosis.^[4-7] The high volume of CM was found to be a predictor of mortality regardless of the complexity of coronary artery disease and fragility of patients. The previous studies recommended the use of maximal acceptable contrast dose to determine the threshold for safe contrast exposure customized for each patient.^[8] However, its utilization is still confined to clinical research and is infrequently applied in clinical practice.^[9,10]

In this study, we aimed to reveal the relation between the amount of CM given during cardiac catheterization and prognosis in patients diagnosed with CVD. We also conducted the study to assess whether the contrast dose was good at predicting 1-year clinical outcomes.

METHODS

Study design

The optimizing antiplatelet therapy in patients with coronary artery disease (OPT-CAD study, Clinicaltrials.gov identifier NCT01735305) registry cohort (the study cohort for our analysis) included patients undergoing PCI in a large registry in 109 hospitals in China. It is a prospective, observational, physician-initiated noncompany sponsored multicenter registry that enrolled consecutive patients undergoing their antiplatelet therapy both outpatient and hospitalized patients with coronary heart disease among 109 centers in China from September 2012 to 2013 (The 109 centers seen: https://www.clinicaltrials.gov/ct2/show/study/NCT01735305?term=opt+cad&rank=1&show_locs=Y#locn). Data for all patients undergoing coronary angiography/percutaneous coronary intervention (CAG/PCI) at the participating hospitals were collected with standardized data collection forms. Baseline data include clinical, demographic, procedural, and angiographic characteristics as well as medications used before, during, and after the procedure and clinical outcomes at 1-year follow-up. Follow-up events were carefully monitored and recorded by trained physicians or nurses through office visits and telephone interviews at 1, 3, 6, and 12 months after CAG.

Ethical approval

All data elements have been prospectively defined, and the protocol was approved by every local Institutional Review Board. The relevant review board or the Ethics Research committees of all 109 participating centers approved the study. Patients gave informed consent to be available for regular follow-ups and telephone checkups for follow-up after discharge. The study was conducted in accordance

with the *Declaration of Helsinki* and was approved by the local Ethics Committee of Guangdong General Hospital (No. GDREC2012119H). Informed written consent was obtained from all patients before their enrollment in this study.

Participants

Inclusion criteria were outpatients or in-hospital patients older than 18 years of age, undergoing antiplatelet therapy. At least, one of the following criteria should be met to identify patients with coronary heart disease: (a) history of MI; (b) more than 50% stenosis of at least one coronary artery diagnosed by CAG; (c) more than 50% stenosis of at least one coronary artery reported/prompted by multi-slice spiral computed tomography CAG; and (d) received PCI or coronary artery bypass grafting (CABG). Exclusion criteria were as follows: (a) patients with malignancy or severe comorbidity and life expectancy <6 months; (b) difficult to follow-up such as immigration, speech impediment, and mental disorders, and (c) participating in an intervention study. We excluded patients who refused participation in the study when contacted for follow-up.

Settings

All procedures were performed with standard coronary intervention technique. The choice of CM was at the discretion of the operating physician within the dictates of the individual hospital policy. Based on the lesions and the patients' other conditions, the choices of guiding catheter, guiding wires, balloon catheters, stents, and procedural approaches were not influenced by strict local rules but was left to the discretion of the operators according to the individuals' experiences and clinical guideline. The contrast volume and types were left to the interventional cardiologist's discretion and depended on the patient's condition. Doppler echocardiography was performed and left ventricular ejection fraction was calculated in all patients.

Variables

The prespecified primary outcome measures included major adverse cardiovascular and cerebrovascular events (MACCE) and bleeding events at 1-year follow-up. MACCE was defined as all-cause mortality, nonfatal MI, stroke, or revascularization.^[11-13] All-cause mortality was traced from hospital records, follow-up visits, and a national vital record database. Death was regarded as cardiac in origin unless obvious noncardiac causes could be identified. Sudden death was defined as unexplained death in previously stable patients. Nonfatal MI was diagnosed according to the universal definition. The diagnosis of MI was based on signs or symptoms consistent with myocardial ischemia, electrocardiogram changes, and creatine kinase and creatine kinase MB isoenzyme (mass) levels. Events compatible with the occurrence of an MI were retrospectively adjudicated by a senior cardiologist who was unaware of observed cardiac troponin T levels while evaluating the imaging records. Stroke was defined as an episode of neurological dysfunction caused by focal cerebral infarction, with subsequent confirmation by imaging. Bleeding events were

defined according to the Bleeding Academic Research Consortium (BARC)-defined bleeding classifications^[14] including type 2 and 3 in the analysis.

