Does contrast media volume affect long-term survival in patients with chronic kidney disease?

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Abstract

Introduction: The aim of this study was to investigate the relationships between survival and related features in patients with chronic kidney disease undergoing cardiac catheterization and coronary angiography.

Material and methods: Three hundred and seven consecutive patients with an estimated glomerular filtration rate (e-GFR) less than 60 ml/min/1.73 m² undergoing coronary angiography were enrolled in the study. The study population was pursued with a median follow-up duration of 41.5 months.

Results: In the Cox proportional hazards regression model, age (HR = 1.047, 95% CI: 1.011–1.084, p = 0.01), contrast media volume (HR = 1.004, 95% CI: 1.001–1.007, p = 0.008), angiotensin II receptor blocker (ARB) use (HR = 0.485, 95% CI: 0.261–0.901, p = 0.02), and e-GFR (HR = 0.978, 95% CI: 0.940–1.016, p = 0.04) were found to be independent predictors of long-term all-cause mortality. The survival analysis showed that the long-term all-cause mortality rate was higher in patients using contrast media volume greater than 140 ml compared to patients given less than or equal to 140 ml during the coronary angiography (3.6% vs. 11.6% log-rank, p = 0.001).

Conclusions: In patients with chronic kidney disease undergoing cardiac catheterization, age, contrast media volume, e-GFR and low ARB use were found to be independent predictors of long-term all-cause mortality. Contrast media volume used > 140 ml was independently associated with long-term all-cause mortality compared to less than or equal to 140 ml during cardiac catheterization.

Key words: chronic kidney disease, mortality, coronary angiography, contrast media volume.

Introduction

Nowadays, cardiac catheterization has become an important tool in the treatment of cardiovascular disease (CVD). The risk of occurrence of a major complication (death, myocardial infarction, or major embolization) during diagnostic cardiac catheterization has become very rare. However, high-risk subgroups such as those aged above 60 years, women, those with New York Heart Association (NYHA) class IV heart failure, those with severe disease of the left main coronary artery and those with
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Material and methods

Patient population

This single-center prospective cohort study included 307 consecutive patients undergoing coronary angiography for suspected coronary artery disease (CAD) between 2010 and 2012. Inclusion criteria were patients older than 21 years of age and with an e-GFR of less than 60 ml/min/1.73 m² as calculated by the Modification of Diet in Renal Disease formula. Exclusion criteria were as follows: (a) patients requiring dialysis and with an e-GFR less than 15 ml/min/1.73 m², (b) patients with uncontrolled hypertension (systolic and diastolic blood pressure greater than 160 and greater than 110 mm Hg, respectively), (c) exposure to radio-contrast agents within 7 days, (d) acute coronary catheterization is elevated and e-GFR is a significant prognostic parameter in patients who have undergone cardiac catheterization [4]. However, no data exist on the prognostic markers in patients with an e-GFR of less than 60 ml/min/1.73 m² undergoing cardiac catheterization.

The aim of the present study was to investigate the predictors of all-cause mortality in patients with an e-GFR less than or equal to 60 ml/min/1.73 m² undergoing cardiac catheterization.

Measurements and definitions

Creatinine and blood urea nitrogen were measured the day before the administration of contrast media and 4, 24, and 48 h after administration. Serum creatinine was measured using the standard laboratory method. The Mehran risk score to estimate the risk of contrast induced nephropathy (CIN) was calculated for each case [7, 8]. Preprocedural creatinine clearance was calculated according to the Modification of Diet in Renal Disease formula [9]. The logistical clinical syntax score (log CSS) core model was calculated according to the formula developed by Farooq et al. [10]. The SYNTAX score was calculated using the criteria of the SYNTAX trial (defined as 50% or greater stenosis in any coronary vessel with a diameter of 1.5 mm or greater) [11]. The SYNTAX score was calculated retrospectively by 2 cardiologists blinded for the study patients. Two-dimensional and pulsed-wave Doppler echocardiography studies were performed with the patient in the left lateral decubitus position and using conventional views using a Vivid S6 device with a 3.5-MHz phased array transducer (GE Medical Systems, Horten, Norway) [12]. Left ventricular ejection fraction (LVEF) was calculated in all patients. The clinical endpoint of the research was all-cause mortality. All patients provided written informed consent. The study protocol was approved by the local Institutional Review Board and Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines.

