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Prognostic impact of proteinuria in diabetic patients without chronic kidney disease undergoing percutaneous coronary intervention

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Abstract

Background Diabetes mellitus (DM) and chronic kidney disease (CKD) are well-established risk factors for adverse outcomes following percutaneous coronary intervention (PCI). However, the combined impact of DM and CKD on prognosis is underexplored, and the role of proteinuria, particularly in non-CKD patients, remains inadequately addressed. This study therefore evaluates the prognostic significance of DM and CKD in post-PCI patients, with a focus on the independent impact of proteinuria.

Methods We retrospectively analyzed 4,887 patients who underwent PCI between 2000 and 2018, categorizing them into four groups based on DM and CKD status. Cardiovascular mortality was assessed using Kaplan-Meier survival analysis and multivariate Cox proportional hazard analysis. The prognostic impact of proteinuria (≥ 0.3 g/gCr) was evaluated within each subgroup.

Results Patients with both DM and CKD exhibited the highest cardiovascular mortality risk (hazard ratio [HR] 3.04, 95% confidence interval [CI] 1.82–5.05; $p < 0.001$). Proteinuria was an independent predictor of cardiovascular mortality, with the strongest association observed in diabetic patients without CKD (HR 6.7, 95% CI 2.7–16.8; $p < 0.001$).

Conclusions The coexistence of DM and CKD synergistically elevates cardiovascular mortality risk after PCI. Proteinuria, especially in diabetic patients without CKD, is a potent prognostic marker. Targeting proteinuria may offer a novel therapeutic approach to improve outcomes in this high-risk population.

Keywords Coronary artery disease, Percutaneous coronary intervention (PCI), Diabetes, Chronic kidney disease, Proteinuria, Prognosis

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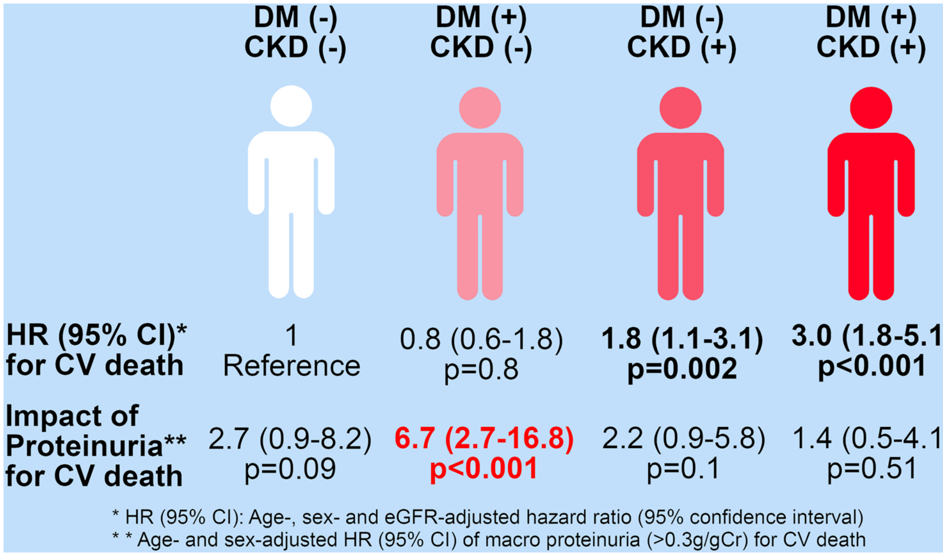
Graphical abstract



Introduction

Coronary artery disease (CAD) remains a leading cause of global mortality and morbidity despite advancements in management strategies. The widespread use of statins and improved technologies in percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have significantly reduced cardiovascular risk and improved outcomes. However, CAD continues to impose a substantial socioeconomic burden, necessitating continuous efforts for prevention and optimized treatment strategies [1].

Diabetes mellitus (DM) and chronic kidney disease (CKD) are both independently associated with poor outcomes in CAD patients [2, 3]. While the individual prognostic impacts of DM and CKD are well-documented, evidence evaluating their combined effect is limited. Notably, patients with both conditions exhibit significantly worse long-term survival rates compared to those with either condition alone, emphasizing the need for risk stratification and tailored treatment strategies [4].

