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ORIGINAL ARTICLE

Prognostic significance of renal dysfunction and its change pattern on outcomes in patients with acute coronary syndrome treated with emergent percutaneous coronary intervention

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Abstract

Renal dysfunction and its change pattern are associated with short- and long-term mortality. However, it remains to be investigated whether or not worsening renal function (WRF) defined by baseline renal function identified from different time points would provide prognostic implication on outcomes in acute coronary syndrome (ACS) patients. This study consists of 334 ACS patients (mean age 68 ± 11 years, 75% male) treated with emergent percutaneous coronary intervention (PCI). Estimated glomerular filtration rate (eGFR) was evaluated on baseline, during hospitalization, at discharge, and at 3-month follow-up. WRF was defined as a relative decrease of eGFR > 20% at 3 months using baseline eGFR identified from different time points. The primary end point was a composite event of major cardiovascular events (MACE), including all-cause death, ACS, and heart failure hospitalization. The associations of chronic kidney disease (CKD), acute kidney injury (AKI), and WRF with MACE were evaluated. During a mean follow-up of 3.3 ± 1.7 years, a total of 64 MACE were observed. Multivariable analysis revealed that CKD (hazard ratio 2.16; $p = 0.018$) and AKI (hazard ratio 1.95; $p = 0.030$) were independent predictors of MACE, but WRF did not remain as an independent predictor of MACE ($p = 0.208$). The highest risk was observed in AKI patients with CKD when stratified by the presence or absence of CKD and AKI. In ACS patients treated with emergent PCI, this study demonstrated that CKD and AKI were independent predictors of MACE, while there was no independent relationship between WRF and MACE.

Keywords Acute coronary syndrome · Chronic kidney disease · Acute kidney injury · Worsening renal function · Prediction

Introduction

Renal function plays a key role in predicting disease progression and short- and long-term outcomes in patients with acute coronary syndrome (ACS) [1–4]. Acute kidney injury (AKI) is frequently observed in ACS patients treated with emergent percutaneous coronary intervention (PCI) that is accelerated by cardiogenic shock, heart failure, and preexisting chronic kidney disease (CKD) [3–7]. Previous studies demonstrated the substantial relationship between AKI and subsequent renal function decline [8–10]. Although several studies emphasize the importance of monitoring renal function after AKI [4, 9–12], limited data exist on the association between change pattern of renal function and long-term outcome in patients who survived ACS event.

Worsening renal function (WRF) has been shown to be associated with outcome in coronary artery disease (CAD) [8, 13, 14], heart failure (HF) [15–17], and other clinical settings [11, 18]. The mechanisms by which WRF increases mortality depend on a variety of different clinical settings, and prognostic implications of decline in renal function are heterogeneous [12, 16]. Since ACS involves acute hemodynamic changes on underlying risks of renal dysfunction, AKI might have started before hospital admission that can be improved by optimized medical therapy and PCI [2, 4]. These findings suggest the need for identification of

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appropriate baseline renal function to examine the prognostic implication of WRF in ACS patients. Thus, it remains to be seen whether WRF defined by baseline renal function identified from different time points would provide prognostic value on outcomes in patients who survived ACS. Furthermore, despite that recent evidence supports the evaluation of estimated glomerular filtration rate (eGFR) rather than serum creatinine to predict outcome [1, 11, 19], many studies have employed the WRF definition of a relative or absolute increase of serum creatinine. The present study aimed to investigate the association of renal function and its change pattern, as assessed by eGFR, with outcomes in ACS patients treated with emergent PCI.

Methods and materials

Study population and design

In this retrospective study, we screened consecutive 402 ACS patients who were treated with emergent PCI at Ishikiri-seiki Hospital between January 2011 and December 2014. The clinical ACS diagnosis of the present study included ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS based on AHA/ACC guidelines [20, 21]. We excluded the following: patients treated with maintenance hemodialysis, $n = 20$; patients who died during hospitalization and within 3 months after discharge, $n = 18$; patients with insufficient blood sample data collection, $n = 27$; and lost follow-up patients, $n = 3$. The final analysis cohort consisted of 334 ACS patients treated with PCI. Informed consent was obtained before urgent invasive coronary angiography in all study patients. The Ethics Committee of Ishikiri-seiki Hospital approved the use of data for the purposes of this research.