Statistical analysis

All statistical calculations were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were presented as percentages. A χ² test was used for the comparison of categorical variables. The differences between normally and abnormally distributed numeric variables were evaluated using Student’s t-test and the Mann-Whitney U test, respectively. Kaplan-Meier analysis was used to identify the cumulative incidence rates of long-term outcomes and the log-rank test was used to compare the groups. P-values of < 0.05 were considered significant. In addition, 95% confidence interval and odds ratios (OR) were presented together. The Cox proportional hazard regression model was created while investigating the influence of parameters on long-term all-cause mortality. Parameters having significance (p < 0.05) and parameters that were found to be significant in previous studies were included in the model. Hazard ratio (HR) values were expressed with 95% confidence intervals. The capacity of the contrast media volume in predicting the presence of mortality was analyzed using receiver operating characteristic (ROC) curve analyses.
Results

Baseline demographic, clinical, and angiographic characteristics of the patients are shown in Table 1, and baseline laboratory characteristics of the patients are presented in Table 2. Three hundred and seven patients were included in the analysis, median age of the patients was 67 (min. 39, max. 82), median body mass index (BMI) of the patients was 27.8 kg/m² (min. 18, max. 43.3), and 63.4% (n = 195) of the study subjects were male. Sixty-three of the patients (20.5%) died during the median follow-up of 41.5 months (1–54 months).

Table I. Baseline clinical characteristics and procedural details of the study population

| Variables                      | Survivors (n = 244) | Non-survivors (n = 63) | P-value |
|--------------------------------|---------------------|------------------------|---------|
| Age, mean ± SD [years]         | 65.1 ±8.7           | 69.2 ±7.3              | 0.001   |
| Male gender, n (%)             | 155 (63.5)          | 40 (63.5)              | 1       |
| Body mass index [kg/m²]        | 28.9 ±4.6           | 27.1 ±4.0              | 0.008   |
| Hypertension, n (%)            | 208 (85.2)          | 47 (74.6)              | 0.045   |
| Systolic blood pressure [mm Hg]| 134.7 ±16.2         | 137 ±15.8              | 0.342   |
| Diastolic blood pressure [mm Hg]| 76.6 ±9.3          | 74.7 ±10               | 0.152   |
| Diabetes mellitus, n (%)       | 126 (51.6)          | 28 (44.4)              | 0.309   |
| CAD history, n (%)             | 135 (55.3)          | 35 (55.6)              | 0.974   |
| Congestive heart failure, n (%)| 18 (7.4)            | 7 (11.1)               | 0.334   |
| Stroke history, n (%)          | 14 (5.7)            | 8 (12.7)               | 0.056   |
| Peripheral arterial disease, n (%)| 31 (12.7)        | 15 (23.8)              | 0.028   |
| Current smoking, n (%)         | 110 (45.1)          | 30 (47.6)              | 0.719   |
| Medications, n (%):            |                     |                        |         |
| ACEI use                        | 95 (38.9)           | 25 (39.7)              | 0.914   |
| ARB use                         | 92 (37.7)           | 14 (22.2)              | 0.021   |
| Statins use                     | 96 (39.3)           | 17 (27)                | 0.070   |
| Diuretics use                   | 82 (33.6)           | 29 (46)                | 0.067   |
| β-Blockers use                  | 150 (61.5)          | 38 (60.3)              | 0.866   |
| Calcium channel blockers use    | 74 (30.3)           | 17 (27)                | 0.604   |
| N-acetyl cysteine use           | 158 (64.8)          | 46 (73)                | 0.216   |
| Angiography, n (%):            |                     |                        | 0.279   |
| No lesion                       | 17 (7)              | 2 (3.2)                |         |
| Non-critical lesion             | 50 (20.5)           | 8 (12.7)               |         |
| One coronary occluded           | 47 (19.3)           | 10 (15.9)              |         |
| Two coronaries occluded         | 54 (22.1)           | 18 (28.6)              |         |
| > 2 coronaries occluded         | 76 (31.1)           | 25 (39.7)              |         |
| Volume of contrast media ≥ 140 ml| 69 (28.3)          | 33 (52.4)              | < 0.001 |
| Contrast induced nephropathy    | 26 (10.7)           | 8 (12.7)               | 0.645   |
| Nephropathy class, n (%):       |                     |                        | 0.492   |
| e-GFR [ml/min/1.73 m²] (59–30)  | 227 (93)            | 57 (90.5)              |         |
| e-GFR [ml/min/1.73 m²] (15–29)  | 17 (7)              | 6 (9.5)                |         |

