

Effects of hemodialysis and reduced estimated glomerular filtration rate in nonhemodialysis on clinical outcomes after fractional flow reserve-guided deferral of revascularization

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Abstract

The effect of renal dysfunction on clinical outcomes following fractional flow reserve (FFR)-guided deferral of revascularization remains unelucidated.

We retrospectively analyzed 224 patients with atherosclerotic coronary lesions who underwent deferred revascularization based on an FFR of >0.80 . The median follow-up interval was 28.1 months. Patients were divided into 2 groups: the hemodialysis (HD) and the non-HD group. The non-HD group was further classified into 2 subgroups according to their estimated glomerular filtration rate (eGFR) level: eGFR <45 , equivalent to chronic kidney disease stage 3b-5 and eGFR ≥ 45 . We evaluated major adverse cardiac events (MACE), defined as a composite of cardiac death, myocardial infarction, and any revascularization.

MACE occurred in 36 patients (16.1%). The rate of HD was significantly higher in the MACE group (19% vs 6%, $P < .01$). In non-HD patients, the eGFR was significantly lower in the MACE group (51.2 vs 63.2 mL/min/1.73 m², $P < .01$). Overall, univariate Cox regression analysis revealed a significant relationship between HD and MACE (HR 2.91, $P = .01$), as did the multivariate model (HR 2.90, $P = .01$). Of the MACE, more deaths occurred in HD patients (15.8% vs 2.9%, $P = .03$). Among non-HD patients, eGFR <45 (HR 2.70, $P = .02$), FFR (per 0.01, HR 0.87, $P < .01$), and low-density lipoprotein cholesterol (per 10 mg/dL, HR 1.17, $P = .02$) were independent predictors of MACE. Any revascularization was more common in patients with eGFR <45 than in those with eGFR ≥ 45 (21.4% vs 7.3%, $P = .02$). Kaplan–Meier estimates revealed that the HD group showed a significantly lower MACE-free survival rate than the non-HD group (log-rank $P < .01$). In non-HD patients, the eGFR <45 group showed a lower MACE-free survival rate than the eGFR ≥ 45 group (log-rank $P = .01$).

HD and reduced eGFR in non-HD patients were associated with adverse cardiac events after FFR-guided deferral of revascularization.

Abbreviations: CAD = coronary artery disease, CAG = coronary angiography, CKD = chronic kidney disease, CRP = C-reactive protein, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, FFR = fractional flow reserve, HbA1c = hemoglobin A1c, HD = hemodialysis, HDL-C = high-density lipoprotein cholesterol, IDTVR = ischemia-driven target vessel revascularization, LDL-C = low-density lipoprotein cholesterol, MACE = major adverse cardiac events, MBD = mineral and bone disorders, MI = myocardial infarction, MVD = multivessel disease, PCI = percutaneous coronary intervention, TC = total cholesterol, TGs = triglycerides.

Keywords: chronic kidney disease, fractional flow reserve, hemodialysis, outcome, renal dysfunction

1. Introduction

Fractional flow reserve (FFR) is an established tool for evaluating the functional severity of coronary artery disease (CAD).^[1]

Previous studies have shown that deferred revascularization of coronary lesions based on an FFR >0.80 is associated with favorable clinical outcomes under optimal medical therapy.^[2] However, some patients experience cardiac events after FFR-

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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guided deferral of revascularization at various rates according to the patient's comorbidities and clinical settings.^[3–6] Therefore, it is important to classify patients according to their risk to optimize treatment after deferred revascularization.

Recently, a strong relationship between renal dysfunction, particularly chronic kidney disease (CKD), and CAD has been highlighted.^[7] In addition to the high prevalence of traditional coronary risk factors, such as diabetes and hypertension, patients with renal failure are also exposed to multiple cardiotoxic factors, including inflammation, oxidative stress, and mineral and bone disorders (MBD), resulting in CAD progression and worse clinical outcomes,^[8] particularly in the advanced stages, including hemodialysis (HD). However, thus far, it remains unclear whether patients with renal dysfunction, especially HD, have a higher risk after deferred revascularization. This study aimed to investigate the prognostic effect of HD and the estimated glomerular filtration rate (eGFR) in non-HD patients on clinical outcomes after deferred revascularization of coronary lesions based on FFR of >0.80 .