Proteinuria is a well-recognized marker of diabetic nephropathy and advanced atherosclerosis, serving as a strong predictor of adverse outcomes in CAD patients, including those undergoing PCI [5–7]. Among proteinuria assessments, albuminuria, quantified using the urine albumin-to-creatinine ratio (UACR) has emerged as both a prognostic marker and an efficacy endpoint for emerging pharmacotherapies. Evidence indicates that reductions in UACR are strongly associated with improved renal and cardiovascular outcomes (DOI: https://doi.org/10.2337/dc20-1622) (DOI: https://doi.org/10.1681/ASN.2020050723). Several therapies, including sodium-glucose cotransporter-2 (SGLT2) inhibitors, non-steroidal mineralocorticoid receptor antagonists (ns MRAs), and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have demonstrated the ability to reduce albuminuria while slowing CKD progression and improving cardiovascular outcomes [8–11]. These agents complement conventional renin-angiotensin system inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [12, 13], providing a multifaceted approach to managing both renal and cardiovascular risk.

In this study, we examined the prognostic impact of DM and CKD on cardiovascular mortality in patients undergoing PCI, with a particular focus on the influence of CKD on diabetic patients. Additionally, we explored the role of proteinuria as a prognostic marker and its potential as a therapeutic target, considering the growing evidence supporting albuminuria as a key measure of therapeutic efficacy in this high-risk population.

Patients and methods

Data source and oversight

We analyzed consecutive PCI cases from the J-PACT (Juntendo Physicians' Alliance for Clinical Trial) prospective PCI registry at Juntendo University Hospital (initiated in 1984; 13,279 patients through August 2024; publicly registered as UMIN-CTR 000035587). Ethical approval and consent procedures (Juntendo University IRB No. E22-0409; opt-out) are detailed in the **Declarations** section. All data were de-identified prior to analysis.

Study population

The present study enrolled consecutive 4,880 patients who underwent their first PCI (index PCI) between 2000 and 2018. Participants were then divided into 4 groups based on the presence or absence of DM and CKD at index PCI. The demographic data and information on coronary risk factors, medications, revascularization-related factors, and co-morbidities were prospectively collected and retrospectively analyzed. A current smoker was defined as a participant who currently smoked for more than 1 year before index PCI. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, and/or treatment with antihypertensive medications. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dl, high-density lipoprotein cholesterol ≤ 40 mg/dl, triglycerides ≥ 150 mg/dl, or treatment with lipid-lowering medications. Diabetes mellitus was defined as hemoglobin A1c ≥ 6.5% and/or any anti-diabetic agents [14]. Chronic kidney disease was defined as eGFR < 60 ml/min/1.73 m2, calculated using the equation of the modification of diet in renal disease, modified with a Japanese coefficient using baseline serum creatinine [15].

Dipstick semiquantitative evaluation of proteinuria

The semiquantitative ratio of urine protein and creatinine concentrations were determined by using dipstick and an automated chemistry analyzer (Roche-Hitachi 911, Roche, Minnesota, USA), in which the former was measured by a turbidimetric method (U/CSF Protein, Roche, Minnesota, USA) and the latter was measure by Jaffe's method (Crea, Roche, Minnesota, USA). The semiquantitative urine protein/ creatinine (P/C) ratio (grams per gram of creatinine: g/gCr) was then calculated as < 0.15, 0.15–0.3, 0.3–0.5 and >0.5 g/gCr [16]. These categories were predefined by analyzer. All laboratory methods were performed in accordance with standard operating procedures.

Outcome measure

The endpoint in this study was cardiovascular mortality/death (CV death). Information regarding the occurrence of CV death was collected by reviewing electronic medical records, telephone contacts, and questionnaire sent by mail in every 3 years for all participants.

Statistical analysis

Quantitative variables are presented as means and standard deviation (SD). Non-normally distributed variables are presented as medians with interquartile ranges (IQRs). One-way analysis of variance or the Kruskal-Wallis tests compared continuous numeric values among groups, while Chi-squared test compared categorical variables. The unadjusted cumulative rates of CV death were assessed across groups using Kaplan–Meier curves followed by the log-rank comparisons. The prognostic risk of diabetes and CKD for CV death was determined by multivariate Cox proportional hazard regression analysis, which included clinically relevant predictors, such as age, sex, ACS, current smoking, hypertension, dyslipidemia, ACEI/ARB, statin use, multivessel disease, BMI, and hemoglobin, in line with established prognostic models avoiding overfitting and ensure interpretability to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). To assess the prognostic impact of proteinuria (> 0.3 g/gCr) in diabetic and non-diabetic patients, Cox model was adjusted by age, sex and eGFR. Moreover, to compare the risk of proteinuria among groups, hazard ratios of proteinuria (> 0.3 g/gCr) was assessed by the age- and sex- adjusted Cox model. A p-value of < 0.05 was considered statistically significant. All analyses were performed using JMP Pro16.0.0 software (SAS Institute Inc, Cary, NC, USA) and IBM SPSS Statistics for Macintosh, Version 29.0.1.0 (Armonk, NY: IBM Corp).

