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ORIGINAL ARTICLE

Prognostic implications of preoperative chronic kidney disease and anemia in patients undergoing coronary artery bypass graft surgery

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Abstract
Purpose Chronic kidney disease (CKD) and anemia are independent preoperative risk factors for coronary artery bypass graft (CABG) surgery. We evaluated the implications of the coexistence of these two factors and their associated prognosis for CABG surgery.
Methods We analyzed, retrospectively, consecutive patients who underwent elective CABG surgery between 2004 and 2014. The patients were classified into four groups depending on the presence or absence of preoperative CKD and anemia. We assessed the major adverse cardiac and cerebrovascular event (MACCE), defined as composite outcomes of cardio- and cerebrovascular death, revascularization through surgery or percutaneous intervention, hospitalization for congestive heart failure, and cerebral infarction.
Results The study population consisted of 510 patients (73 % male; median age 71 years old), followed up for a median period of 2.8 years. Multivariate analysis indicated that neither the CKD/no-anemia group [hazard ratio (HR) 0.98, 95 % confidence interval (CI) 0.39–2.51, $P = 0.973$] nor the no-CKD/anemia group (HR 1.20, 95 % CI 0.69–2.09, $P = 0.512$) had significantly poorer prognoses than the no-CKD/no-anemia group. However, the CKD/anemia group had a significantly higher risk of a MACCE (HR 2.01, 95 % CI 1.01–3.98, $P = 0.046$).
Conclusion The presence of both CKD and anemia in patients undergoing CABG for coronary artery disease is synergistically associated with a worse outcome.

Keywords Coronary artery disease · Renal function · Hemoglobin · Prognosis

Introduction

The increasing prevalence of hypertension, diabetes mellitus, and metabolic syndrome, which all predispose to chronic kidney disease (CKD), accompanies a marked increase in the number of CKD patients worldwide. Anemia is a major complication of CKD. The National Health and Nutrition Examination Survey (NHANES) report indicated a CKD prevalence rate of 12–14 % among the non-institutionalized civilian population in the USA and anemia rates of 7.6 and 15.4 % among subjects without vs. those with CKD, respectively [1].

CKD is also recognized as a risk factor associated with the poorer outcome of patients who require coronary artery bypass grafting (CABG) for coronary artery disease (CAD). Indeed, some studies of CABG patients suggest that CKD was associated with perioperative complications [2, 3] and even mortality after surgery [4, 5]. Similarly, anemia has also been shown to be an independent risk factor of poorer outcomes among patients undergoing CABG surgery. As oxygen supply to the myocardium is expected to be limited in coronary artery stenosis patients, those undergoing CABG would be the most sensitive to the harmful effects of anemia [6–8]. Thus, the simultaneous presence of CKD and anemia is synergistically associated with poor prognosis in the general population and in patients with cardiovascular disease [9–11]. However, it is unclear

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whether these results are also applicable to patients undergoing CABG surgery. The present study was performed to evaluate the prognostic relationship between anemia and CKD in patients undergoing CABG surgery.

Methods

Study subjects

All consecutive patients who underwent isolated CABG in our institution between January, 2004 and June, 2014 were included in this retrospective study, which was approved by the local ethics committee of Kameda Medical Center. Patients on hemodialysis and those who underwent emergency CABG were excluded from the analysis. Patients with systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, and those taking antihypertensive agents were considered to have hypertension. Hypercholesterolemia was defined as total cholesterol >220 mg/dL or the requirement for treatment with lipid-lowering agents. Diabetes mellitus was diagnosed according to the World Health Organization (WHO) criteria [12].

A baseline blood sample was collected within 5 days before surgery. Renal function was assessed by estimated glomerular filtration rate (eGFR), which was calculated using the Modification of Diet in Renal Disease (MDRD) equation coefficients, modified for Japanese patients [13]. A diagnosis of CKD was made if the eGFR was <60 mL/min/1.73 m^2, in accordance with the guidelines of the National Kidney Foundation [14]. Anemia was diagnosed according to the WHO definition (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men). All baseline blood samples were obtained in the fasting state. The left ventricular ejection fraction was measured within 1 month before surgery.

The severity of coronary artery stenosis was assessed and classified according to the American Heart Association System [15]. Significant angiographic coronary stenosis was defined as the presence of stenosis >70 % of the luminal diameter in the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCx), and right coronary artery (RCA), and >50 % in the left main coronary trunk artery (LMT), with the LMT counted as two diseased vessels. Euro Score II was assessed for each patient [16].