2. Materials and methods

2.1. Study population

This was a retrospective observational single-centered study conducted in Japan from April 2011 to January 2020, which included 4640 patients with suspected CAD who underwent coronary angiography (CAG) at our institute. Of these, 530 patients presented with 1 or more atherosclerotic lesions and underwent FFR measurements. Among them, 232 had deferred revascularization based on an FFR of >0.80 . After excluding patients who had acute coronary syndrome or lacked follow-up data, we analyzed 224 patients (Fig. 1). The median follow-up interval was 28.1 months (interquartile range 15.9–48.2 months). The research protocol was approved by the Nagoya City University Graduate School of Medical Sciences and the

Nagoya City University Hospital Institutional Review Board (reference number: 60-21-0042). The need for written informed consent was waived because of the retrospective study design. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki.

2.2. Blood sampling and assessment of renal function

Venous blood samples were collected after the patients had fasted overnight. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), C-reactive protein (CRP), creatinine, and hemoglobin A1c (HbA1c) levels were measured using standard laboratory procedures. Low-density lipoprotein cholesterol (LDL-C) levels were measured using a direct homogenous assay (Kyowa Medex Co., Tokyo, Japan). eGFR was calculated using the following formula recommended by the Japanese Society of Nephrology: $eGFR (mL/min/1.73 m^2) = 194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} (\times 0.739, \text{ if female}).$ ^[9] The study population was divided into 2 groups: the HD group and the non-HD group; The non-HD group was further classified into 2 subgroups according to their eGFR level: $eGFR <45$ (equivalent to CKD stage 3b-5) and $eGFR \geq 45$.

2.3. Analysis of CAG and FFR

CAG was performed using the standard Judkins technique with intracoronary administration of nitroglycerin (0.2 mg) after intravenous administration of 3000 U heparin. We excluded lesions of grafted vessels and those within 20 mm of anastomotic stenosis in patients after coronary artery bypass graft surgery. A stenosis $>50\%$ was considered angiographically significant, and multivessel disease (MVD) was defined as ≥ 2 vessels with angiographically significant stenosis.

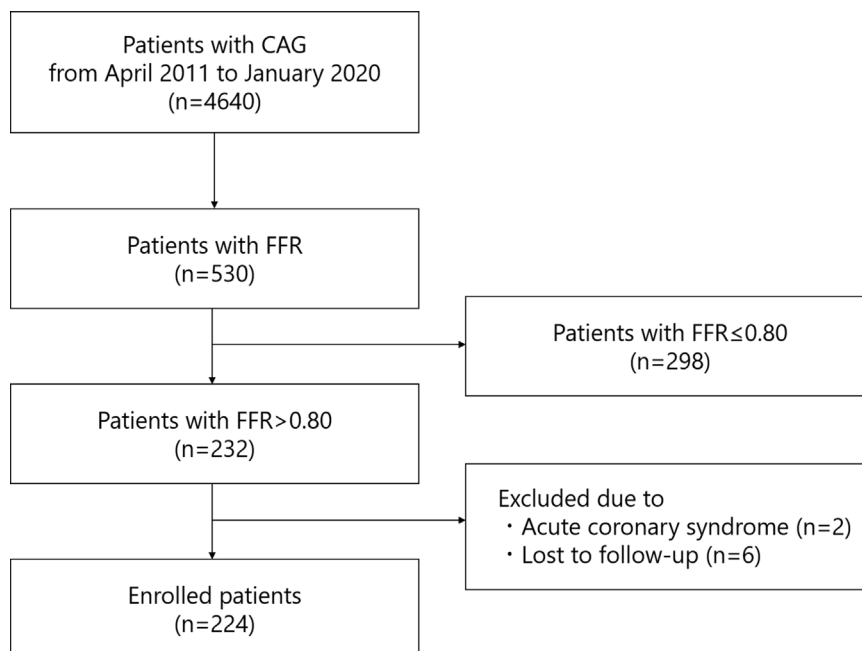


Figure 1. Flow chart of patient enrollment. CAG = coronary angiography, FFR = fractional flow reserve.