Results

Background demographics, comorbidities, medications and PCI-related factors in 4 patient groups with and without DM and CKD

The median follow-up duration since PCI procedure of entire participants was 5.2 years. A total of 4,887 patients were divided into 4 following groups based on the presence or absence of DM and CKD, such as DM−/CKD − group (n = 2,029, 41.5%), DM+/CKD − group (n = 1,415, 29.0%), DM−/CKD + group (n = 755, 15.4%), and DM+/CKD + group (n = 688, 14.1%) (Figure S1). The baseline characteristics of these groups are listed and compared in Table 1. Patients with CKD (DM-/CKD + or DM+/CKD+) were older, predominantly male, and had a higher prevalence of hypertension compared to those without CKD, groups DM-/CKD- or DM+/CKD-. They also exhibited lower cardiac contractility, a lower frequency of acute coronary syndrome (ACS), a higher prevalence of multivessel disease, and elevated hsCRP levels. In contrast, patients with diabetes, groups DM+/CKD- or DM+/CKD+, had a higher proportion of current smokers, a lower incidence of ACS, and a greater prevalence of multivessel disease compared to non-diabetic patients, groups DM-/CKD- or DM-/CKD+. Furthermore, in diabetic patients, the use of ACE inhibitors/ARBs was more frequent compared to non-diabetics, while statin use was similar, though LDL-C levels were lower in diabetic patients. Moreover, stents implanted in diabetic patients were longer and had a smaller diameter. Among patients with CKD, the presence of diabetes was associated with increased CKD severity compared to those without diabetes. The proportion of patients with a urinary protein level of ≥ 0.3 g/gCr increased

Table 1 Baseline clinical characteristics of the study participants

	Overall *n* = 4,887	DM-/ CKD- *n* = 2,029	DM+/ CKD- *n* = 1,415	DM-/ CKD + *n* = 755	DM+/ CKD + *n* = 688	*p*
Age, year	66.4 ± 10.7	64.2 ± 11.0	65.3 ± 9.8	71.3 ± 10.0	70.0 ± 9.7	< 0.0001
Male, *n* (%)	3994 (81.8)	1678 (82.7)	1203 (85.3)	590 (78.3)	523 (76.1)	< 0.0001
BMI, kg/m^2	24.2 ± 3.5	24.2 ± 3.3	24.6 ± 3.6	23.4 ± 3.4	24.2 ± 3.7	< 0.0001
Current smoking, *n* (%)	1197 (24.6)	560 (27.7)	393 (27.9)	123 (16.4)	121 (17.7)	< 0.0001
Hypertension, *n* (%)	3466 (71.0)	1302 (64.2)	1014 (71.9)	588 (78.0)	562 (81.8)	< 0.0001
Dyslipidemia, *n* (%)	3501 (71.7)	1411 (71.1)	1065 (75.5)	496 (65.8)	499 (72.6)	< 0.0001
Hemodialysis, *n* (%)	270 (5.5)	0 (0)	0 (0)	101 (13.4)	169 (24.6)	< 0.0001
Hemoglobin, g/dL	13.3 ± 1.9	13.8 ± 1.7	13.6 ± 1.7	12.4 ± 1.9	12.2 ± 2.0	< 0.0001
LDL-C[*1], mg/dL	108.6 ± 33.8	112.0 ± 34.9	105.6 ± 33.0	111.0 ± 33.3	102.2 ± 31.2	< 0.0001
HDL-C[*2], mg/dL	44.8 ± 13.2	46.5 ± 13.2	44.0 ± 13.4	45.0 ± 12.8	41.6 ± 12.5	< 0.0001
Fasting blood glucose, mg/dL	118.0 ± 48.1	102.9 ± 23.0	140.6 ± 57.6	101.9 ± 28.6	133.9 ± 70.4	< 0.0001
HbA1c, %	6.3 ± 1.2	5.7 ± 0.4	7.3 ± 1.3	5.7 ± 0.5	7.0 ± 1.1	< 0.0001
hs-CRP[*3], mg/dl	0.12 [0.05, 0.36]	0.1 [0.04, 0.3]	0.11 [0.04, 0.34]	0.16 [0.07, 0.54]	0.16 [0.07, 0.5]	< 0.0001
Left ventricular ejection fraction (LVEF), %	61.0 ± 12.5	62.0 ± 11.3	61.4 ± 11.8	59.8 ± 13.7	58.2 ± 15.3	< 0.0001
eGFR[*4]	66.9 ± 24.7	77.8 ± 16.4	79.3 ± 17.8	41.9 ± 16.3	36.8 ± 18.9	< 0.0001
CKD[*5] stages						
1	811 (16.6)	450 (22.2)	361 (25.5)	0 (0)	0 (0)	
2	2631 (53.8)	1579 (77.8)	1052 (74.5)	0 (0)	0 (0)	
3	1135 (23.2)	0 (0)	0 (0)	634 (84.0)	501 (72.8)	< 0.0001
4	55 (1.1)	0 (0)	0 (0)	22 (2.9)	33 (4.8)	
5	253 (5.2)	0 (0)	0 (0)	99 (13.1)	154 (22.4)	
Urine protein/ urine creatinine (g/gcr)						
< 0.15	2091 (73.6)	1054 (83.4)	636 (76.7)	248 (64.4)	153 (42.3)	
0.15 ≥, < 0.3	352 (12.4)	134 (10.6)	106 (12.8)	529 (13.5)	60 (16.6)	
0.3 ≥, ≤ 0.5	160 (5.6)	49 (3.9)	47 (5.7)	27 (7.0)	37 (10.2)	< 0.0001
0.5 >	237 (8.3)	27 (2.1)	40 (4.8)	58 (15.1)	112 (30.9)	
ACEis / ARBs[*6], *n* (%)	2404 (50.1)	894 (45.0)	733 (52.6)	383 (52.0)	394 (58.0)	< 0.0001
β-blockers, *n* (%)	2283 (47.6)	935 (47.0)	656 (47.1)	358 (48.6)	334 (49.2)	0.7
Statins, *n* (%)	3260 (67.7)	1420 (71.2)	996 (71.1)	427 (57.6)	417 (61.3)	< 0.0001
Acute coronary syndrome, *n* (%)	1506 (30.9)	717 (35.4)	409 (29.0)	226 (30.0)	154 (22.4)	< 0.0001
Multivessel disease, *n* (%)	2770 (57.4)	997 (49.7)	854 (61.4)	448 (60.0)	471 (68.9)	< 0.0001
Stent length, mm	20 [16, 30]	20 [16, 28]	21.5 [16, 32]	20 [15, 28]	22 [15, 33]	0.005
Stent size, mm	3.0 [2.75, 3.5]	3.0 [2.75, 3.5]	3.0 [2.5, 3.0]	3.0 [2.75, 3.5]	3.0 [2.5, 3.0]	< 0.0001