PCI procedures were performed according to the guidelines for current clinical practice using a biplane X-ray system (Philips, Allura 115 Xper FD 10-10). Nonionic contrast agent (Omnipaque 350, Daiichi Sankyo Co., Tokyo, Japan) was used for the invasive coronary angiography and PCI. In our institution, consecutive intravenous saline injection was performed during and after emergent PCI [20, 21]. According to the current guidelines, the discontinuation of nephrotoxic medication was decided after the completion of emergent PCI [19, 22]. Clinical data were obtained by reviewing the medical records. Baseline blood sample tests were taken before the emergent PCI. Serum creatinine measurements were recorded at different time points, including on hospital admission, within 72 h after PCI, at discharge, and at 3-month follow-up after discharge. Furthermore, serum creatinine before hospitalization was used to assess baseline renal function if present.

Definitions

Renal function was assessed by eGFR using the CKD-EPI equation [23, 24]. CKD was defined as baseline eGFR on admission < 60 ml/min/1.73 m^2. AKI was defined as an increase in serum creatinine of ≥ 0.3 mg/dl and/or ≥ 50% within 72 h after hospital admission [3, 6]. For the definition of CKD and AKI, the higher eGFR or the lower serum creatinine value measured before hospitalization ($n = 153$) or on hospital admission ($n = 181$) was used as baseline renal function, respectively. WRF was defined as a relative decrease in eGFR of > 20% at 3 months [25–27]. Since PCI may improve cardiac function and lead to improvement of renal dysfunction that is caused by AKI started before hospitalization, we evaluated baseline renal function at different time points for the definition of WRF. For the calculation of WRF, the highest eGFR value was used as a "baseline eGFR" identified from different time points, including before hospitalization, on hospital admission, and at discharge. Contrast-induced nephropathy (CIN) risk score was calculated using parameters on hospital admission as described previously [28].

End point

The primary end point was defined as a composite event of all-cause death, ACS requiring coronary revascularization, and HF hospitalization. Outcome data were collected and adjudicated by two cardiologists (H.K. and N.K.) through the medical records for a period starting with hospital admission and ending with the last visit to our hospital up to 5 years in all study patients. All-cause death and ACS requiring coronary revascularization were judged according to the medical record in our hospital. HF hospitalization was recorded when patients were admitted to hospital with HF symptoms showing any evidence of congestion and/or biomarker increase in association with transthoracic cardiac echocardiographic examination. All patients were followed with a scheduled revaluation at every 2–3 months after discharge in our institution. Further assessments were planned according to the clinical status of each patient.

Statistical analysis

Continuous variables were expressed as mean ± SD and were compared by using the unpaired Student's t test. Categorical variables were summarized as frequencies with percentages and compared by Pearson χ^2 analysis. Comparisons between continuous variables at baseline, after PCI, and follow-up examination of eGFR were performed with paired t test. Univariate and multivariate Cox regression analyses were carried out to determine the predictors of WRF. The effect of variables on outcome was investigated with univariate and multivariate Cox proportional-hazard model. Multivariate model included the variables with a p value $<$ 0.05 in the univariate analysis except for medications. Furthermore, considering the underlying high-risk clinical profile and condition, we performed Cox proportional-hazard analysis to investigate independent predictors of MACE in patients with STEMI as a sub-analysis. For survival analysis, time-to-event data for ACS and STEMI patients were presented as Kaplan–Meier estimates. All statistical analyzes were performed using the SPSS software version 22 (SPSS Japan Inc, Tokyo, Japan) and p values < 0.05 (2-sided) were considered statistically significant.