Demographic, angiographic, and procedural data were collected from the hospital charts or databases in each center by independent clinical research coordinators, as previously described. The data were collected by a dedicated staff member and forwarded to the coordinating center. Medical records of all patients who underwent multiple procedures or CABG or died in hospital were reviewed to ensure data accuracy. Follow-up data were obtained from the hospital charts or by contacting patients or referring physicians. Clinical events, such as death, MI, stroke, revascularization, and bleeding, were adjudicated by the clinical event committee.

Statistical analysis

We divided the cohort into patients on the basis of CM volume of ≤ 100 , 100–140, 141–200, and >200 ml. Continuous variables of each group are presented with the mean \pm standard deviation (SD) (for normally distributed data) or median and interquartile range (for nonnormal distributions) and compared using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test based on their distributions. Categorical variables are expressed as frequencies or percentages and compared using Pearson's Chi-square test or Fisher exact test. Multiplicity issues resulting from the pairwise comparisons were approached with the Bonferroni adjustment. $P < 0.05$ was considered statistically significant. Rates of MACCE and bleeding were calculated for these categories in the entire cohort. The risks of MACCE (all-cause mortality, nonfatal MI, stroke, or revascularizations) and all bleeding relative to different CM volume quartiles (median value based on the quartiles) were estimated in unadjusted and adjusted logistic regression analyses. In addition, 95% confidence interval (CI) and odds ratios (ORs) were presented together. Kaplan-Meier analysis was used to identify the cumulative incidence rates of 1-year outcomes, and the log-rank test was used to compare the groups. Time-to-event data were visualized by Kaplan-Meier curves for each group. Only the available rates were assessed, and cases with missing data were excluded from the study. All statistical calculations were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). The authors had full access to the data and take full responsibility for its integrity. All authors have read and approved the manuscript as written.

RESULTS

Between September 2012 and 2013, a total of 14,032 patients diagnosed with CAD underwent CAG/PCI. The remaining 10,961 patients composed the follow-up cohort to assess the association between contrast volume and incidence of MACCE and all-cause bleeding. Survival analysis was performed at 12 months after the index CAG/PCI to assess the effects of contrast volume on 1-year clinical outcomes.

The mean age of the 10,961 patients (8128 men, 74.15%) was 60.7 years, and the patients were stratified into CM volume quartiles: ≤ 100 , 101–140, 141–200, and >200 ml. Mean body mass index (BMI) of the patients was 24.63 kg/m². A total of 178 of the patients (1.62%) died at 1-year follow-up. Baseline characteristics were significantly different among patients with varying CM volume. Table 1 shows the baseline demographic, clinical, biochemical, and angiographic characteristics of the patients according to the CM volume quartiles. In general, BMI of patients was significantly higher accompanying more use of CM volume ($P < 0.001$). The prevalence of hypertension and diabetes were higher accompany the more use of CM volume ($P = 0.02$ and $P < 0.001$, respectively). Patients with greater CM volume were more likely to have more complex lesions. Notably, there was no significant difference in the remaining baseline characteristics [Table 1].

Patients were followed for 1 year after study entry. During follow-up, the primary composite endpoint occurred in 948 patients (8.65%), whereas bleeding events developed in 685 patients (6.25%). Patients with a higher volume of contrast volume had a higher incidence of MACCE, MI, revascularization, and bleeding ($P < 0.001$, $P = 0.020$, $P < 0.001$, and $P < 0.001$, respectively), but a similar stroke rate ($P = 0.739$). Table 2 shows the occurrence of MACCE and all-cause bleeding by quartiles of CM volume. The incidence of MACCE and bleeding events in patients who underwent PCI was associated with increasing CM volume. When the cohort was divided into quartiles of CM volume, the risk for MACCE and bleeding increased when the contrast volume exceeded and was dramatically elevated in patients with a contrast volume >200 ml [Figure 1]. Notably, there was no significant difference in all-cause mortality, MI, stroke, BARC type 2 or 3 bleeding among the quartile of CM volume.

The incidence of the 1-year follow-up of clinical outcomes according to the CM volume quartiles is shown in Table 3. To investigate the association between the CM volume and adverse event, logistic regression analysis was performed. After adjusting for all baseline characteristics, multivariate stepwise logistic regression analysis indicated that compared with a low CM volume quartile (Q1 as reference), the moderate and high CM volumes (Q2–Q4) were significantly associated with an increased risk of MACCE, revascularization, and all bleeding events [Table 3].

