Effects of acute kidney injury and chronic kidney disease on long-term mortality after coronary artery bypass grafting

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Background Both acute kidney injury (AKI) and chronic kidney disease (CKD) are important issues in patients undergoing coronary artery bypass grafting (CABG), particularly with regard to mortality. However, their synergistic or discrete effects on long-term mortality remain unresolved.

Methods A total of 1,899 patients undergoing CABG were retrospectively analyzed. The adjusted hazard ratios for all-cause mortality were calculated after stratifying the timeframes. To evaluate the synergistic effects between AKI and CKD, the relative excess risk due to interaction was applied.

Results The presence of AKI, CKD, or both increased the hazard ratios for mortality, compared with the absence of both: AKI alone, 1.84 (1.464-2.319); CKD alone, 2.46 (1.735-3.478); and AKI and CKD together, 3.21 (2.301-4.488). However, the relationships with mortality were different between AKI and CKD, according to the timeframes: AKI primarily affected early mortality, particularly within 3 years, whereas CKD had a relatively constant effect on both the early and late periods. When the parameters from the relative excess risk due to interaction were obtained, there was a synergistic additive effect on early mortality between AKI and CKD.

Conclusions The relationships with mortality after CABG were different between AKI and CKD. However, their effects were not exclusive but synergistic. (Am Heart J 2015;169:419-25.)

Coronary artery bypass grafting (CABG) is one of the most common surgical procedures, and it has been proven to improve the survival of patients with severe angina.[1] The perioperative mortality rate has reached approximately 5%,[2] but this rate is highly dependent on comorbid disease and postoperative complications.[3] In this regard, current predictive models using these conditions have successfully predicted the short-term or mid-term mortality risks after CABG.[3,4]

Regarding the comorbid conditions from predictive models, chronic kidney disease (CKD) strongly affects mortality; in particular, in the advanced stages of CKD, the short-term mortality rate reaches 10%.[5] As a postoperative complication, acute kidney injury (AKI) develops in up to 30% of cases after CABG, and it is a major cause of morbidity and mortality.[6] Despite a decreasing trend in its incidence, the current rate of AKI remains high.[7] CKD and AKI have often been studied with regard to mortality after CABG, but no studies have examined the effects of AKI and CKD together on overall mortality. Furthermore, studies with extended periods have been limited.[8-10] The relationship of AKI or CKD with mortality might be different according to the timeframe (eg, short term or long term), particularly in cases of AKI recovery or CKD progression. Therefore, we aimed to address the following issues from a CABG cohort: the difference between AKI and CKD in the correlations with short- and long-term mortality, possible synergistic effects between AKI and CKD, and the clinical significance of recovery after AKI.

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Methods

Participants and data collection

Data on patients undergoing CABG were obtained retrospectively from a cohort, consisting of patients from 2 tertiary referral centers (Seoul National University

Hospital and Seoul National University Bundang Hospital). A total of 2,278 patients consecutively underwent CABG from January 2004 to December 2010. Patients were excluded from the analysis if they were undergoing renal replacement therapy before surgery (n = 44), if they had end-stage renal disease (n = 30), if they underwent redo-CABG (n = 30), if they underwent concomitant valve surgery (n = 168), or if their electronic medical records were incomplete (n = 107). Therefore, 1,899 patients were ultimately analyzed in the present study.

The clinical parameters recorded included the following: age; sex; height; weight; current smoking status; systolic blood pressure; diastolic blood pressure; hypertension; diabetes mellitus; histories of myocardial infarction or stroke; peripheral vascular disease; medications such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, diuretics, and statins; history of coronary angiography within 1 week before surgery; intraoperative use of cardiopulmonary bypass; and perioperative use of an intra-aortic balloon pump. Body mass index was calculated as body weight (kilograms) divided by the square of body height (meters). Left ventricular ejection fraction was determined by Simpson's modified biplane method from the apical 2-chamber and 4-chamber views on echocardiography. Preoperative blood findings, including creatinine, white blood cells, hemoglobin level, albumin, and cholesterol, were measured. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation[11] and the validated coefficient for Korean subjects[12] as follows: 107.904 × serum creatinine $(\text{mg/dL})^{-1.009}$ × age $(\text{years})^{-0.02}$ (×0.667, if female). According to the guideline proposed by Kidney Disease Improving Global Outcomes (KDIGO),[13] CKD was defined and categorized from stage 3a to stage 5 using preoperative eGFR. The risk of AKI was measured from surgery to 48 hours. For the definition and staging of AKI, concentrations of both preoperative and postoperative serum creatinine were used. In adherence to the KDIGO guideline,[14] AKI was defined in the case with either an increase in serum creatinine by ≥0.3 mg/dL or ≥1.5 times from the baseline. Recovery from AKI was considered at 1 and 3 months after CABG. When the subsequent serum creatinine level was equal to or lower than the preoperative creatinine, this case was determined to have recovered from AKI. Cases in which the subsequent creatinine level was higher than the baseline level or a patient with AKI died within the decision time were defined as nonrecovery cases.

The primary outcome was all-cause mortality after surgery. Except the death-censored cases, all subjects were followed till May 31, 2014. The mortality data were obtained from the national database of Statistics Korea; all Koreans have a resident registration number, and death events are recorded and stored at a national level.

The study protocol complies with the Declaration of Helsinki and received full approval from the institutional review boards at both the Seoul National University Bundang Hospital (no. B-1403/244-112) and the Seoul National University Hospital (H-1403-059-565). No extramural funding was used to support this work.

Statistical analysis

All of the analyses and calculations were performed using STATA software (version 12.0; Stata Corp LP, College Station, TX). The data are presented as the means ± SDs for continuous variables and as proportions for categorical variables. Based on variable distributions using histograms, the variables with nonnormal distributions are expressed as the median (interquartile ranges). The χ^2 test was used to compare categorical variables. Comparisons between normally and nonnormally distributed continuous variables were performed using the Student *t* test and Mann-Whitney *U* test, respectively. Survival curves were drawn using the Kaplan-Meier method. To compare survival curves between groups, the log-rank test was initially applied. To calculate the hazard ratios (HRs) and CIs of mortality risk, a Cox proportional hazard model was used, with and without the adjustment of all covariates or according to the timeframes. When examining the log-minus-log plot, the assumption of proportional hazards was reasonable. The discrimination of predicting mortality was assessed by calculating the receiver operating characteristic (ROC) curve and the area under the curve (AUC), in which both the definitions and stages of AKI or CKD were considered. For AUCs of long-term outcomes (eg, ROC curve for the prediction of 7-year mortality), patients who were alive and followed up <7 years were excluded. To evaluate the synergistic effects on mortality between AKI and CKD, the relative excess risk due to interaction (RERI) was used, based on the logistic regression analyses.[15] The RERI is an approach for estimating the additive interaction of 2 variables. From the RERI method, we present 3 scales: RERI (part of the total effect that is due to interaction), attributable proportion (AP) (proportion of the combined effect that is due to interaction), and synergy index (ratio between combined effect and individual effects). Positive results for the RERI and AP and a value >1 for the synergy index indicate a positive interaction or more than additive between the variables. $P < .05$ was considered to be significant.

The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

Results

Baseline characteristics

The baseline characteristics of the patients are shown and compared between the groups in Table I. Among the subjects, 11.4% and 33.3% had baseline CKD and postoperative AKI, respectively. A total of 46.5% of the