Results

Patient characteristics and serial changes in renal function

In the present study, WRF was observed in 71 patients (21%). The baseline clinical and angiographic characteristics in patients with and without WRF are shown in Table 1. Compared to the non-WRF patients, WRF patients had advanced age ($p = 0.004$), lower eGFR ($p < 0.001$) and higher BNP ($p = 0.001$). When compared to non-WRF patients, WRF patients were more likely to have NYHA III/IV ($p < 0.001$), CKD ($p < 0.001$), AKI ($p < 0.001$), diuretics therapy ($p < 0.001$) and CIN risk score > 17 ($p < 0.001$). Figure 1 shows the serial changes in eGFR in patients with and without CKD, AKI, WRF and MACE, respectively. CKD patients had lower eGFR than non-CKD patients at all the different time points, while both CKD and non-CKD patients had slightly but significantly decreased eGFR at 3 months ($p < 0.001$) compared to baseline (Fig. 1a). Both AKI and non-AKI patients had significantly decreased eGFR at 3 months compared to baseline (Fig. 1b). When compared with non-AKI patients, AKI patients showed a greater change in eGFR at 3 months. Although there was significant difference in baseline eGFR between WRF and non-WRF patients, the difference between the two groups was more highlighted at 3 months (Fig. 1c). Compared to the non-MACE group, the MACE group showed significantly lower eGFR at all the different time points and decreased eGFR at 3 months over baseline as well as non-MACE patients (Fig. 1d). When analyzing the 153 patients who had baseline renal function before hospitalization, the eGFR on hospital admission was significantly decreased compared to baseline eGFR before hospitalization (75 ± 20 versus 67 ± 22 ml/min/1.73 mm^2; $p < 0.001$). Decreased eGFR was observed in 75% of the patients who had baseline eGFR ($n = 153$). Furthermore,

Table 1 Demographic, clinical, and procedural data in patients with and without WRF

	WRF $n = 71$	Non-WRF $n = 263$	p value
Age, years	71 ± 10	67 ± 11	0.004
Male, n (%)	50 (70)	202 (77)	0.279
BMI, kg/m^2	23.6 ± 3.3	23.9 ± 3.2	0.672
Hypertension, n (%)	57 (80)	191 (73)	0.222
Diabetes mellitus, n (%)	36 (51)	86 (33)	0.008
Dyslipidemia, n (%)	55 (77)	219 (83)	0.226
Current smoking, n (%)	14 (20)	60 (23)	0.632
CAD history, n (%)	13 (18)	53 (20)	0.867
STEMI, n (%)	50 (70)	153 (58)	0.075
NYHA III/IV, n (%)	30 (42)	46 (17)	< 0.001
LVEF < 40%, n (%)	21(30)	30 (11)	0.001
LAD culprit, n (%)	33 (46)	119 (45)	0.894
Multi-vessel disease, n (%)	38 (54)	127 (48)	0.504
Femoral artery access	15 (21)	36 (14)	0.137
IABP use, n (%)	10 (14)	21 (8.0)	0.163
Renal replacement therapy after PCI	2 (3.5)	0 (0)	0.045
Contrast volume, ml	109 ± 43	114 ± 39	0.340
CKD	35 (49)	29 (11)	< 0.001
AKI	27 (38)	24 (9.1)	< 0.001
Laboratory tests on hospital admission			
Hemoglobin, g/dl	13.2 ± 2.1	14.1 ± 1.9	0.001
eGFR, ml/min/1.73 m^2	67.5 ± 24	80.1 ± 15	< 0.001
HDL cholesterol, mg/dl	50 ± 13	48 ± 13	0.46
LDL cholesterol, mg/dl	140 ± 43	136 ± 38	0.501
HbA1c, %	6.8 ± 2.1	6.3 ± 1.3	0.037
BNP, pg/ml	407 ± 510	211 ± 328	0.001
Medications on hospital admission			
ACE-I or ARB, n (%)	41 (58)	156 (59)	0.892
β-blocker, n (%)	21 (30)	74 (28)	0.882
Calcium-channel blocker, n (%)	14 (20)	73 (28)	0.222
Diuretics, n (%)	31 (44)	53 (20)	< 0.001
Statins, n (%)	48 (68)	173 (66)	0.888
CIN risk score, n (%)			
< 5	17 (24)	158 (60)	< 0.001
6–10	22 (31)	59 (22)	0.160
10–17	15 (21)	36 (14)	0.137
> 17	17 (24)	12 (4.5)	< 0.001