Intracoronary pressure was measured using a 0.014-inch pressure guidewire (PressureWire Certus, St. Jude Medical, St. Paul, MN, USA; Verrata, Philips Volcano, San Diego, CA, USA; or Optowire, Opsens, Quebec, Canada) and 5–7 Fr guiding catheter without a side hole. After calibration and equalization, a pressure guidewire was introduced into the coronary artery, and the pressure sensor was positioned at the far distal side of the target vessel. Continuous intravenous infusion of adenosine 5-triphosphate (180 $\mu\text{g}/\text{kg}/\text{min}$) was used to induce maximal hyperemia. The pressure guidewire was slowly pulled back manually from the far distal to the ostium of the coronary artery. When the pressure sensor was pulled back into the guiding catheter, both pressures were checked to rule out transducer drift. FFR was calculated as the mean distal coronary pressure divided by the mean aortic pressure during maximal hyperemia.

2.4. Clinical follow-up and definition of major adverse cardiac events

The attending physicians decided on the choice and duration of antiplatelet therapy according to the patients' clinical background and history of treatment. Lipid-lowering therapy, mainly with statins, was used to prevent CAD progression according to the Japan Atherosclerosis Society Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in 2012 and 2017.^[10,11] Antihypertensive and antidiabetic drugs were prescribed at the discretion of the attending physicians according to patient age and other comorbidities. Smoking cessation, a healthy diet, maintaining a healthy weight, and physical activity according to the patient's exercise capacity were recommended for each patient.

Patients were followed up for clinical outcomes by reviewing their medical records or telephone interviews. Major adverse cardiac events (MACE) were defined as a composite of cardiac death, myocardial infarction (MI), and any revascularization. All deaths without unequivocal non-cardiac causes were considered cardiac deaths. MI was diagnosed according to the criteria of the Fourth Universal Definition of Myocardial Infarction.^[12] Any revascularization was defined as all percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery in the presence of objective ischemic signs or symptoms, except planned revascularization within 3 months of FFR measurement. Target vessel failure (TVF) was defined as a composite of target vessel-related MI and ischemia-driven target vessel revascularization (IDTVR).

2.5. Statistical analysis

Continuous variables were compared using Student *t* test or the Mann–Whitney *U* test as appropriate. The Chi-Squared test and Fisher exact test were used to compare categorical variables. Cox regression analysis was performed to identify potential predictors of MACE. Covariates in the univariate analysis for overall patients were age, male sex, hypertension, dyslipidemia, diabetes mellitus (DM), MVD, HD, TC, LDL-C, HDL-C, TGs, HbA1c, CRP, and FFR. The variables included in the multivariate analysis for all patients were HD, FFR, and LDL-C. Covariates in the univariate analysis for non-HD patients were age, male sex, hypertension, dyslipidemia, DM, MVD, eGFR <45, TC, LDL-C, HDL-C, TGs, HbA1c, CRP, and FFR. The variables included in the multivariate analysis for non-HD patients were eGFR <45, FFR, and LDL-C. MACE-free survival curves were generated using Kaplan–Meier

estimates. The log-rank test was performed to evaluate the differences between the MACE-free survival curves of each group. Statistical significance was set at $P < .05$. All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY).

3. Results

The patients' clinical, biochemical, and angiographic data are summarized in Table 1. MACE was detected in 36 (16.1%) patients during follow-up; 9 patients experienced cardiac death, 5 patients had MI, and 22 patients had revascularization, of which 16 patients had IDTVR. TVF was observed in 18 patients (8.0%). The percentage of HD was significantly higher in the MACE group than in the non-MACE group. There were no significant differences between the 2 groups in terms of other clinical parameters and medications. In the laboratory data, the eGFR of non-HD patients was significantly lower in the MACE group. Although not statistically significant, TC, LDL-C, TGs, and CRP levels were numerically higher, and HDL-C levels were lower in the MACE group than in the non-MACE group. Lesion characteristics were similar between the 2 groups, but the MACE group had a significantly lower FFR than the non-MACE group.