Follow-up

Baseline demographic and clinical data were obtained by reviewing the medical records and procedural reports. Clinical follow-up data were obtained from outpatient record reviews or a telephone interview with patients or their relatives, and ended in March 2015. The study endpoint in this investigation was a major adverse cardiac and cerebrovascular event (MACCE), including death caused by cardio- and cerebrovascular disease (sudden cardiac death or death from vascular disease or cerebral hemorrhage), revascularization through surgery or percutaneous intervention, hospitalization for congestive heart failure, and/or cerebral infarction. Revascularization included target vessel revascularization and revascularization for de novo lesions by percutaneous coronary intervention or CABG. The indications for repeat revascularization were based on anginal symptoms and significant angiographic stenosis. Congestive heart failure was defined as dyspnea and/or edema that required hospitalization and was accompanied by pulmonary congestion on chest roentgenogram and left ventricular dysfunction on echocardiography. Stroke was diagnosed as a neurological deficit confirmed by computed tomography (CT) or magnetic resonance imaging (MRI).

Statistical analysis

Data are expressed as means ± standard deviation for normally distributed variables, and as the median with interquartile range for non-normally distributed data. Categorical data are expressed as numbers and percentages. The whole cohort was divided into four groups according to the presence of CKD and anemia, and baseline characteristics were compared by one-way analysis of variance (ANOVA), Kruskal–Wallis test, or the Chi squared test where appropriate. When necessary, variables were transformed for further analyses. Survival curves were constructed using the Kaplan–Meier survival method and compared with log-rank statistics. The survival period was defined as the interval between the day of surgery and the time of the first MACCE event. Multivariate analyses were performed using the Cox proportional hazard models to evaluate the prognostic effect of the presence of CKD and anemia over the study period.

All statistical test values were two-sided and $P < 0.05$ was taken to indicate significance in all analyses. Results are expressed as means ± SD, numbers (%), and hazard ratio (HR) with 95 % confidence interval (CI). Statistical analyses were performed using R version 3.1.2 (R foundation for Statistical Computing, Vienna, Austria) and the graphical user interface EZR [17].

Results

A total of 626 patients underwent isolated CABG at our hospital during the study period. After excluding 70 patients on dialysis and 46 patients who underwent emergency CABG, 510 patients were included in the final

Table 1 Baseline characteristics of the patients

Variables	CKD/Anemia (−/−) ($n = 244$)	CKD/Anemia (∓) ($n = 149$)	CKD/Anemia (±) ($n = 28$)	CKD/Anemia (+/+) ($n = 89$)	*P* value
Age (years old)	66.2 ± 10.3	71.0 ± 9.8	72.3 ± 9.8	74.0 ± 8.8	<0.001
Male (%)	194 (79.5)	21 (75.0)	103 (69.1)	56 (37.1)	0.011
Number of diseased vessels	2.45 ± 1.52	2.43 ± 0.75	2.43 ± 0.84	2.34 ± 0.80	0.905
Left ventricular ejection fraction (%)	60.4 ± 11.7	59.3 ± 13.8	57.7 ± 13.3	57.5 ± 13.7	0.33
Euro Score II	1.28 [0.85–2.09]	1.92 [1.26–3.17]	3.30 [2.37–4.37]	4.16 [2.85–6.12]	<0.001
Prescription before surgery (%)					
ACE-I	42 (17.2)	29 (19.5)	4 (14.3)	14 (15.7)	0.848
ARB	74 (30.3)	49 (32.9)	11 (39.3)	36 (40.4)	0.323
Beta blocker	106 (43.4)	70 (47.0)	8 (28.6)	40 (44.9)	0.347
HMG-CoA inhibitor	135 (55.3)	82 (55.0)	11 (39.3)	45 (50.6)	0.384
Oral anticoagulants	21 (8.6)	5 (17.9)	24 (16.1)	10 (11.2)	0.108
Aspirin	169 (69.3)	89 (59.7)	19 (67.9)	57 (64.0)	0.275
Comorbidities (%)					
Hypertension	177 (72.5)	108 (72.5)	25 (89.3)	79 (88.8)	0.004
Dyslipidemia	176 (72.1)	106 (71.1)	21 (75.0)	64 (71.9)	0.981
Diabetes mellitus	110 (45.1)	69 (46.3)	13 (46.4)	49 (55.1)	0.441
Atrial fibrillation	14 (5.7)	14 (9.4)	4 (14.3)	13 (14.6)	0.053
History of myocardial infarction	57 (23.4)	34 (22.8)	8 (28.6)	16 (18.0)	0.627
History of percutaneous coronary intervention	42 (17.4)	35 (23.6)	4 (14.3)	14 (15.7)	0.315
Peripheral artery disease	52 (21.3)	25 (16.8)	10 (35.7)	31 (34.8)	0.004
Smoking history (ex- or current smoker)	170 (69.7)	89 (59.7)	19 (67.9)	62 (69.7)	0.204
Conduit use (%)					
Right internal thoracic artery	35 (14.3)	15 (10.1)	5 (17.9)	8 (9.0)	0.461
Right gastroepiploic artery	66 (27.0)	32 (21.5)	5 (17.9)	10 (11.2)	0.056
Left internal thoracic artery	215 (88.1)	123 (82.6)	23 (82.1)	72 (80.9)	0.274
Radial artery	86 (35.2)	43 (28.9)	5 (17.9)	16 (18.0)	0.031
Saphenous vein graft	91 (37.3)	66 (44.3)	15 (53.6)	53 (59.6)	0.003
On-pump CABG	69 (28.3)	44 (29.9)	8 (28.6)	31 (34.8)	0.715
Laboratory data before surgery					
Hemoglobin (g/dL)	10.66 ± 1.33	10.03 ± 1.04	10.20 ± 1.17	10.29 ± 1.19	<0.001
Albumin (g/mL)	4.04 ± 0.38	3.68 ± 0.52	3.92 ± 0.48	3.45 ± 0.52	<0.001
Total cholesterol (mg/dL)	175.7 ± 37.5	174.3 ± 39.3	175.2 ± 29.7	168.7 ± 45.3	0.565
Creatinine (mg/dL)	0.91 ± 0.24	1.02 ± 0.87	1.64 ± 0.68	2.02 ± 1.21	<0.001
eGFR (mL/min/1.73 m^2)	88.16 ± 13.38	82.90 ± 12.60	47.29 ± 10.49	36.84 ± 14.29	<0.001
Blood urea nitrogen (mg/dL)	15.0 [7.0, 40]	26.0 [13.0, 47.0]	16.0 [6.0, 38.0]	27.0 [15.0, 76.0]	<0.001
Serum potassium (mEq/L)	4.26 ± 0.37	4.32 ± 0.42	4.50 ± 0.35	4.46 ± 0.53	<0.001
C-reactive protein (g/dL)	0.13 [0.06, 0.36]	0.26 [0.09, 1.03]	0.12 [0.09, 0.35]	0.38 [0.10, 1.59]	<0.001