After adjusting for baseline clinical and other procedural variables and for clustering, the increased CM volume had a significantly higher 1-year adverse events risk compared with Q1 (as reference). Using CM volume of Q1 as reference, CM volume of Q2–Q4 was significant to predict the risk for clinical outcomes (adjusted OR for MACCE: 1.06, 95% CI: 0.83–1.34; 1.19, 95% CI: 1.00–1.41; 1.43, 95% CI: 1.18–1.72, respectively, $P < 0.001$; adjusted OR for revascularization: 1.24, 95% CI: 0.92–1.66; 1.27, 95% CI: 1.03–1.57; 1.48, 95% CI: 1.18–1.86, respectively, $P < 0.001$; adjusted OR for all bleeding: 1.23, 95% CI: 0.93–1.63; 1.30,

Table 1: Baseline characteristics of patients according to the CM volume quartiles

Variables	Contrast volume quartiles (n = 10,961)				P*
	Q1 (≤100 ml, n = 4105)	Q2 (101–140 ml, n = 1636)	Q3 (141–200 ml, n = 3600)	Q4 (>200 ml, n = 1620)	
Demographics					
Age (years)	61.0 ± 10.7	59.8 ± 10.8	60.8 ± 10.6	60.6 ± 10.6	0.002
Sex (male), n (%)	2936 (71.52)	1246 (76.16)	2687 (74.64)	1259 (77.72)	<0.001
BMI (kg/m ²)	24.50 ± 2.89	24.59 ± 2.98	24.65 ± 2.91	24.95 ± 3.04	<0.001
Laboratory examinations					
Blood glucose (mmol/L)	6.31 ± 2.54	6.48 ± 2.70	6.44 ± 2.72	6.35 ± 2.57	0.086
HB (g/L)	136.22 ± 16.41	137.69 ± 16.45	135.97 ± 16.60	136.56 ± 16.61	0.005
SBP (mmHg)	134.14 ± 20.46	134.07 ± 20.67	134.27 ± 21.10	135.72 ± 21.24	0.054
DBP (mmHg)	78.56 ± 12.44	79.09 ± 12.61	78.75 ± 12.47	78.92 ± 12.78	0.476
eGFR (ml·min ⁻¹ ·1.73 m ⁻²), MDRD	107.27 ± 37.30	114.41 ± 38.37	112.47 ± 41.34	114.16 ± 38.51	<0.001
LVEF (%)	60.61 ± 9.03	60.16 ± 8.68	60.03 ± 8.65	59.97 ± 9.05	0.012
TC (mmol/L)	4.35 ± 1.24	4.36 ± 1.16	4.34 ± 1.15	4.23 ± 1.19	0.003
TG (mmol/L)	1.83 ± 1.42	1.91 ± 1.39	1.90 ± 1.45	2.01 ± 1.47	<0.001
LDL-C (mmol/L)	2.52 ± 1.04	2.52 ± 0.99	2.51 ± 0.99	2.43 ± 1.04	0.020
HDL-C (mmol/L)	1.07 ± 0.34	1.08 ± 0.35	1.05 ± 0.34	1.02 ± 0.33	<0.001
Procedural results, n (%)					
Complex lesions	955 (23.26)	895 (54.71)	2126 (59.06)	1133 (59.94)	<0.001
Historical diseases, n (%)					
Hypertension	2421 (58.98)	970 (59.53)	2143 (59.53)	1026 (63.33)	0.020
DM	953 (23.22)	385 (23.53)	909 (25.25)	461 (28.46)	<0.001
Smoker	1935 (47.14)	877 (53.61)	1819 (50.53)	901 (55.62)	<0.001
Previous stroke	254 (6.19)	117 (7.15)	293 (8.14)	130 (8.02)	0.006
Arrhythmia	321 (7.82)	121 (8.01)	250 (6.94)	115 (7.10)	0.366

Values are mean ± SD, n (%), or median (interquartile range). 1 mmHg = 0.133 kPa. *Comparisons among quartiles of CM volume. eGFR: Estimated glomerular filtration rate; we assessed the GFR as estimated by the MDRD equation; BMI: Body mass index; MDRD: Modification of Diet in Renal Disease; DM: Diabetes mellitus; HB: Hemoglobin; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; TC: Total cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVEF: Left ventricular ejection fraction; GFR: Glomerular filtration rate; SD: Standard deviation; CM: Contrast media.

Table 2: Incidence of clinical outcomes at 1 year according to the CM volume quartiles

End points	Contrast volume quartile (n = 10,961)				P*
	≤100 ml (n = 4105)	101–140 ml (n = 1636)	141–200 ml (n = 3600)	>200 ml (n = 1620)	
MACCE	294 (7.16)	129 (7.89)	335 (9.31)	190 (11.73)	<0.001
All-cause mortality	65 (1.58)	21 (1.28)	55 (1.53)	37 (2.28)	0.119
MI	36 (0.88)	15 (0.92)	37 (1.03)	29 (1.79)	0.020
Stroke	49 (1.19)	21 (1.28)	53 (1.47)	23 (1.42)	0.739
Revascularization	172 (4.19)	88 (5.38)	223 (6.19)	130 (8.02)	<0.001
All bleeding	193 (4.70)	97 (5.93)	262 (7.28)	133 (8.21)	<0.001
BARC2-5	69 (1.68)	31 (1.89)	65 (1.81)	41 (2.53)	0.194
BARC3-5	28 (0.68)	11 (0.67)	23 (0.64)	6 (0.37)	0.575

Values are n (%). *Comparisons among quartiles of CM volume. BARC: Bleeding Academic Research Consortium; MACCE: Major adverse cardiac and cerebrovascular events; MI: Myocardial infarction; CM: Contrast media.