Univariate Cox regression analysis of the overall population revealed that HD and FFR were significantly associated with MACE. In the multivariate model, HD was an independent predictor of MACE (Table 2A). As for the non-HD patients, the variables associated with a significantly higher risk of MACE were FFR, eGFR <45, LDL-C, and TGs. In the multivariate analysis, FFR, eGFR <45, and LDL-C were identified as independent predictors of MACE (Table 3Table B). The clinical outcomes of patients according to their renal function are summarized in Table 4. The HD group had a significantly higher rate of MACE and cardiac death than the non-HD group. Although not significant, the rates of MI, any revascularization, IDTVR, and TVF were also higher in the HD group (Table 3A). Among the non-HD patients, patients with eGFR <45 had a significantly higher risk of MACE and any revascularization than those with eGFR ≥ 45 (Table 5Table 3B). During follow-up, the MACE-free survival rate was significantly lower in the HD group than in the non-HD group (Fig. 2A). In the non-HD population, patients with eGFR <45 had a lower MACE-free survival rate than those with eGFR ≥ 45 (Fig. 2B).

4. Discussion

The present study investigated the prognostic impact of HD and eGFR in non-HD patients after FFR-guided deferred revascularization and revealed that HD was an independent predictor of MACE after FFR-guided deferral. Furthermore, in non-HD patients, eGFR <45 (equivalent to CKD stage 3b–5) was significantly associated with MACE, as well as FFR value, which is an indicator of myocardial ischemia, and serum LDL-C level, the most popular coronary atherosclerotic risk factor.

4.1. Adverse cardiac events after FFR-guided deferral in daily clinical practice

Coronary pressure-derived FFR is a standard index of the functional severity of epicardial coronary artery stenosis.^[1] Previous studies have reported a significant relationship between FFR and the incidence of adverse cardiac events,^[13] and the

Table 1
Baseline patient characteristics.

Variables	All (n = 224)	MACE (n = 36)	NonMACE (n = 188)	P value
Age (years)	71.8 ± 9.2	73.1 ± 9.5	71.6 ± 9.2	.36
Male	169 (75%)	26 (72%)	143 (76%)	.67
BMI (kg/m ²)	23.8 ± 3.5	23.6 ± 3.2	23.9 ± 3.5	.63
Hypertension	177 (79%)	30 (83%)	147 (78%)	.66
Dyslipidemia	143 (64%)	25 (69%)	118 (63%)	.57
Diabetes mellitus	91 (41%)	17 (47%)	74 (39%)	.46
Smoking	49 (22%)	12 (33%)	37 (20%)	.08
LVEF (%)	61.6 ± 13.7	60.5 ± 14.2	61.8 ± 13.6	.61
Previous PCI	85 (38%)	14 (39%)	71 (38%)	.99
Previous CABG	6 (3%)	1 (3%)	5 (3%)	.99
Renal function				
Nonhemodialysis				
eGFR ≤60	115 (51%)	13 (36%)	102 (54%)	
eGFR 45–60	62 (28%)	8 (22%)	54 (29%)	
eGFR 0–45	28 (13%)	8 (22%)	20 (11%)	
Hemodialysis	19 (9%)	7 (19%)	12 (6%)	<.01
Medications				
Aspirin	144 (64%)	25 (69%)	119 (63%)	.57
DAPT	65 (29%)	10 (28%)	55 (29%)	.99
ACEI/ARB	124 (55%)	15 (42%)	109 (58%)	.14
Beta-blocker	81 (36%)	12 (33%)	69 (37%)	.43
Calcium-channel blocker	109 (49%)	17 (47%)	92 (49%)	.86
Statin	144 (64%)	22 (61%)	122 (65%)	.71
Ezetimibe	12 (5%)	3 (8%)	9 (5%)	.42
Laboratory data				
Creatinine (mg/dL)*	0.88 (0.72–1.08)	0.96 (0.80–1.16)	0.87 (0.72–1.03)	.09
eGFR*	62.5 (50.6–74.4)	51.2 (41.5–69.0)	63.2 (51.5–74.5)	.03
TC (mg/dL)	173.9 ± 35.9	179.5 ± 36.4	172.8 ± 35.8	.32
LDL-C (mg/dL)	98.9 ± 29.5	105.4 ± 29.9	97.6 ± 29.4	.16
HDL-C (mg/dL)	55.1 ± 15.9	51.3 ± 13.6	55.8 ± 16.2	.09
TGs (mg/dL)	132.2 ± 63.2	147.7 ± 71.5	129.2 ± 61.2	.15
CRP (mg/dL)	0.09 (0.05–0.23)	0.16 (0.07–0.25)	0.09 (0.05–0.20)	.08
HbA1c (%)	6.4 ± 1.0	6.4 ± 1.2	6.3 ± 1.0	.73
Lesion characteristics				
Vessel				
LAD	103 (46%)	19 (53%)	84 (45%)	
LCX	53 (24%)	8 (22%)	45 (24%)	
RCA	68 (30%)	9 (25%)	59 (31%)	.53
Multivessel disease	119 (53%)	21 (58%)	98 (52%)	.59
Bifurcation	75 (33%)	13 (36%)	62 (33%)	.70
Calcification	47 (21%)	10 (28%)	37 (20%)	.27
ACC/AHA classification				
Type A	52 (23%)	9 (25%)	43 (23%)	
Type B1	92 (41%)	14 (39%)	78 (41%)	
Type B2	59 (26%)	11 (31%)	48 (26%)	
Type C	21 (9%)	2 (6%)	19 (10%)	.95
FFR	0.86 ± 0.05	0.85 ± 0.04	0.87 ± 0.05	.03