Variables are expressed by mean ± SD or number (%). The baseline eGFR for WRF and non-WRF group was calculated using the highest eGFR identified in different time points, including before hospitalization, on hospital admission, and at discharge

ACE-I angiotensin-converting enzyme inhibitor, *AKI* acute kidney injury, *ARB* angiotensin receptor blocker, *CAD* coronary artery disease, *CIN* contrast induced nephropathy, *eGFR* estimated glomerular filtration rate, *HDL* high-dense lipoprotein, *IABP* intra-aortic balloon pump, *LDL* low-dense lipoprotein, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *STEMI* ST-segment elevation myocardial infarction, and *WRF* worsening renal function

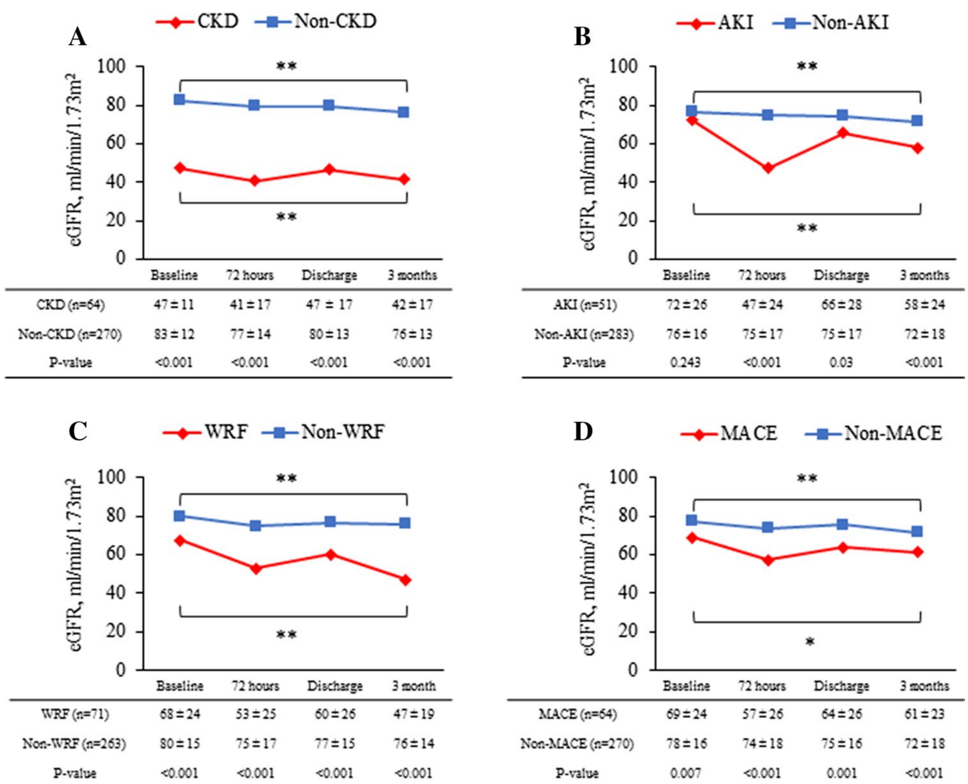

Fig. 1 Serial change of eGFR according to the presence or absence of CKD, AKI, WRF, and MACE. Serial change of eGFR in patients with and without CKD (**a**), AKI (**b**), WRF (**c**), and MACE (**d**). Tables below the graphs show the mean ± SD of eGFR at each time point. *p* value in the tables indicates statistical difference in eGFR between the two groups at each time point. *p* value in the graph indicates statistical difference in eGFR between baseline and 3-month (** and * indicate $p<0.001$ and $p<0.05$, respectively). *AKI* acute kidney injury, *CKD* chronic kidney disease, *MACE* major adverse cardiovascular event, and *WRF* worsening renal function