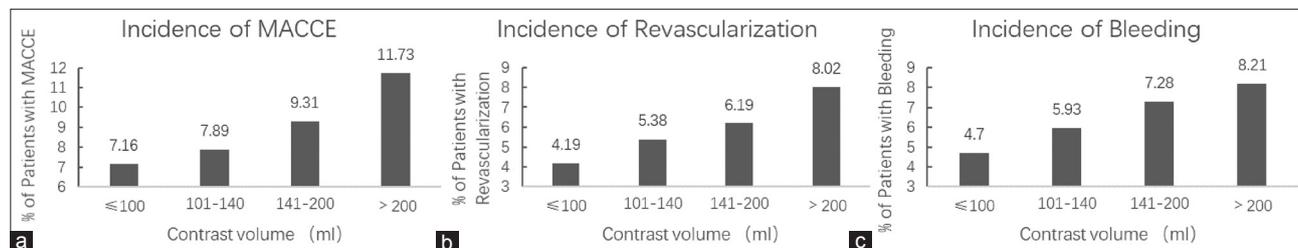


Figure 1: Incidence of MACCE (a), revascularization (b), and all bleeding by categories of CM volume quartiles (c) in the entire study population. The Y-axis scale is different in each category and reflects the difference in baseline risk among different clinical outcomes). MACCE: Major adverse cardiac and cerebrovascular event; CM: Contrast media.

95% CI: 1.06–1.58; 1.36, 95% CI: 1.09–1.69, respectively, $P < 0.001$) and was elevated in patients with increasing CM volume [Figure 2].

The rate of 1-year MACCE was 8.65%, and the rate of all bleeding events was 6.25% in the overall patient group. The survival analysis showed that the 1-year MACCE rate was higher with increased CM volume compared to patients given less volume during the procedure (7.16%, 7.89%, 9.31%, and 11.73%, $P < 0.001$).

Among the 10,961 patients eligible for the survival analyses at 1 year, there were 948 patients (8.65%) with MACCE including 178 patients with all-cause death (1.62%),

117 patients with MI (1.07%), 146 patients with stroke (1.33%), 613 patients with revascularization (5.59%), and 685 patients (6.25%) with bleeding events. Patients with less contrast volume during angiography had better clinical outcomes. There was a significant incremental increase in the cumulative incidence of MACCE accompanying the increase of contrast volume [Figure 3]. The incidences of all-cause death, MI, stroke, and revascularization in each group were as follows: 65 (1.58%), 36 (0.88%), 49 (1.19%), and 172 (4.19%) in quartile range 1; 21 (1.28%), 15 (0.92%), 21 (1.28%), and 88 (5.38%) in quartile range 2; 55 (1.53%), 37 (1.03%), 53 (1.47%), and 223 (6.19%) in quartile range 3; 37 (2.28%), 29 (1.79%), 23 (1.42%), and 130 (8.02%) in