Data are expressed as n (%), mean ± standard deviation, or median (interquartile range). Asterisk (*) means that the data were acquired only from patients without hemodialysis.

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, CABG = coronary artery bypass grafting, CRP = C-reactive protein, DAPT = dual antiplatelet therapy, eGFR = estimated glomerular filtration rate, FFR = fractional flow reserve, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, MACE = major adverse cardiac events, PCI = percutaneous coronary intervention, RCA = right coronary artery, TC = total cholesterol, TGs = triglycerides.

safety of deferred revascularization based on FFR >0.80 with a reduction in unnecessary revascularization and procedure-related clinical events.^[2] The FFR-based treatment strategy is simple, robust, and cost-effective;^[14] therefore, it is widely applied in daily clinical practice. However, cardiac events still occur even after deferred revascularization during long-term follow-up,^[3–6] indicating the presence of residual risk after deferral of revascularization. Classifying patients according to

their risk and optimizing treatment are important to prevent cardiovascular events after FFR-guided deferred revascularization. Although DM^[5] and elevated malondialdehyde-modified low-density lipoprotein^[6] have been previously reported as predictors of cardiac events, clinical data regarding residual risk after FFR-guided deferred revascularization are lacking. This study focused on renal dysfunction, a risk factor for atherosclerosis and cardiovascular events, and investigated the effects of

Table 2**Predictors of major adverse cardiac events (overall).**

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Hemodialysis	2.91	1.27–6.67	.01	2.90	1.26–6.69	.01
FFR, per 0.01	0.92	0.85–0.99	.04	0.93	0.86–1.00	.06
LDL-C, per 10 mg/dL	1.09	0.98–1.21	.12	1.11	0.99–1.24	.08
HDL-C, per 10 mg/dL	0.82	0.64–1.06	.13	–	–	–
TGs, per 10 mg/dL	1.03	0.99–1.08	.16	–	–	–
Age	1.02	0.99–1.06	.24	–	–	–
TC, per 10 mg/dL	1.05	0.96–1.15	.26	–	–	–
Diabetes mellites	1.36	0.71–2.61	.36	–	–	–
Hypertension	1.43	0.59–3.43	.43	–	–	–
CRP	1.33	0.55–3.27	.53	–	–	–
HbA1c	1.10	0.79–1.52	.58	–	–	–
Male	1.21	0.59–2.52	.60	–	–	–
MVD	1.18	0.61–2.29	.63	–	–	–
Dyslipidemia	1.12	0.55–2.27	.76	–	–	–

CI = confidence interval, CRP = C-reactive protein, FFR = fractional flow reserve, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HR = hazards ratio, LDL-C = low-density lipoprotein cholesterol, MVD = multivessel disease, TC = total cholesterol, TGs = triglycerides.