CAD – coronary artery disease, ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, e-GFR – estimated glomerular filtration rate.
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The non-survivors were elderly (69.2 ± 7.3 vs. 65.1 ± 8.7, \( p = 0.001 \)) and the prevalence of peripheral arterial disease (PAD) was higher among the non-survivors (23.8% vs. 12.7%, \( p = 0.02 \)). Body mass index was lower among the non-survivors (\( p = 0.008 \)). The prevalence of hypertension and angiotensin II receptor blocker (ARB) use were higher among the survivors than the non-survivors (\( p = 0.04 \) and \( p = 0.02 \), respectively). The MEHRAN score and log CSS were higher among the non-survivors (8.7 ± 3.1 vs. 7.6 ± 3.2; \( p = 0.01 \); 9.7 ± 3.1 vs. 8.9 ± 2.8; \( p = 0.04 \), respectively). Estimated GFR was lower among the non-survivors (42.7 ± 9.9 vs. 45.5 ± 8.9; \( p = 0.04 \)), and there was no difference between the two groups in terms of the occurrence of CIN after cardiac catheterization. The levels of hs-CRP were higher among the non-survivors than the survivors (\( p = 0.007 \)). The neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio were higher among the non-survivors than the survivors (\( p = 0.001 \) and \( p = 0.01 \), respectively). In terms of angiographic procedure, the amount of contrast media volume was significantly higher among the non-survivors (158.0 ± 89.2 vs. 116.3 ± 67.5, \( p = 0.001 \)) and the duration of the procedure was longer in the non-survivors than the survivors (31.3 ± 20.3 vs. 22.4 ± 16.1, \( p < 0.001 \)). A receiver operating characteristics (ROC) curve was generated to investigate the predictive value of the contrast media volume for mortality in patients undergoing coronary angiography. It was found that a contrast media volume of greater than 140 ml had 52.4% sensitivity and 71.7% specificity in the prediction of mortality among the patients (AUC = 0.656, 95% CI: 0.581–0.731; \( p < 0.001 \)) (Figure 1).