Table 2 Multivariable Cox regression analysis for predictors of worsening renal function

	β	Standard error	*p* value
Age per 1 increase	0.007	0.016	0.672
Diabetes mellitus	0.348	0.335	0.299
STEMI	0.384	0.335	0.253
LVEF < 40%	0.424	0.412	0.303
CKD	1.68	0.373	< 0.001
AKI	1.255	0.381	0.001
Diuretics therapy	0.574	0.357	0.108
NYHA III/IV,	− 0.140	0.480	0.770
CIN risk per 1 increase	0.033	0.041	0.426

AKI acute kidney injury, *CIN* contrast induced nephropathy, *CKD* chronic kidney disease, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, and *STEMI* ST-segment elevation myocardial infarction

when analyzing the difference in eGFR between hospital admission and discharge in 334 ACS patients, the eGFR at discharge was significantly improved from the value measured on hospital admission (71.4 ± 20 versus 73.2 ± 19; $p=0.005$). The improvement of eGFR at discharge was observed in 46% of ACS patients. Multivariable regression analysis revealed that CKD (β = 1.68, $p<0.001$) and AKI (β = 1.255, $p=0.001$) were independent predictors of WRF, as shown in Table 2.

Patient outcome

During a mean follow-up of 3.3 ± 1.7 years, a total of 64 patients were in primary end point (all-cause death, $n=25$; ACS requiring revascularization, $n=21$; and HF hospitalization, $n=18$), as shown in Table 3. The baseline patient and angiographic characteristics in patients with and without MACE are shown in Table 4. Compared with the non-MACE group, the MACE group was more likely to have advanced age ($p=0.003$), decreased eGFR ($p=0.007$) and lower hemoglobin levels ($p=0.014$) and had higher prevalence of left ventricular ejection fraction (LVEF) ≤ 40% ($p=0.011$), diuretic therapy ($p=0.002$) and statin therapy ($p=0.018$). For angiographic characteristics, there was no significant difference in prevalence of LAD culprit lesion ($p=0.88$) and contrast volume ($p=0.94$). The lower risks of CIN risk score were more common in the non-MACE group (Table 4). Figure 2 shows the incidence of MACE in patients with and without CKD, AKI and WRF. When compared to patients without each renal complication, significantly higher incidence for MACE was observed in patients with CKD ($p<0.001$), AKI ($p<0.001$) and WRF ($p<0.001$), respectively.

Predictors of MACE

Table 5 shows the univariate and multivariate Cox hazard analyzes to predict MACE for all study patients (model 1)

Table 3 Number of patients resulting in MACE according to the presence or absence of WRF

ACS patients	Over all ($n=334$)	WRF ($n=71$)	Non-WRF ($n=263$)
MACEa	64	27	37
All-cause death	25	11	14
ACS requiring coronary revascularization	22	6	16
HF hospitalization	17	10	7
Sub-analysis in STEMI	Overall ($n=203$)	WRF ($n=40$)	Non-WRF ($n=163$)
MACE	40	20	20
All-cause death	12	8	4
ACS requiring coronary revascularization	15	4	11
HF hospitalization	13	8	5

ACS acute coronary syndrome, *HF* heart failure, *MACE* major cardiovascular event, *WRF* worsening renal function.