ACE-I angiotensin-converting inhibitor, *ARB* angiotensin receptor blocker, *HMG-CoA* 3-hydroxy-3-methyl-glutaryl-CoA reductase, *eGFR* estimated glomerular filtration rate

analysis. Table 1 summarizes the baseline characteristics of these 510 patients. Using the definitions outlined in Methods, 117 (22.9 %) patients had CKD and 238 (46.7 %) had anemia. We divided the cohort into four groups according to the presence or absence of anemia and renal dysfunction. There were significant differences in age, gender, hypertension, and peripheral artery disease among the groups. Moreover, the CKD and anemia group had low levels of albumin and high levels of potassium and C-reactive protein.

The median follow-up period was 2.8 (IQR 0.9–5.9) years. During follow-up, there were 96 (18.8 %) incidences of MACCE, consisting of 37 admissions for heart failure, 26 revascularization procedures, 16 strokes, and

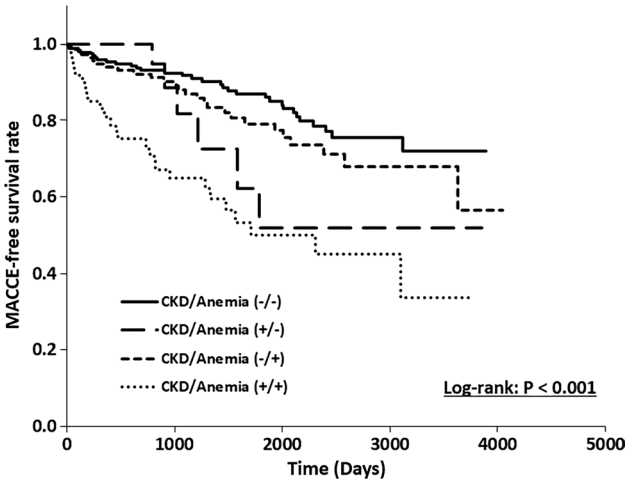

Fig. 1 Kaplan–Meier curves for major cardiac and cerebrovascular event-free survival. *CKD* chronic kidney disease, *MACCE* major cardiac and cerebrovascular event