### Table II. Comparisons of baseline laboratory results and other measurements among groups

| Variables                        | Survivors (\( n = 244 \)) | Non-survivors (\( n = 63 \)) | \( P \)-value |
|----------------------------------|---------------------------|-----------------------------|--------------|
| Hematocrit level (%)             | 38.1 ±5.1                 | 37.1 ±5.7                   | 0.179        |
| White blood cell count \( \times 10^9/l \) | 7.5 ±1.8                  | 8.5 ±2.5                    | 0.192        |
| Neutrophil count \( \times 10^9/l \) | 4.8 ±1.5                  | 5.5 ±2.2                    | 0.011        |
| Lymphocyte count \( \times 10^9/l \) | 2.0 ±0.6                  | 2.5 ±0.2                    | 0.957        |
| Platelet count \( \times 10^9/l \) | 231.1 ±58.1               | 245.5 ±92.1                 | 0.665        |
| Neutrophil-to-lymphocyte ratio   | 2.7 ±1.3                  | 3.5 ±2.1                    | 0.001        |
| Platelet-to-lymphocyte ratio     | 129.1 ±50.1               | 152.5 ±75.2                 | 0.012        |
| Fasting glucose [mg/dl]          | 136 ±65                   | 124 ±48                     | 0.640        |
| Baseline blood urea nitrogen [mg/dl] | 26.1 ±8.1                 | 29.7 ±9.6                   | 0.006        |
| Baseline serum creatinine [mg/dl] | 1.5 ±0.3                  | 1.6 ±0.4                    | 0.100        |
| Uric acid [mg/dl]                | 6.8 ±1.6                  | 7.3 ±1.7                    | 0.031        |
| Triglycerides [mg/dl]            | 193.0 ±117.4              | 153.8 ±95.6                 | 0.001        |
| Total cholesterol [mg/dl]        | 191.1 ±47.6               | 181.2 ±49.9                 | 0.148        |
| LDL-C [mg/dl]                    | 118.3 ±40.1               | 113.8 ±39.3                 | 0.429        |
| HDL-C [mg/dl]                    | 40.8 ±11.3                | 41.2 ±11.9                  | 0.912        |
| hs-CRP [mg/dl]                   | 4.9 ±3.5                  | 6.3 ±4.1                    | 0.007        |
| LVEF (%)                         | 53 ±10                    | 52 ±11                      | 0.427        |
| LVEF < 40, n (%)                 | 21 (8.6)                  | 10 (15.9)                   | 0.088        |
| Baseline e-GFR [ml/min/1.73 m²]  | 45.5 ±8.9                 | 42.7 ±9.9                   | 0.041        |
| Procedure time [min]             | 22 ±16                    | 31 ±20                      | < 0.001      |
| Contrast media volume [ml]       | 116 ±67                   | 158 ±89                     | < 0.001      |
| Mehran risk score                | 7.6 ±3.2                  | 8.7 ±3.1                    | 0.017        |
| Log CSS                          | 8.9 ±2.8                  | 9.7 ±3.1                    | 0.049        |

Values are presented as mean ± SD. hs-CRP – high-sensitivity C-reactive protein, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, e-GFR – estimated glomerular filtration rate, LVEF – left ventricular ejection fraction, Log CSS – Logistic Clinical Syntax Score.
median follow-up duration was 41.5 months (1–54 months). The rate of long-term all-cause mortality was 20.5% in the overall patient group. The survival analysis showed that the long-term all-cause mortality rate was higher among patients given greater than 140 ml of contrast media volume compared to patients given less than or equal to 140 ml during the procedure (3.6% vs. 11.6% log-rank, \( p = 0.001 \)) (Figure 2). Univariate analyses showed that age, BMI, e-GFR, hypertension (HT), log CSS, PAD, uric acid, hs-CRP and the amount of contrast media volume differed significantly between the survivors and non-survivors (Table 3). In the Cox proportional hazards regres-

![Figure 1. ROC analyses of the amount of contrast media for predicting total mortality](image1)

![Figure 2. Kaplan-Meier analyses for long-term all-cause mortality rate according to the amount of contrast media](image2)