and STEMI patients (model 2). Multivariable analysis model 1 revealed that baseline CKD [hazard ratio (HR) 2.16; 95% confidence interval (CI) 1.14–4.09; $p=0.018$] and AKI (HR 1.95; 95% CI 1.06–3.58; $p=0.030$) were independent predictors of MACE (Table 5 model 1), while WRF did not remain as an independent predictor of MACE ($p=0.208$) in ACS patients. To investigate the prognostic implication of WRF defined by serum creatinine, we also performed multivariate analysis to predict MACE in ACS patients, where WRF was defined by an increase in serum creatinine of $\geq$ 0.3 mg/dl and/or $\geq$ 50% within 72 h. Similarly, independent predictors of MACE were CKD (HR 2.49; 95% CI 1.350–4.613, $p=0.004$) and AKI (HR 2.13; 95% CI 1.176–3.875, $p=0.013$). In the sub-analysis of STEMI patients, the multivariate model 2 demonstrated that CKD (HR 2.56; 95% CI 1.14–5.70; $p=0.021$) and AKI (HR 3.18; 95% CI 1.52–6.63; $p=0.002$) were independent predictors of MACE. The cumulative rates of MACE are shown as Kaplan–Meier estimates in Fig. 3. Figure 3a demonstrates a graded risk of MACE when stratified by the presence or absence of CKD and AKI. Although the AKI patients with WRF had the worst prognosis during follow-up, non-AKI patients with or without WRF showed similar outcomes (Fig. 3b). The non-CKD patients without WRF had benign outcome compared to other groups (Fig. 3c). Similar results were obtained when analysis was performed only in STEMI patients (Fig. 3d–f).

Discussion

This study demonstrated that baseline renal dysfunction and AKI were independent predictors of MACE, while WRF did not remain as an independent predictor of MACE in ACS patients treated with emergent PCI. Our findings confirm the prognostic significance of renal dysfunction and AKI and may provide practical insights into change pattern of renal dysfunction and long-term outcomes in ACS patients treated with emergent PCI.

Prognostic significance of CKD and AKI

The high prevalence of renal dysfunction among ACS patients is well documented with its substantial association of adverse outcomes [1–6]. In the present study, baseline CKD was observed in 20% of patients, which is similar to that in previous reports (17.9–34%) [1–4, 6, 7, 14, 29]. Anavekar et al. demonstrated that even mild decline in renal function, as assessed by the eGFR, was associated with increased risk of cardiovascular events after acute myocardial infarction [1]. Renal dysfunction is known to be associated with worse prognosis in CAD [3, 4, 6–8], HF [15–17] and other clinical settings [11, 18]; however, few studies have reported its change pattern in ACS patients treated with PCI.

This study demonstrates that AKI was a robust predictor of MACE, while there was no independent relationship between WRF and outcome in ACS. It is well established that AKI is a frequent complication and associates with worse prognosis in multiple populations [3, 4, 6–10, 18, 30], independent of residual kidney function [31]. In the present study, we observed a graded risk when patients were stratified by the presence of CKD and AKI. Watabe et al. have found that contrast-induced AKI was an incremental predictor of cardiovascular outcome at each stage of CKD in ACS patients [3]. Furthermore, accumulating evidence demonstrated that a greater decline in renal function during AKI, such as severe AKI resulting in renal replacement

Table 4 Demographic, clinical, and procedural data in patients with and without MACE