Table 3**Predictors of major adverse cardiac events (non-hemodialysis).**

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
FFR, per 0.01	0.86	0.78–0.95	<.01	0.87	0.78–0.96	<.01
eGFR <45	2.72	1.20–6.15	.02	2.70	1.17–6.27	.02
LDL-C, per 10 mg/dL	1.12	0.99–1.26	.06	1.17	1.03–1.32	.02
TGs, per 10 mg/dL	1.05	1.00–1.09	.04	–	–	–
HbA1c	1.27	0.92–1.76	.15	–	–	–
Diabetes mellites	1.59	0.77–3.30	.21	–	–	–
Dyslipidemia	1.78	0.72–4.37	.21	–	–	–
TC, per 10 mg/dL	1.06	0.96–1.16	.28	–	–	–
HDL-C, per 10 mg/dL	0.87	0.67–1.13	.29	–	–	–
Age	1.02	0.98–1.07	.29	–	–	–
Hypertension	1.77	0.62–5.09	.29	–	–	–
Male	1.34	0.61–2.95	.46	–	–	–
MVD	1.16	0.56–2.44	.69	–	–	–
CRP	1.13	0.34–3.71	.84	–	–	–

CI = confidence interval, CRP = C-reactive protein, FFR = fractional flow reserve, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HR = hazards ratio, LDL-C = low-density lipoprotein cholesterol, MVD = multivessel disease, TC = total cholesterol, TGs = triglycerides.

Table 4**Summary of clinical outcomes (overall).**

	All	HD	NonHD	P value
Number of patients	224	19	205	
MACE	36 (16.1%)	7 (36.8%)	29 (14.1%)	.02
Cardiac death	9 (4.0%)	3 (15.8%)	6 (2.9%)	.03
MI	5 (2.2%)	1 (5.3%)	4 (2.0%)	.36
Any Revascularization	22 (9.8%)	3 (15.8%)	19 (9.3%)	.41
IDTVR	16 (7.1%)	2 (10.5%)	14 (6.8%)	.63
TVF	18 (8.0%)	3 (15.8%)	15 (7.3%)	.19

HD = hemodialysis, IDTVR = ischemia-driven target vessel revascularization, MACE = major adverse cardiac events, MI = myocardial infarction, TVF = target vessel failure.

Table 5
Summary of clinical outcomes (non-hemodialysis).

	eGFR <45	eGFR ≥45	P value
Number of patients	28	177	
MACE	8 (28.6%)	21 (11.9%)	.02
Cardiac death	2 (7.1%)	4 (2.3%)	.15
MI	0 (0.0%)	4 (2.3%)	.42
Any Revascularization	6 (21.4%)	13 (7.3%)	.02
IDTVR	3 (10.7%)	11 (6.2%)	.38
TVF	3 (10.7%)	12 (6.8%)	.46

eGFR = estimated glomerular filtration rate, IDTVR = ischemia-driven target vessel revascularization, MACE = major adverse cardiac events, MI = myocardial infarction, TVF = target vessel failure.

HD and eGFR in non-HD on adverse cardiac events after FFR-guided deferral of revascularization.