**Table III.** Factors predicting total mortality on univariate COX regression analysis

| Variables                        | \( P \)-value | HR     | 95% CI          |
|----------------------------------|--------------|--------|-----------------|
| Hypertension                     | 0.042        | 0.554  | 0.314–0.978     |
| Age                              | 0.001        | 1.055  | 1.022–1.090     |
| Hs-CRP                           | 0.005        | 1.103  | 1.030–1.181     |
| Body mass index                  | 0.011        | 0.924  | 0.870–0.982     |
| Peripheral arterial disease      | 0.028        | 1.919  | 1.074–3.428     |
| ARBs use                         | 0.029        | 0.516  | 0.285–0.934     |
| Statins use                      | 0.075        | 0.603  | 0.346–1.053     |
| LVEF                             | 0.228        | 0.986  | 0.963–1.009     |
| Volume of contrast media         | < 0.001      | 1.005  | 1.003–1.008     |
| Contrast induced nephropathy     | 0.656        | 1.184  | 0.564–2.485     |
| Uric acid                        | 0.042        | 1.158  | 1.006–1.334     |
| e-GFR                            | 0.028        | 0.973  | 0.949–0.997     |
| N-acetyl cysteine use            | 0.226        | 1.410  | 0.808–2.460     |
| Neutrophil/lymphocyte ratio      | < 0.001      | 1.224  | 1.108–1.353     |
| Platelet/lymphocyte ratio        | 0.002        | 1.005  | 1.002–1.009     |
| Log CSS                          | 0.053        | 1.083  | 0.999–1.174     |

HR – hazard ratio, CI – confidence interval, hs-CRP – high-sensitivity C-reactive protein, ARB – angiotensin receptor blocker, LVEF – left ventricular ejection fraction, e-GFR – estimated glomerular filtration rate, Log CSS – logistic clinical Syntax score.
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Table IV. Factors predicting total mortality on multivariate COX regression analysis

| Variables                      | P-value | HR   | 95% CI       |
|--------------------------------|---------|------|--------------|
| e-GFR                          | 0.04    | 0.972| 0.946–0.999  |
| Uric acid [mg/dl]              | 0.127   | 1.134| 0.965–1.332  |
| Volume of contrast media [ml]  | 0.002   | 1.005| 1.002–1.008  |
| Statin use                     | 0.98    | 0.617| 0.347–1.094  |
| ARB use                        | 0.015   | 0.458| 0.244–0.858  |
| Peripheral arterial disease    | 0.973   | 0.989| 0.516–1.894  |
| Hypertension                   | 0.43    | 0.785| 0.427–1.444  |
| Body mass index                | 0.265   | 0.964| 0.905–1.028  |
| Age                            | 0.002   | 1.054| 1.019–1.091  |
| hs-CRP                         | 0.062   | 1.070| 0.997–1.150  |
| Log CSS                        | 0.526   | 1.029| 0.942–1.124  |

HR – hazard ratio, CI – confidence interval, e-GFR – estimated glomerular filtration rate, ARB – angiotensin receptor blocker, hs-CRP – high-sensitivity C-reactive protein, Log CSS – logistic clinical Syntax score.

Discussion

The present study revealed that contrast media volume was the strongest predictor of mortality in patients undergoing cardiac catheterization with an e-GFR of less than or equal to 60 ml/min/1.73 m², and it was irrespective of CIN development. In this study, the other predictors of all-cause mortality were age, e-GFR and low ARB use.