	MACE (+) $n=64$	MACE (−) $n=270$	*p* value
Age, years	70 ± 10	66 ± 11	0.003
Male, *n* (%)	49 (76)	203 (75)	0.87
BMI, kg/m^2	23.0 ± 3.5	24.1 ± 3.0	0.15
Hypertension, *n* (%)	52 (81)	196 (73)	0.20
Diabetes mellitus, *n* (%)	27 (42)	95 (35)	0.31
Dyslipidemia, *n* (%)	51 (80)	223 (83)	0.58
Current smoking, *n* (%)	15 (23)	59 (22)	0.86
CAD history, *n* (%)	12 (19)	54 (20)	0.99
STEMI, *n* (%)	40 (63)	163 (60)	0.77
NYHA III/IV, *n* (%)	18 (28)	58 (21)	0.25
LVEF < 40%, *n* (%)	17 (27)	34 (13)	0.011
LAD culprit, *n* (%)	30 (47)	122 (45)	0.88
Multi-vessel disease, *n* (%)	39 (61)	126 (47)	0.051
Femoral artery access	13 (20)	38 (14)	0.24
IABP use, *n* (%)	9 (14)	22 (8.1)	0.15
Renal replacement therapy after PCI	2 (3.1)	0 (0)	0.036
Contrast volume, ml	112 ± 39	113 ± 40	0.94
Laboratory tests on hospital admission			
Hemoglobin, g/dl	13.3 ± 2.1	14.0 ± 2.0	0.014
eGFR, ml/min/1.73 m^2	68.9 ± 24	77.5 ± 16	0.007
HDL cholesterol, mg/dl	48 ± 16	48 ± 11	0.98
LDL cholesterol, mg/dl	137 ± 40	137 ± 39	0.96
HbA1c, %	6.4 ± 1.4	6.3 ± 1.5	0.77
BNP, pg/ml	326 ± 346	239 ± 390	0.21
Medications on hospital admission			
ACE-I or ARB, *n* (%)	30 (47)	167 (62)	0.067
β-blocker, *n* (%)	14 (22)	81 (30)	0.22
Calcium-channel blocker, *n* (%)	18 (28)	69 (26)	0.75
Diuretics, *n* (%)	26 (41)	58 (21)	0.002
Statins, *n* (%)	34 (53)	187 (69)	0.018
CIN risk score, *n* (%)			
< 5	19 (30)	156 (58)	<0.001
6–10	25 (39)	56 (21)	0.003
10–17	10 (16)	41 (15)	1.00
> 17	12 (19)	17 (6.2)	0.005

Variables are expressed by mean ± SD or number (%). The baseline eGFR for MACE and non-MACE group was calculated using the highest eGFR obtained before hospitalization or on hospital admission

ACE-I angiotensin-converting enzyme inhibitor, *AKI* acute kidney injury, *ARB* angiotensin receptor blocker, *CAD* coronary artery disease, *CIN* contrast induced nephropathy, *eGFR* estimated glomerular filtration rate, *HDL* high-dense lipoprotein, *IABP* intra-aortic balloon pump, *LDL* low-dense lipoprotein, *LVEF* left ventricular ejection fraction, *STEMI* ST-segment elevation myocardial infarction, *WRF* worsening renal function

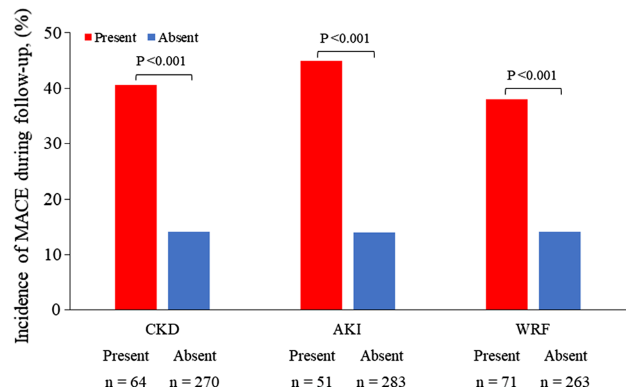

Fig. 2 Incident rates of MACE during follow-up. Accumulating rates for MACE during follow-up according to the presence (red bar) and absence (blue bar) of each group, including CKD, AKI, and WRF. *AKI* acute kidney injury, *CKD* chronic kidney disease, *MACE* major adverse cardiovascular event, and *WRF* worsening renal function

therapy, was associated with a poorer patient prognosis [2, 4, 19]. As a surrogate end point of outcome, the identification of AKI rather than WRF may serve as a robust predictor of long-term outcomes in ACS patients.

Worsening renal function and outcome

The mechanisms by which WRF increases hazard risk of outcomes may involve the progression to CKD, side effects of medical therapies and heterogeneity of underlying causes and diseases. AKI severity and multiple hits of AKI predispose patients to faster progression of subsequent CKD progression [10]. Nemoto et al., demonstrated that continuous deterioration in kidney function was an independent predictor of mortality in ACS patients; however, AKI was not included in the multivariate model to predict the outcome [14]. In the present study, we found that CKD and AKI were robust factors associated with WRF, contributing to reducing the prognostic significance of WRF.