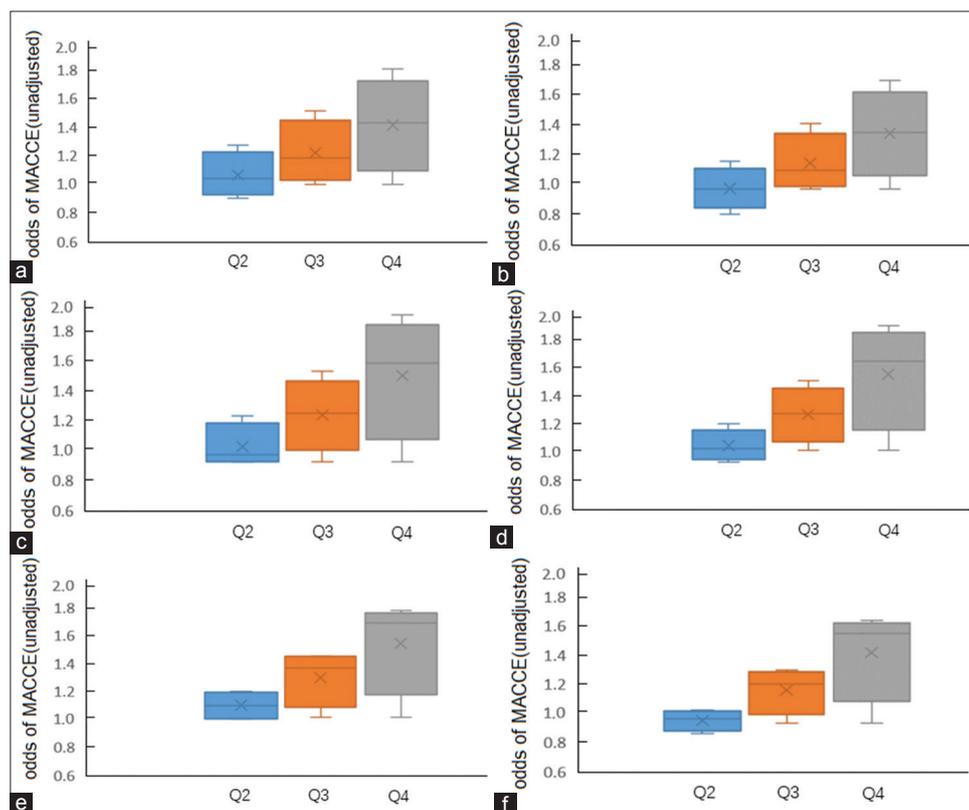


Figure 2: Unadjusted and adjusted ORs of the logistic regression model for MACCE (a and b), revascularization (c and d), and all bleeding (e and f) when Q2, Q3, and Q4 compared to Q1 as the reference ($OR = 1.00$). Blue: Q2, Orange: Q3, Gray: Q4. “x” in the figures means regression analysis OR value. ORs: Odds ratios; MACCE: Major adverse cardiac and cerebrovascular event.

Table 3: Logistic regression analysis between 1-year clinical outcomes and the CM volume quartiles

Outcomes	OR (95% CI)				P for trend
	Group 1 Median: 100 ml	Group 2 Median: 120 ml	Group 3 Median: 180 ml	Group 4 Median: 280 ml	
MACCE (unadjusted)	1.00 (reference)	1.11 (0.90–1.38)	1.26 (1.08–1.47)	1.51 (1.27–1.80)	<0.001
MACCE (adjusted)	1.00 (reference)	1.06 (0.83–1.34)	1.19 (1.00–1.41)	1.43 (1.18–1.72)	<0.001
Revascularization (unadjusted)	1.00 (reference)	1.30 (0.999–1.69)	1.33 (1.10–1.60)	1.59 (1.30–1.96)	<0.001
Revascularization (adjusted)	1.00 (reference)	1.24 (0.92–1.66)	1.27 (1.03–1.57)	1.48 (1.18–1.86)	<0.001
All bleeding (unadjusted)	1.00 (reference)	1.28 (0.99–1.64)	1.41 (1.18–1.68)	1.43 (1.17–1.75)	<0.001
All bleeding (adjusted)	1.00 (reference)	1.23 (0.93–1.63)	1.30 (1.06–1.58)	1.36 (1.09–1.69)	<0.001

The model was adjusted for all baseline characteristics. Test for trend was based on median value for every group. OR: Odds ratios; CI: Confidence interval; CM: Contrast media; MACCE: Major adverse cardiac and cerebrovascular events.