*1: low-density lipoprotein cholesterol, *2: high-density lipoprotein cholesterol, *3: C-reactive protein, *4: estimated glomerular filtration rate, *5: chronic kidney disease, *6: angiotensin converting enzyme inhibitors/ angiotensin receptor blockers

progressively across the groups in the following order: DM-/CKD- (19.1%), DM+/CKD- (21.9%), DM-/CKD+ (22.1%), and DM+/CKD+ (41.2%). These findings suggest that the presence of DM and/or CKD, particularly when combined, is associated with greater complexity of the cases and coronary lesions.

Impact of DM and CKD at index PCI on cardiovascular mortality

To evaluate impact of DM and CKD on CV death separately in the present population, unadjusted Kaplan-Meier analyses followed by log-rank comparisons demonstrated that both DM and CKD individually increased the cumulative incidence of cardiovascular death (Figure S2a and S2b), and these findings provided the basis for the subsequent four-group comparison. Subsequently, cumulative incidences of CV death were compared among four groups simultaneously stratified based on the presence or absence of DM and CKD: groups of DM-/CKD-, DM+/CKD-, DM/-CKD+, and DM+/CKD+. A Kaplan-Meier analysis revealed that the incidence of CV death was highest in the DM + CKD + group, followed by the DM-CKD+, DM + CKD-, and DM-CKD- groups. The DM + CKD + group exhibited a significantly higher incidence of CV death compared to the other three groups. Additionally, the presence of CKD was associated with an elevated incidence of CV death regardless of DM status, whereas the absence of CKD corresponded with a lower incidence of CV death, even in those with DM (Fig. 1).

Consistent with unadjusted Kaplan-Meier analysis, the categorical multivariate Cox proportional hazard analysis adjusted by age, sex, ACS, current smoking,