4.2. Advanced renal failure as a predictor of adverse cardiac events after revascularization deferral

High cardiovascular risk in patients with renal dysfunction, particularly CKD, has attracted attention worldwide.^[15] CKD is an independent risk factor for CAD development and adverse cardiac events^[16] and is associated with worse clinical outcomes after PCI, even under optimal medical therapy.^[17] Moreover, the prevalence and severity of CAD increase as renal function deteriorates.^[18]

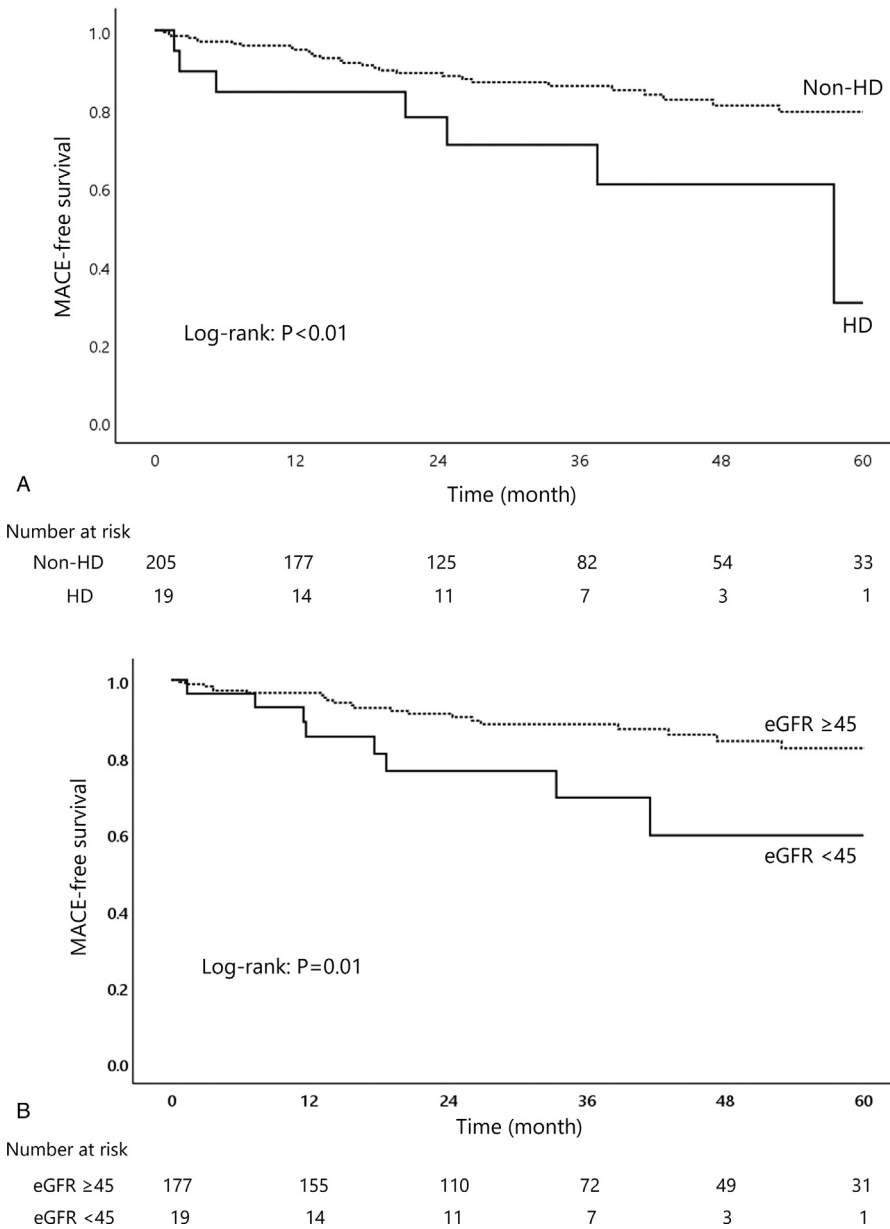


Figure 2. (A) Major adverse cardiac event (MACE)-free survival curves after fractional flow reserve-guided deferral of revascularization according to the presence or absence of hemodialysis (HD). (B) Major adverse cardiac event (MACE)-free survival curves after fractional flow reserve-guided deferral of revascularization according to the estimated glomerular filtration rate (eGFR) level in patients without hemodialysis