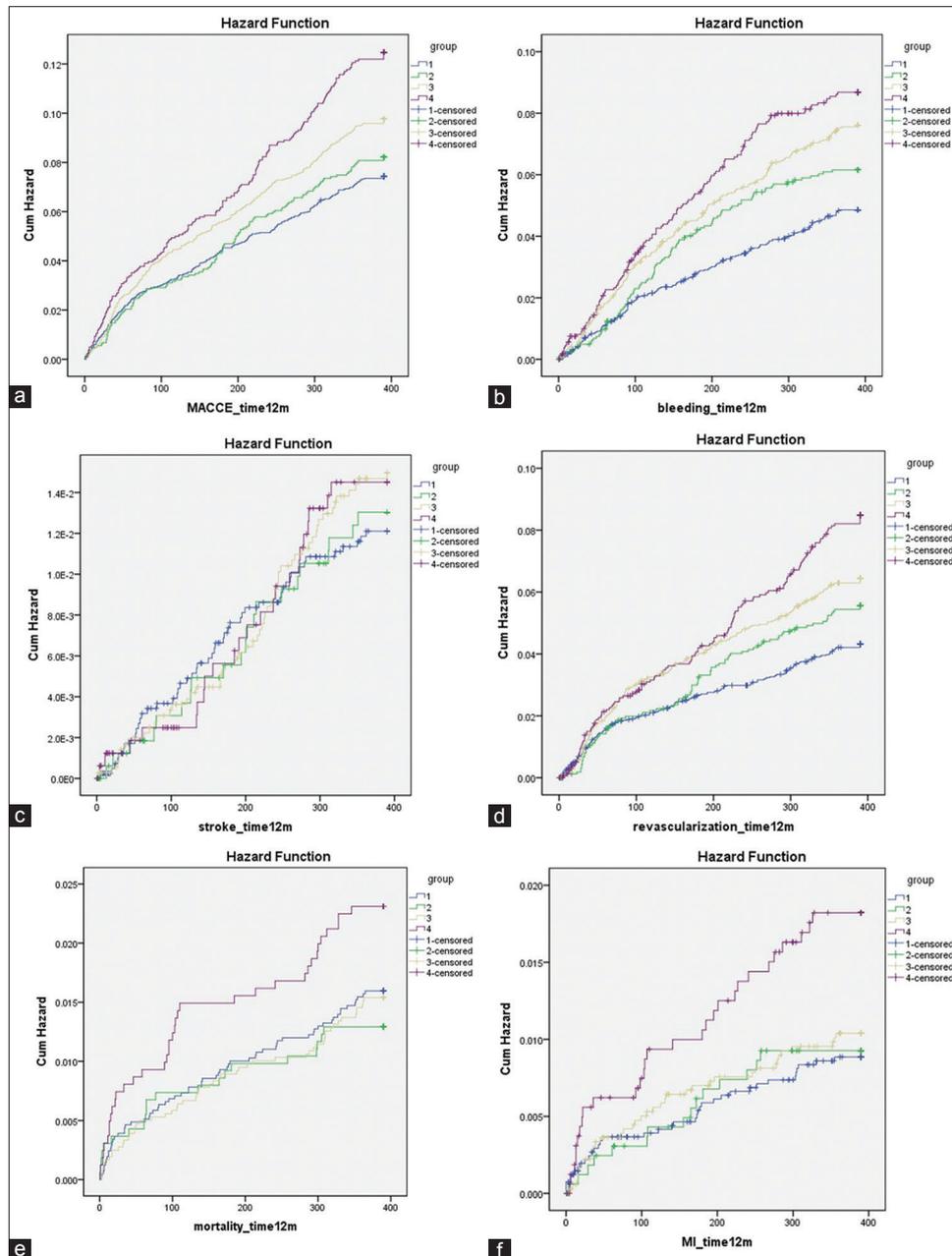


Figure 3: Kaplan-Meier curves showing the cumulative probability of MACCE (a) (log rank $P < 0.001$), all bleeding (b) (log rank $P < 0.001$), stroke (c) (log rank $P = 0.739$), revascularization (d) (log rank $P < 0.001$), all-cause mortality (e) (log rank $P = 0.117$), and MI (f) (log rank $P = 0.019$) and according to the CM volume quartiles. MACCE: Major adverse cardiac and cerebrovascular event; CM: Contrast media; MI: Myocardial infarction.

quartile range 4, respectively. These differences are presented graphically in Figure 3 in terms of the cumulative incidence of the primary endpoint in the four groups. There was no significant variation in the 1-year all-cause death rate and stroke rate across quartiles of contrast volume ($P = 0.119$ and $P = 0.739$). Kaplan-Meier curve analyses showed that the risk of MACCE, revascularization and all-bleeding events during follow-up increased accompanying the more CM volume quartiles [Figure 3]. There was no significant variation in the 1-year all-cause death rate and stroke rate across quartiles of contrast volume ($P = 0.119$ and $P = 0.739$). In addition, no significant difference was observed in BARC bleeding

type 2 ($P = 0.158$) or 3 ($P = 0.613$) according to the CM volume quartiles.

DISCUSSION

The main finding of this multicenter, prospective, observant registry is that the CM volume is a simple tool that can help predict the 1-year clinical outcomes in patients with CAD undergoing CAG/PCI. The risk of MACCE, revascularization and all bleeding events are increased when the CM use was greater. Our findings corroborate and significantly extend prior work in the field. Because

CM volume is routinely recorded and readily obtained for patients undergoing invasive cardiac procedures, it can be an easy construct to implement in clinical practice. Multiple moderate-sized studies have implicated CM volume as a key risk factor for CI-AKI in patients undergoing PCI and have supported the use of different threshold as the safe upper limit for contrast. Our study, however, focused on assessing the relationship between CM volume and 1-year clinical outcomes, whereas there was the development of CI-AKI or not. In this respect, the results from our data suggest that efforts to achieve better clinical outcomes need to focus on not only CM volume but also the clinical features underlying different CM volumes administer during CAG/PCI.

CVD is known as a significant cause of mortality, especially in patients with worse cardiac function and coronary culprits. Pre-existing subclinical atherosclerosis could potentially account for the observed increase in CVD mortality, even though in patients without typical symptoms and signs. Therefore, CAG remains a gold standard diagnostic tool for the CAD, and the numbers of cardiac intervention procedure are increasing year by year. Baseline comorbidity, hemodynamic instability, medications, complex lesions and additional patient-specific factors probably interact in a unique fashion to increase the risk of long-term outcomes for a given patient. We recruited real-life consecutive patients with CAD. The results from our study suggest that the baseline high-risk factors of CVD are rather different among CM volume quartiles.