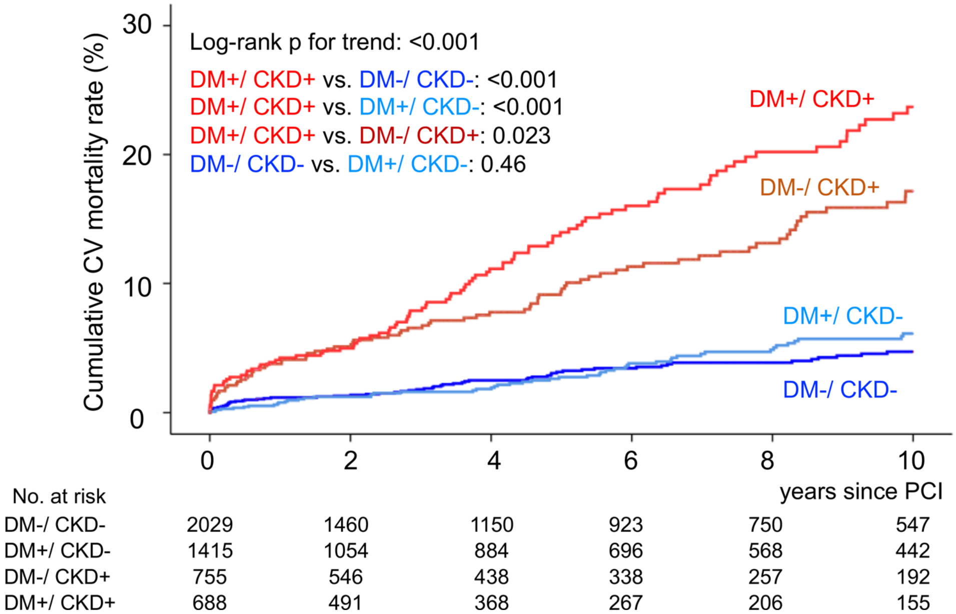


Fig. 1 Cumulative incidences of cardiovascular (CV) death in four patient groups stratified by presence or absence of DM and CKD. Log-rank analysis compared each Kaplan-Meier curve. DM: diabetes mellites, CKD: chronic kidney disease, PCI: percutaneous coronary intervention

Table 2 Categorical adjusted Cox proportional hazard analysis for CV death

	Hazard ratio	95% Confidence interval	*p*
DM-/ CKD-	1 (reference)		
DM+/ CKD-	1.06	0.62–1.83	0.832
DM-/ CKD+	1.84	1.09–3.08	0.022
DM+/ CKD+	3.04	1.82–5.05	< 0.001

Cox model was adjusted by age, sex, acute coronary syndrome, current smoking, hypertension, dyslipidemia, ACEIs/ARBs, statins, multi vessel disease, body mass index, and hemoglobin

hypertension, dyslipidemia, taking ACEIs/ ARBs and statins, multivessel disease, BMI and hemoglobin, showed 3 times higher risk for CV death in patients having both DM and CKD (DM + CKD+) (hazard ratio (HR): 3.0, 95% confidence interval (95% CI): 1.8-5.0, p-value: <0.001), while very similar risk in those with only DM without CKD (DM + CKD-)(HR: 1.1, 95% CI: 0.6–1.8, p-value:0.8) compared to those with neither of them (DM- CKD-), as a reference (Table 2). The presence of a synergistic effect would indicate that when DM and CKD are combined, their joint effect on the outcome is greater than the product of their individual effects (Hazard ratio of DM + CKD+: 3.04 > DM + CKD-: 1.06 x DM- CKD+: 1.84). This suggests a multiplicative interaction where the combined influence of DM and CKD amplifies the risk for CV death beyond their independent contributions.

Prognostic significance of proteinuria for CV death in patients stratified by the presence and absence of DM and CKD following PCI

Data of dipstick proteinuria was available in 2840 out of 4887 entire participants in this study. Distribution in the level of proteinuria < 0.15, 0.15–0.3, 0.3–0.5 and > 0.5 g/gCr were 73.6% ($n = 2091$), 12.4% ($n = 352$), 5.6% ($n = 160$) and 8.3% ($n = 237$), respectively. Unadjusted Kaplan-Meier analysis of entire study population showed the association between higher level of proteinuria and higher cumulative CV mortality rate (Fig. 2). In the Cox proportional hazards analysis adjusted for age, sex, eGFR, and the use of ACE inhibitors/ARBs, proteinuria greater than 0.3 g/gCr was significantly associated with an increased risk of cardiovascular mortality, regardless of the presence or absence of DM (Table 3). In this analysis, no significance of interaction between proteinuria > 0.3 g/gCr and eGFR was observed in both diabetic and non-diabetic patients (interaction $p = 0.774$ and 0.246, respectively), suggesting that the impact of proteinuria was independent from eGFR. Moreover, age-, sex- and eGFR-adjusted Cox proportional hazard analysis compared the impact of proteinuria on CV death following PCI in four patient groups and showed that hazard ratio of proteinuria greater than 0.3 g/gCr was substantially high in DM+/ CKD- group (HR:6.7, 95% CI: 2.7–16.8, $p < 0.001$) compared to other three groups (Fig. 3).