Patients with renal failure are exposed to multiple factors that play crucial roles in the pathophysiology of CAD formation and progression.^[19] In patients with renal dysfunction, not only traditional coronary risk factors, such as hypertension and DM, but also non-traditional factors, such as inflammation, oxidative stress, endothelial dysfunction, MBD, and accelerated coagulation, contribute to the progression and destabilization of coronary atherosclerotic lesions.^[8,19] Notably, patients with HD exhibit extremely high mortality due to their HD-specific systemic factors, including fluid overload, blood pressure instability, and electrolyte imbalance.^[20] In our study, HD patients presented a five-times higher incidence of cardiac death, and non-HD patients with eGFR <45 presented a significantly higher revascularization rate. Although the difference was not statistically significant due to the small sample size, HD patients experienced a higher incidence of revascularization, and the incidence of cardiac death was higher in non-HD patients with eGFR <45. Our results indicate that advanced renal failure, especially HD, strongly predicts worse clinical outcomes after FFR-guided deferred revascularization.

4.3. Application of FFR-guided deferral in patients with renal dysfunction

Regarding the clinical management of CAD in patients with renal failure, the initial conservative strategy consisting of medical therapy and reserved angiography has been reported to be useful;^[21] however, we often make decisions based on invasive FFR in daily clinical practice.^[22] The utility of the FFR-guided strategy in patients with advanced renal failure remains unelucidated because patients with renal dysfunction are underrepresented in large-scale clinical studies of FFR.^[22,23] In patients with renal dysfunction, the morphology of coronary lesions tends to be more complex (calcified, diffuse, and multi-vessel),^[24] and rapid lesion progression with a large necrotic core and calcified nodules may occur.^[25,26] Furthermore, unstable rupture-prone plaques and calcified nodules might cause an acute coronary syndrome.^[19,27] Considering these unique high-risk lesion characteristics, it is uncertain whether the conventional FFR-guided strategy is applicable in such cases.

In addition, endothelial dysfunction and coronary microvascular dysfunction, which are common in patients with renal failure, may also contribute to the high incidence of cardiovascular events.^[7] FFR, an ischemic index of epicardial coronary stenosis, is insufficient to assess the overall cardiac risk in patients with renal dysfunction. In our study, patients with FFR >0.80 were treated conservatively, assuming that deferral would be safe according to the widely used FFR criteria. In this common strategy, MACE occurred with a high frequency of 36.8% in HD patients and 28.6% in non-HD patients with eGFR <45 during the follow-up period. Our results indicated that the safety of deferred revascularization based on FFR >0.80 could not be directly applied to patients with advanced renal failure.

4.4. Clinical implication

The major clinical implication of this study is that the post-deferral clinical course of patients with advanced renal failure is different from that of those without advanced renal failure, and patients with advanced renal dysfunction need special attention after deferred revascularization. Therefore, careful clinical follow-up is essential even after deferred revascularization. Moreover, it may

be insufficient to provide uniform guideline-directed anti-atherosclerotic therapy, and comprehensive intervention for entire patient risk, including non-traditional factors, may improve clinical outcomes after deferred revascularization. Larger prospective studies are needed to investigate the utilization of FFR in patients with CAD and advanced renal failure.

4.5. Limitations

This study has several limitations. First, it was a retrospective observational single centered study with a relatively small number of recruited CAD patients in Japan. In addition, the indication of FFR was decided by the operators without strict criteria. Therefore, the study population was biased. Second, the intensity of lipid-lowering therapy may be different during follow-up because medical therapy was at the discretion of the attending physicians, and the target LDL-C level had been changed in the 2017 guidelines. Third, we did not incorporate an analysis of intravascular imaging or computed tomography; thus, data on plaque burden and morphology were lacking. Fourth, subclinical acute kidney injury, which might have occurred after diagnostic CAG and FFR procedure can influence the study result. Fifth, since the patients with deferral of revascularization despite their FFR ≤0.80 were excluded from this study, the impact of FFR value itself on clinical outcomes after deferral of revascularization has not been fully estimated. Finally, data on renal dysfunction-specific risk factors, such as oxidative stress and MBD, could not be confirmed in our database.

5. Conclusions

HD and reduced eGFR in non-HD patients were associated with adverse cardiac events after FFR-guided deferral of revascularization.

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