The former studies suggested the amount of CM was found to be a predictor of mortality in patients who underwent CAG. Although an association between CM volume and death was previously reported, the relation between the clinical outcome during follow-up and CM volume has not been adequately studied. Current guidelines recommend the use of iso-osmolar CM as a preventive measure for high-risk patients especially those with chronic kidney disease and/or CVD.^[15,16] However, in reality, the choice of CM agents is largely influenced by several reasons including availability, hospital protocols, purchasing agreements, operator's preference, the presence of allergic reactions, cost, and expense. Apart from the selection of different CM, the impact of CM volume is highly variable between operators, making it even harder to control the appropriate CM volume merely out of prevention of adverse events.^[17] It is fully studied that CM consists of hyperosmotic compounds, and CM injections directly affect the endothelium and inhibit NO production, leading to the deterioration of endothelium regulatory system.^[4] It also causes changes in intracellular pH, mitochondrial dysfunction, and apoptosis. Zhang *et al.*^[4] demonstrated that radiographic CM is related to apoptosis of human vascular endothelial cells, and they considered that this relation may be dependent on the osmolality of the CM and the chemical structure of this agents.

The amount of CM administered in CAG procedure is one of the most important causes of CI-AKI, ascribing to the nephrotoxicity of CM, which is related to high mortality and morbidity rates.^[18-22] However, Caspi *et al.*^[23] results are at

odds with prior studies that reported a positive association between higher contrast volume and incident acute kidney injury (AKI) in patients undergoing primary PCI (pPCI). Moreover, previous randomized trials of complete versus lesion-only revascularization in patients undergoing pPCI indicated similar CI-AKI rates despite the higher contrast volume for the multivessel-PCI group.^[24,25] Recently, Kooiman *et al.*^[26] reported that old age, baseline renal dysfunction, heart failure, or hemodynamic instability were major determinants of AKI risk for all ST-segment elevation MI (STEMI) patients. These results suggest that CM might not be accountable for most post-pPCI AKI events. Therefore, the predictive value of CM volume for clinical outcomes may not definitely be under the mechanism of CI-AKI. The association between CM use and CI-AKI, other renal complications, or dialysis has been demonstrated in prior studies of patients with CAD, and the risk markedly increases in the settings of acute MI.^[27-29] Our analyses, however, have not been sufficient to establish a causal relationship between CI-AKI and worse 1-year clinical outcomes. In the present study, there was no significant association between contrast volume and 1-year mortality. AKI was strongly predictive of adverse outcomes; however, some study showed the impact of AKI on clinical outcomes was similar among patients with and without contrast exposure. These results suggest that contrast volume did not directly contribute to the increase in adverse events. Of note, risk variables that predicted prognosis were also strongly involving in greater CM use. Rudnick *et al.*^[30] reported that most patients in observational studies had the underlying risk factors, which could directly increase CI-AKI risk, suggesting that CI-AKI is just a marker of increased mortality. However, we could not draw any definitive conclusion due to missing data or serum creatinine.

Caspi *et al.*^[32] provided evidence that CM exposure might not be associated with increased rate of AKI by comparing STEMI patients undergoing pPCI with those treated with thrombolysis or without reperfusion (not exposed to CM). In an analysis of AKI events that accrued among propensity score-matched patients who were or were not exposed to CM, the rates of AKI were not significantly different. The slope of the creatinine rise over the first 72 h of hospitalization was similar in patients with and without CM exposure. In the radiology literature, these controlled studies demonstrated similar rates of AKI, dialysis, and death between patients in the groups that received CM and the control groups of patients who did not receive CM, underscoring the crucial need in a control group of participants who do not receive CM.

Based on the discussed evidence, higher CM use is associated with an increased long-term MACCE and all bleeding risk compared with lower CM use, whereas the long-term mortality, MI, and stroke risk are neutral. Greater CM volume is not the reason for the worse long-term outcome but is a marker for increased risk of adverse events.

Notably, our study revealed that CM volume was the predictor of MACCE, revascularization, and bleeding in

patients undergoing cardiac catheterization. CVD is known as a significant cause of mortality in patients with chronic kidney disease in which subclinical atherosclerosis has already begun before end-stage kidney disease. Pre-existing subclinical atherosclerosis could potentially account for the observed increase in CVD mortality in patients with renal failure. Biyik *et al.*^[31] conducted the study to assess the predictors of all-cause mortality in patients with an estimated glomerular filtration rate of $<60 \text{ ml}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$. It turned out the strongest predictor of total mortality that was found during this study is the amount of CM. It showed a contrast volume of $>140 \text{ ml}$ was found to be related to mortality. The amount of CM used in a CAG procedure is one of the most important causes of CI-AKI, which is related to high mortality and morbidity rates. There was no difference between survivors and non-survivors in terms of the development of CI-AKI.