17 cardio- and cerebrovascular deaths. During the follow-up period, there were 61 deaths from all causes. The death rates in each group were 9.0 % in the non-CKD/non-anemia group, 17.9 % in the CKD/non-anemia group, 12.1 % in the non-CKD/anemia group, and 18.0 % in the CKD/anemia group ($P = 0.112$). The CKD and anemia group had a lower MACCE-free survival rate than the other groups (log-rank: $P < 0.001$; Fig. 1). In univariate analysis, the presence of both CKD (HR 2.94, 95 % CI 1.94–4.46, $P < 0.001$) and anemia (HR 1.95, 95 % CI 1.30–2.93, $P = 0.001$) was significantly associated with MACCE. The presence of CKD (HR 1.46, 95 % CI 0.83–2.57, $P = 0.194$) or anemia (HR 1.43, 95 % CI 0.90–2.27, $P = 0.129$) alone was not an independent predictor of MACCE; however, the coexistence of both CKD and anemia (CKD/anemia group) showed an independent and significant association with poorer outcomes than the group with non-CKD/non-anemia in both univariate and multivariate Cox regression analyses (Table 2).

Discussion

In the present series, 17.5 % of patients undergoing CABG, who did not have end-stage renal disease, had co-existing CKD and anemia. The prognosis of patients whose condition was complicated by only one of these two comorbidities was not worse than that of the non-CKD non-anemia group, but the coexistence of CKD and anemia had a deleterious impact on prognosis. This finding suggested a synergistic negative effect of these two known comorbidities on the prognosis of patients undergoing CABG. This interaction was also observed in the general population and in patients with cardiovascular disease (CVD). Jurkovitz et al. reported a similar correlation in a prospective study on a cohort of 13 329 middle-aged participants with no history of CVD [18]. They defined renal insufficiency as a serum creatinine value of ≥1.2 mg/dL for women and ≥1.5 mg/dL for men, and evaluated the associations of both renal insufficiency and anemia with the incidence of

Table 2 Univariate and multivariate Cox regression analyses for a major cardiac and cerebrovascular event (MACCE)

Variable	Univariate		Multivariate	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age	1.04 (1.02–1.07)	<0.001	1.02 (0.99–1.04)	0.247
Male gender	0.68 (0.44–1.04)	0.074	0.85 (0.49–1.49)	0.577
Smoking	0.66 (0.44–0.99)	0.048	0.66 (0.39–1.13)	0.128
Dyslipidemia	0.66 (0.44–1.00)	0.050	0.57 (0.37–0.90)	0.015
Atrial fibrillation	3.87 (2.27–6.60)	<0.001	2.94 (1.45–5.95)	0.003
History of myocardial infarction	1.47 (0.95–2.29)	0.086	1.56 (0.96–2.53)	0.073
ACE-I or ARB use	1.71 (1.14–2.56)	0.009	1.85 (1.21–2.85)	0.005
Oral anticoagulants use	3.10 (1.60–5.98)	<0.001	1.11 (0.44–2.77)	0.825
Peripheral artery disease	2.41 (1.58–3.67)	<0.001	1.82 (1.16–2.86)	0.009
Albumin	0.67 (0.45–0.99)	0.048	1.29 (0.91–2.05)	0.281
Blood urea nitrogen	1.06 (1.04–1.07)	<0.001	1.04 (1.02–1.06)	<0.001
CKD/Anemia groups				
CKD/Anemia (−/−)	1 (Reference)		1 (Reference)	
CKD/Anemia (±)	1.98 (0.83–4.75)	0.124	0.98 (0.39–2.51)	0.973
CKD/Anemia (∓)	1.40 (0.84–2.33)	0.194	1.20 (0.69–2.09)	0.512
CKD/Anemia (+/+)	3.93 (2.39–6.46)	<0.001	2.01 (1.01–3.98)	0.046

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CKD* chronic kidney disease

future coronary heart disease (CHD). Although there was no apparent effect on the risk of future CHD in patients without anemia, renal insufficiency almost tripled the risk of CHD in patients with anemia. A significant interaction was observed between the prognostic impact of renal insufficiency and the presence of anemia, which suggested that renal insufficiency has a greater impact on the prognosis of patients with anemia than on those without anemia. The BMES study revealed similar findings in an Australian general population of 3654 subjects [9]. In this previous study, low hemoglobin was defined as the lowest quintile of hemoglobin in the whole population. Low hemoglobin was associated with worse outcome only for patients with CKD but not for those without CKD. These results support our findings, indicating a significant association with adverse prognosis only for patients with renal insufficiency complicated by anemia versus those with neither anemia nor renal insufficiency. Anderson et al. also reported that the combination of both anemia and CKD was an adverse risk factor for mortality in patients with CVD. While CKD alone showed two-fold negative trends for mortality, CKD complicated by even mild anemia was significantly related to a fourfold adverse risk of mortality [10].