Discussion

In this study, we analyzed the impact of DM and CKD on CV death following PCI by stratifying patients into four groups and it demonstrated that both DM and CKD

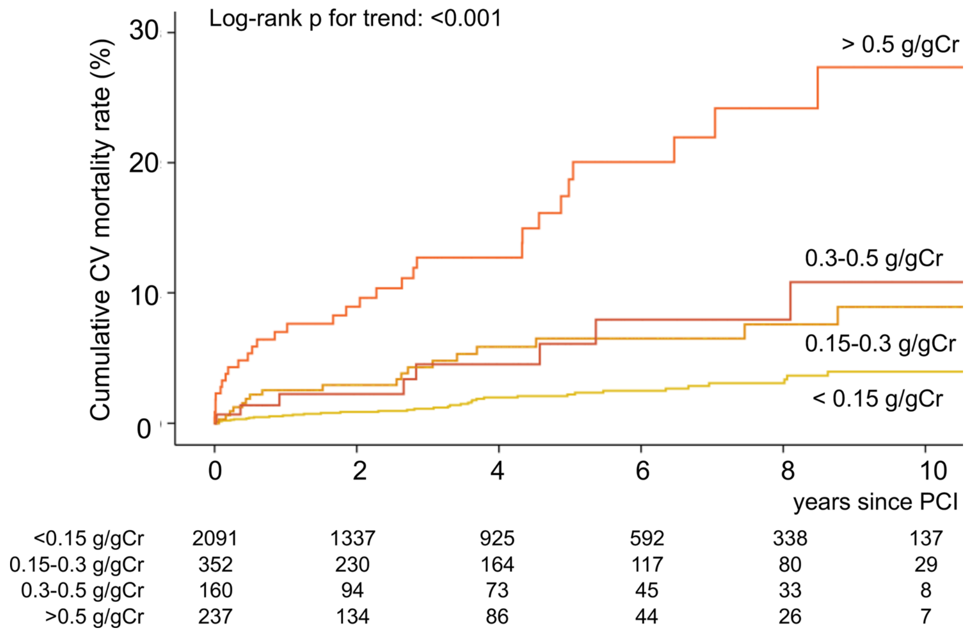


Fig. 2 Cumulative incidences of cardiovascular (CV) death by levels of proteinuria. Log-rank comparison analysis analyzed *P*-value for trend

Table 3 Adjusted hazard ratio of proteinuria > 0.3 g/gCr for CV death in patients with and without diabetes

DM-	Hazard Ratio	95% confidence interval	*P*
Age	1.08	1.05–1.12	< 0.001
Sex	1.41	0.68–2.93	0.358
eGFR	0.98	0.97-1.00	0.016
ACEI/ARB	0.78	0.44–1.38	0.4
Proteinuria > 0.3 g/gCr	**2.73**	**1.39–5.38**	**0.004**
DM+	**Hazard Ratio**	**95% confidence interval**	***P***
Age	1.03	1.00-1.07	0.035
Sex	1.85	0.78–4.41	0.166
eGFR	0.98	0.97-1.00	0.012
ACEI/ARB	1.26	0.67–2.39	0.477
Proteinuria > 0.3 g/gCr	**3.44**	**1.72–6.86**	**< 0.001**

eGFR: estimated glomerular filtration rate, ACEI/ARB: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

independently contribute to an increased risk of CV death, with the highest risk observed when both conditions coexist. Particularly, among diabetic patients, the cumulative incidence and risk of CV death markedly increased when CKD was also present, while those without CKD had a comparable risk to non-DM patients. Additionally, proteinuria was identified as a significant risk indicator for CV death, independent of eGFR in both DM and non-DM patients. In particular, proteinuria greater than 0.3 g/gCr was a strong predictor of CV death in three of the four groups, excluding only those with neither of DM or CKD, with the highest hazard ratio in patients with DM but without CKD. Interestingly, the prognostic impact of proteinuria was independent from eGFR and use of ACEIs/ARBs [17]. This study highlights the significant impact of renal dysfunction on prognosis in diabetic patients following PCI, suggesting that sparing renal function in these patients might be crucial for reducing cardiovascular mortality risk. The finding in this study that proteinuria serves as a sensitive prognostic marker, particularly in diabetic patients without renal dysfunction, underscores its important clinical value in this population.