The association of cardiovascular risk factors and complexity and severity of CAD with CM volume remains unknown. In our analysis, clinical and angiographic parameters were routinely collected and readily available at baseline characteristics. The percentage of complex lesions simply described the procedural feature in our study. Complex lesions consisted of chronic total occlusions, bifurcations, thrombotic lesions, diffuse lesions, and very small vessels. The ratio of complex lesions increased along with increased CM volume use. More recently, cardiac interventionists have devoted themselves to improve procedural technique, which resulted in significant reductions over time in fluoroscopy times, CM volumes, and numbers of catheters needed to complete the procedure. In contrast, growing in popularity among patient complexity has been anticipation that fluoroscopy time and CM volume may increase, along with the frequency and complexity of *ad hoc* PCI.^[32] Bhatt *et al.*^[33] demonstrated that besides coronary intervention (stent placement or angioplasty), the important predictors of CM volume were the extent of CAD, acuity or urgency of the event, and a marker of cardiac hemodynamics. Moreover, these clinical features are possibly the predictors of prognosis as well. Assali *et al.*^[34] indicated that in the setting of contemporary catheter-based reperfusion strategy for acute MI, the extent of CAD, failure to achieve complete reperfusion, the amount of CM used during angioplasty, and deterioration of renal function following the procedure were significant factors related to mortality. Regarding insufficiency of our study, we did not address the association between the cardiovascular risk factors including procedural complexity above-mentioned and 1-year outcomes.

The present study has certain limitations. First, as this prospective observational study was conducted at multiple research centers, selection bias is an inherent concern, and the evidence may not be as strong as that obtained from a randomized controlled trial. Although this might decrease the validity of our comparisons, registries are important for collecting real-life data on unselected patients. Second, we did not have serum creatinine data a few days or weeks to

estimate the occurrence of CI-AKI and the information of the relevant administration during the follow-up period. Third, data on the type of contrast material were not available because of methodological limitations. Different CM has different iodine concentration. This measure is not routinely assessed in clinical practice, and these data were not available for this cohort. Fourth, measurement was not collected in a standardized fashion may have led to limited control over bias and confounding variables. Fifth, patients were excluded due to the absence of follow-up information, and this introduced potential selection bias. Finally, there might be some unmeasured confounders in spite of the adjustment, because baseline characteristics were significantly different among groups; however, after adjusting for all baseline characteristics, the *ORs* were still significantly associated with an increased risk of MACCE, revascularization, and all bleeding among quartiles of CM volume.

The total number of patients with MACCE and all bleeding was low, despite the overall large cohort, and our study might be underpowered to detect differences in the discriminatory ability of different dosing that were evaluated. In relation to the amount of CM given during cardiac catheterization, long-term survival has not been studied adequately to date.

In this study, a higher contrast volume was associated with a significantly higher MACCE, and bleeding rates in patients who underwent CAG. Our study supports the need for identifying the potential cardiovascular risk factors, evaluating the extent of CAD and minimizing the contrast dose in patients undergoing invasive cardiac procedures. Since this study is observational in nature and cannot ascribe causality, further randomized studies are needed.

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Conflicts of interest

There are no conflicts of interest.

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行冠状动脉造影术患者中造影剂用量与一年临床结局之间的关系

摘要

背景：冠状动脉严重病变及介入手术延长导致造影剂的用量明显增加。然而，尚不清楚造影剂用量是否与临床结果的恶化直接相关。本文探讨经皮冠状动脉介入术和冠状动脉造影术中造影剂用量与一年主要不良心脑血管事件（MACCE）及全因出血事件发生率的关系。

方法：我们前瞻性地登记了2012年至2013年间确诊为冠心病并需要行冠状动脉造影的患者10961例。研究人群随访1年。使用Logistic回归分析评估造影剂的用量（分为四分位数）对MACCE和全因出血事件的风险的预测价值。

结果：1年MACCE累积发生率为8.65%，与造影剂用量增加直接相关。特别值得注意的是，在造影剂用量四分位数Q1（ ≤ 100 毫升（ml））、Q2（101-140ml）、Q3（141-200ml）和Q4（ > 200 ml）的情况下，分别观察到MACCE分别为7.16%、7.89%、9.31%、11.73%（ $P < 0.001$ ）。同时，Q1、Q2、Q3和Q4患者的1年全因出血事件发生率分别为4.70%、5.93%、7.28%和8.21%（ $P < 0.001$ ）。生存分析结果显示，冠状动脉造影术中造影剂用量越大，患者的一年MACCE率越高。造影剂用量 > 140 ml与一年MACCE的发生有关，超过200ml的MACCE显著升高（ $P = 0.007$ ）。

结论：我们的结果显示，较高的造影剂用量与冠脉介入术患者的MACCE和各种原因的出血事件的风险显著相关。