There are several possible explanations for the negative prognostic impact of anemia in patients with CKD. Anemia is a common complication of CKD and has a number of etiologies, including reduced production of erythropoietin, as well as inhibition of erythropoiesis associated with nutritional deficiencies or inflammation [19]. It is possible that a mutual adverse reaction occurs between anemia and renal insufficiency, or that anemia reflects more severe stage of CKD. In the present study, neither anemia nor CKD alone was an independent risk factor for MACCE, whereas the coincidence of both anemia and CKD was significantly associated with poorer outcome. The concept of cardiorenal anemia syndrome involves the adverse consequences of the triangle of anemia, CKD, and heart failure. Heart failure is aggravated by the coexistence of anemia and CKD [20]. The etiologies are considered to involve interaction of the sympathetic nervous system, the renin–angiotensin–aldosterone system, imbalance of nitric oxide and reactive oxygen species, and/or inflammation. Our previous study indicated an increased risk of heart failure by the simultaneous presence of anemia and CKD in patients with acute myocardial infarction undergoing percutaneous coronary intervention [21]. In a randomized clinical trial, Wellenius et al. found that a preoperative eGFR <60 mL/min/1.73 m^2 in patients undergoing CABG was a significant risk factor for saphenous vein graft occlusion, when compared with the population of patients with an eGFR >75 mL/min/1.73 m^2 (OR 1.62, 95 % CI 1.06–2.46) [22]. This result suggested that CKD could adversely affect prognosis even for patients revascularized with CABG.

The present study also demonstrated that a history of dyslipidemia, peripheral artery disease, and atrial fibrillation was independently associated with adverse outcome. Moreover, ACE-I or ARB use before surgery and high BUN levels were associated with worse outcome, in accordance with the findings of previous studies. An observational study using a multicenter registered database of patients who underwent CABG in China revealed that preoperative atrial fibrillation was associated with mortality [23]. The GOPCABE trial also showed that preoperative atrial fibrillation was adversely associated with the combined endpoint, including death, myocardial infarction, dialysis, and revascularization, and even the 30-day mortality rate of CABG patients [24]. Similarly, the presence of peripheral artery disease was found to be an independent risk factor for early and late death in a study of 3003 patients undergoing isolated CABG [25]. The findings of these reports were consistent with ours. The association between high BUN levels and worse outcome in patients undergoing CABG was also suggested in the American College of Surgeons National Surgical Quality Improvement Program database [26]. Several studies, including meta-analyses, have shown that the perioperative use of ACE-I was associated with adverse events following CABG [27, 28].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines include some recommendations for anemia in patients with CKD [29], including iron supplementation, erythropoiesis stimulating agents (ESA), and red blood cell transfusion. However, perioperative blood transfusion has been associated with renal failure, infection, and cardiac complications [30]. Randomized controlled trials (RCTs) have been performed to assess the use of perioperative ESA among patients undergoing CABG surgery. Weltert et al. reported that the perioperative administration of human erythropoietin for 4 days significantly reduced blood transfusion and raised hemoglobin levels in patients undergoing off-pump CABG surgery [31]. Moreover, Tasanarong et al. reported that prophylactic recombinant human erythropoietin administration before on-pump CABG surgery significantly reduced the occurrence of acute kidney injury and the length of hospital stay [32]. Although these studies did not focus on patients with CKD, their results suggest that ESA administration is a promising strategy for CAD patients with anemia and CKD. Randomized clinical trials are required to evaluate the prognostic efficacy of preoperative ESA administration for this high-risk population.

This study had several limitations. First, it was a retrospective observational study and we could not exclude that the findings may have been influenced by unknown confounding factors. Second, as it was a single-center study, the study population was limited. The lack of independent significance of anemia and CKD may have been due

to insufficient statistical power; however, the main finding of this study, that there is a synergistic effect between anemia and CKD on prognosis, would not have been affected. Third, preoperative renal function was based on a single measurement. Fourth, the limited availability of data in the community setting did not define the etiology of anemia.

In conclusion, the findings of this study provide further evidence that the preoperative coexistence of CKD and anemia has an adverse effect on the prognosis of patients undergoing CABG. This supports the potential usefulness of appropriate treatment of anemia before CABG; however, randomized clinical studies are required to investigate this hypothesis.

Compliance with ethical standards

Conflict of interest YM received honoraria from SUNRISE Lab. as a manuscript fee. The other authors have no conflicts of interest.

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