Diabetes impacts long-term survival rates following PCI, leading to poorer outcomes compared to non-diabetic patients. Previous studies indicate that diabetic patients exhibit reduced event-free survival for outcomes, including all-cause and CV mortality, myocardial infarction, stroke and repeated PCI compared to their non-diabetic counterparts [4, 18]. Similarly, CKD is also an independent established risk factor for poor outcomes after PCI, which significantly associated with increased risk of all-cause and CV mortality and cardiovascular events including the need for repeat revascularization compared to those with normal or only mildly impaired kidney function [19, 20]. These previous findings underscore the importance of DM and CKD as independent critical factors in determining long-term prognosis after PCI, highlighting the need for careful management strategies for this high-risk group. In particular, the presence of both DM and CKD in a CAD patient significantly worsens long-term prognosis following PCI [2]. Although the number of studies is relatively limited which simultaneously estimate these major risk factors, accumulating

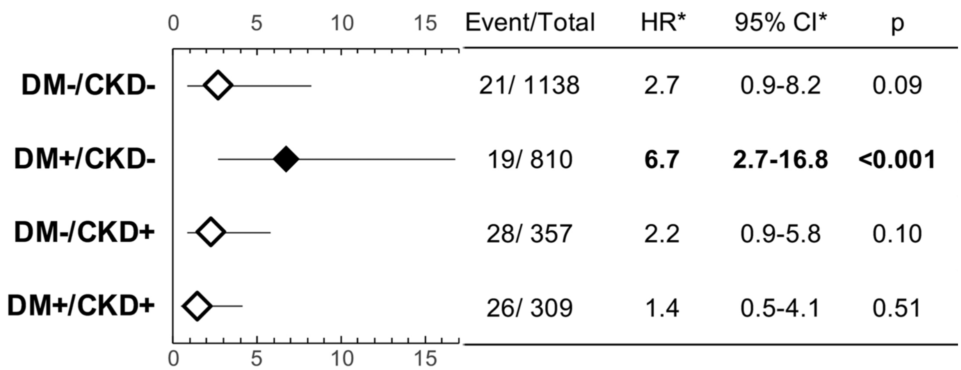


Fig. 3 Age- and sex-adjusted risk of proteinuria > 0.3 g/gCr for CV death in four patient groups.
Cox proportional hazard model showed hazard ratios (HRs) and 95% confidence interval (95% CI) in the model adjusted by age and sex. DM: diabetes mellites, CKD: chronic kidney disease, PCI: percutaneous coronary intervention

evidence have suggested that patients with both conditions exhibit the highest all-cause and cardiovascular mortality rates compared to those with either condition alone or neither condition in various populations including those after PCI [2, 19, 21]. In consistent with these previous studies, the present study showed that CV mortality rate after PCI was highest in patients complicated by both of DM and CKD, lowest in patients with neither of DM nor CKD and those with only DM or CKD were in between. Moreover, of particular interest, it was significantly different between in patients with only DM and in those with CKD in addition to DM. These findings were consistent with previous studies [3, 22] and these findings indicate the adverse prognostic impact of the complication of CKD over DM in patients with CAD following PCI.

For further accurate risk estimation following PCI particularly in patients with DM, this study evaluated the usefulness of proteinuria as a prognostic indicator. While its elevated level was significantly associated with increased risk of CV mortality in entire participants and all of the groups, hazard ratio of proteinuria >0.3 g/gCr was almost 3 times higher in the group of DM+/CKD-. These findings indicate that proteinuria was particularly important for this population. Proteinuria serves as a marker for diabetic nephropathy and may indicate advanced atherosclerosis, making it a valuable predictor of poor outcomes [5]. It is associated with a poorer long-term prognosis in patients with coronary artery disease, including those who have undergone PCI [6]. Previous studies showed that proteinuria significantly worsens the long-term prognosis of diabetic patients following PCI and it is an independent predictor of mortality, with diabetic patients who have preexisting proteinuria showing worse survival rates after PCI compared to those without proteinuria [21]. Particularly, dipstick proteinuria has been identified as a surrogate marker for long-term mortality after acute myocardial infarction, which is relevant for diabetic patients undergoing PCI [23]. Moreover, the macroalbuminuria defined as a urinary albumin to creatinine level of more than 0.3 g/gCr is associated with poorer long-term prognosis in various population [24–26]. However, few have reported that macroalbuminuria significantly affects the prognosis of those after PCI especially in the group of DM+/CKD-.

Overall, proteinuria has been recognized as an independent risk factor for renal function loss, significantly impacting the long-term outcomes of diabetic patients after PCI. This highlights the importance of monitoring and managing proteinuria in these patients for the improvement of their post-PCI outcomes.

ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to be effective in reducing proteinuria in patients with chronic kidney disease by unloading intraglomerular pressure and restoring the size and charge selectivity of the glomerular filtration barrier [12, 27, 28]. However, exploratory analyses did not demonstrate a significant association between RAS inhibitor use and either proteinuria or cardiovascular mortality in the present cohort (data not shown). Moreover, sodium-glucose cotransporter-2 (SGLT2) inhibitors [9, 10, 29], mineral corticoid receptor antagonists (MRAs) [8, 30, 31] and GLP-1 receptor agonists [32, 33] have emerged to be promise in reducing proteinuria in patients with CKD. This relationship holds true in various renal diseases other than diabetic kidney dysfunction [34, 35]. These findings support the use of proteinuria reduction as a therapeutic target and a potential surrogate endpoint in clinical trials for kidney disease. When combined with renin-angiotensin system inhibitors and GLP-1 receptor agonists, these agents may offer additive renoprotective effects [36]. SGLT2 inhibitors work by inhibiting glucose reabsorption in the kidneys, leading to glycosuria and osmotic diuresis, which helps to reduce proteinuria in CKD patients whether with or without diabetes [9]. Moreover, the relative kidney benefits were consistent over a range of albuminuria levels, with greatest absolute kidney benefit in those with extensive albuminuria [37]. A non-steroidal MRA, finerenone, has been demonstrated significant promise in reducing proteinuria and improving renal and cardiovascular outcomes in patients with CKD associated with DM [8, 30, 31, 38].

In this study, we examined Japanese patients who underwent PCI between 2000 and 2018. Given that SGLT2 inhibitors were introduced in Japan later than 2014, the number of participants in this study who were treated with SGLT2 inhibitors or non-steroidal MRAs was extremely limited, preventing this study from evaluating their prognostic effects. However, present findings demonstrated that proteinuria has a strong impact on prognosis, particularly in diabetic patients without CKD. This suggests that agents known to reduce proteinuria, such as MRAs and SGLT2 inhibitors in addition to ACEs/ARBs, may provide significant benefits to this subgroup of patients.

Limitations

This study has several limitations that should be considered. It is a retrospective analysis of a prospectively enrolled single-center registry database, and the sample size may be insufficient for subgroup analyses. Additionally, there is a possibility that unknown confounding factors may have influenced the results, making it challenging to fully elucidate the causal mechanisms underlying the observed phenomena. Furthermore, as the study was conducted in Japan with the vast majority of participants being Japanese, caution should be exercised when extrapolating the findings to other countries or ethnicities. While this study suggests the potential of proteinuria as a therapeutic target in diabetic patients undergoing PCI, prospective interventional trials are necessary to confirm this hypothesis. Finally, as noted earlier, the PCI procedures included in this study were performed between 2000 and 2018, and thus the impact of more recent advancements in pharmacological and interventional treatments cannot be evaluated within the scope of this study.

Conclusions

Despite these limitations, the findings of the present study have significant clinical implications. Our results underscore the profound impact of renal dysfunction on prognosis in diabetic patients undergoing PCI. Furthermore, this study demonstrates that in diabetic PCI patients without renal dysfunction, proteinuria, independent of eGFR, is a strong risk factor for cardiovascular mortality, with the risk increasing in parallel with its degree. These findings highlight the importance of addressing proteinuria in this population. In the future, prospective randomized trials with adequate sample sizes are necessary to evaluate the efficacy of targeting proteinuria or urinary albumin as a therapeutic strategy for improving outcomes in diabetic patients with coronary artery disease.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40842-025-00243-7.

Supplementary Material 1

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Author contributions

Soshi Moriya: Writing – original draft, Data curationHiroshi Iwata: Conception and design of the study, Formal analysis, Investigation, Project administration, Writing – review & editingYuichi Chikata: Data curation, SupervisionTakehiro Funamizu: Data curation, Supervision, Shinichiro Doi: Data curation, Supervision, Takuma Koike: Data curation, Keiki Abe: Data curation, Ryotaro Matsuo: Data curation, Hideki Wada: Data curation, Supervision, Project administrationRyo Naito: Formal analysis, Manabu Ogita: Data curation, Supervision, Iwao Okai: Data curation, Supervision, Tomotaka Dohi: Data curation, Takatoshi Kasai: Data curation, Supervision, Shinya Okazaki: Data curation, Supervision, Katsumi Miyauchi: Supervision, Project administrationHiroyuki Daida: Supervision, Tohru Minamino: Supervision.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Human ethics and consent to participate

The study protocol was approved by the Institutional Review Board of Juntendo University (IRB No. **E22-0409**) and conducted in accordance with the Declaration of Helsinki. Given the observational design using data obtained during routine clinical care and minimal risk to participants, the IRB granted a waiver of written informed consent; an opt-out procedure was implemented by publicly posting study information on the Juntendo University Hospital website. The prospective PCI registry (Juntendo Physicians' Alliance for Clinical Trial, J-PACT) is publicly registered (UMIN-CTR 000035587).

Consent for publication

Not applicable (no identifiable individual data are included).

Competing interests

The authors declare no competing interests.

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