Cardiovascular disease 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 [6, 13]. Pre-existing subclinical atherosclerosis could potentially account for the observed increase in CVD mortality in patients with renal failure. Beddhu et al. [6] demonstrated the relation with baseline e-GFR and death. Despite the increased complication rate among patients with renal failure, coronary angiography remains a gold standard diagnostic tool in the diagnosis of CAD. Hemmelgarn et al. investigated the impact of renal insufficiency on survival after coronary angiography, and renal insufficiency was found to be an independent predictor of mortality after coronary angiography in both dialysis-dependent and -independent patients [13]. In another study, Hemmelgarn et al. [4] demonstrated an increased risk of death in patients with an e-GFR of less than 79 ml/min/1.73 m². The complications of renal failure such as anemia and deterioration of calcium phosphate metabolism increase with an e-GFR of less than 60 ml/min/1.73 m² [14, 15]. In the present study, the aim was to assess the predictors of all-cause mortality in patients with an e-GFR of less than 60 ml/min/1.73 m². In the present study, as with previous studies, e-GFR was found to be an independent predictor of all-cause mortality. The strongest predictor of total mortality that was found in this study is the amount of contrast media. The amount of contrast media used in a coronary angiography procedure is one of the most important causes of CIN, which is related to high mortality and morbidity rates [16–18]. The most important predictors of CIN are e-GFR and contrast media volume. In the present study, there was no difference between survivors and non-survivors in terms of the development of CIN. However, independent of the development of CIN, the amount of contrast media was found to be a predictor of mortality in patients with an e-GFR of less than 60 ml/min/1.73 m² who underwent coronary angiography. In the Kaplan-Meier analysis, a contrast volume of greater than 140 ml was found to be related to mortality. It is known that contrast agents have hyper-osmotic compounds and they contact endothelial cells. Contrast media injections directly affect the endothelium and inhibit nitric oxide (NO) production, and they lead to deterioration of the shear stress-induced stimulation of NO production [19]. The endothelium regulates vascular tone by releasing NO, the endothelium-derived hyperpolarizing factor prostacyclin, or natriuretic peptides. Furthermore, these mediators prohibit thrombus formation and vascular stenosis via anti-aggregator properties. In addition, the en-
dothelium acts synergistically with a regulatory system, which consists of vasoconstrictors such as catecholamines and other vasoactive peptides (i.e., angiotensin, vasopressin, and endothelin) [20]. The deterioration of this regulatory system by exposure to contrast media may be one of the reasons for the relation between contrast media volume and mortality that was found in this study. Contrast media injections also cause changes to intracellular pH, mitochondrial dysfunction, and apoptosis [19–22]. Zhang et al. demonstrated that radiographic contrast media are related to reduced proliferation and increased apoptosis of human vascular endothelial cells, and they considered that this relation may be dependent on the osmolality of the contrast media and the chemical structure of these agents [19]. Then, irrespective of the development of CIN, increased mortality with the use of a high volume of contrast media may be due to endothelial injury. The log CSS, a combined risk score, developed by Farooq et al. [10], includes patient’s clinical (age, LVEF, and creatinine clearance) and anatomical (SYNTAX score) parameters. The log CSS was calculated in the present study to evaluate the complexity of coronary artery disease and fragility of patients. It was found higher in the non-survivors than survivors but was not found to be a predictor of mortality in the multivariate analysis. However, high volume of contrast media was found to be a predictor of mortality regardless of the complexity of coronary artery disease and fragility of patients.

The activity of the renin-angiotensin-aldosterone system (RAAS) is elevated both in the circulation and in the renal tissue of diabetic and non-diabetic nephropathies [23]. The increased RAAS activity plays an important role in the hemodynamic and non-hemodynamic pathogenetic mechanisms involved in chronic kidney disease [23]. Randomized crossover and parallel blind studies in patients with diabetic nephropathy have demonstrated that angiotensin-converting enzyme (ACE) inhibition and ARBs induce favorable changes in systemic blood pressure, renal hemodynamics and proteinuria [23–26]. These medications have been shown to preserve kidney function by slightly reducing the filtration rate in the kidneys. Similarly, in this study, lower use of ARBs was found to be a predictor of all-cause mortality in patients with an e-GFR of less than 60 ml/min/1.73 m² who underwent coronary angiography. This study does have some limitations. The main limitations of our study were that it was single centered and had a small patient population size. We were not able to establish clear and detailed causes of mortality such as cardiovascular or others, so we used all-cause mortality in the analyses. In relation to the amount of contrast media given during cardiac catheterization, long-term survival has not been studied adequately to date. Despite the limitations, the importance of the present study results from the fact that it reveals the relation between contrast media volume and long-term mortality in this patient group.

In conclusion, in patients with chronic kidney disease undergoing cardiac catheterization, age, contrast media volume, e-GFR and low ARB use were found to be independent predictors of long-term all-cause mortality. Contrast media volume used > 140 ml was independently associated with long-term all-cause mortality compared to less than or equal to 140 ml during cardiac catheterization. Reducing the volume of contrast agent used could contribute significantly to the reduction in long-term mortality in patients with chronic kidney disease.

Conflict of interest

The authors declare no conflict of interest.

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