Sawhney et al., suggest that the long-term prognosis after AKI varies depending on the clinical setting with underlying pre- and post-AKI renal function rather than zthe AKI itself [12]. Maioli et al., demonstrated that persistent renal damage after AKI showed poorer outcomes compared to those with transient AKI in CAD patients with estimated creatinine clearance < 60 ml/min [8]. In line with the previous study, we found that patients having AKI and WRF showed poorer outcomes compared to other groups, both in ACS and STEMI patients. On the other hand, we observed that non-AKI with WRF had similar outcomes compared to non-AKI without WRF. Considering the substantial associations of CKD and its severity with outcomes [1–4], it is likely that CKD influences the prognosis in non-AKI patients with or without WRF, and appropriate definition for WRF may be

Table 5 Univariate and multivariate Cox hazard regression analyzes for prediction of MACE in ACS and STEMI

	Univariate model			Multivariable model		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Model 1: Cox hazard model in all patients ($n=334$)						
Age per 1 increase	1.03	1.01–1.06	0.002	1.01	0.98–1.03	0.478
LVEF ≤ 40%	2.26	1.29–3.95	0.004	1.31	0.69–2.47	0.408
Hemoglobin per 1 g/dl increase	0.85	0.76–0.95	0.007	0.97	0.85–1.11	0.703
CKD	1.43	2.52–6.95	< 0.001	2.16	1.14–4.09	0.018
AKI	3.64	2.18–6.08	< 0.001	1.95	1.06–3.58	0.030
WRF	3.44	2.09–5.69	< 0.001	1.48	0.80–2.75	0.208
CIN risk score per 1 increase	1.09	1.05–1.13	< 0.001	1.03	0.97–1.07	0.299
Model 2: Cox hazard model in patients with STEMI ($n=203$)						
Age per 1 increase	1.05	1.02–1.08	0.001	1.03	0.99–1.06	0.128
LVEF ≤40%	1.99	1.01–3.91	0.046	1.19	0.54–2.64	0.657
Hemoglobin per 1 g/dl increase	0.85	0.74–0.97	0.020	0.89	0.77–1.04	0.147
CKD	5.32	2.76–10.26	< 0.001	2.56	1.14–5.70	0.021
AKI	5.18	2.76–9.71	< 0.001	3.18	1.52–6.63	0.002
WRF	3.47	1.86–6.46	< 0.001	1.15	0.53–2.51	0.717
CIN risk score per 1 increase	1.09	1.04–1.13	< 0.001	0.99	0.94–1.06	0.942

Multivariable model included the variables that had a *p* value of < 0.05 in the univariate analysis

AKI acute kidney injury, *CIN* contrast induced nephropathy, *CKD* chronic kidney disease, *LVEF* left ventricular ejection fraction, *MACE* major cardiovascular event, STEMI= and WRF = worsening renal function

different among patients with and without CKD, and also among patients with different CKD stages. Furthermore, pre-existing AKI starting before hospital admission may cause misclassification of WRF in ACS patients. An observational study demonstrated that 11% of ACS patients had improved renal function during hospitalization [2]. In fact, we observed deterioration of eGFR on hospital admission in patients having baseline renal function before hospitalization, which was improved at discharge. These observations suggest that AKI might have started before hospitalization in the ACS population, which can be improved by appropriate medical therapy and PCI [2, 4]. Since no effective therapy for AKI is available [32], early identification of AKI may help better risk stratification of ACS patents treated with emergent PCI.

Study limitations

This study has several limitations. First, this was a single-center retrospective study consisting of a relatively small number of patients. Second, this study excluded patients who died in hospital and within 3 months in the study cohort. These exclusions may have attenuated the prognostic value of baseline renal dysfunction and AKI as well as other clinical predictors on patient prognosis. In addition, the prognostic significance of advanced age may also have been attenuated, since these high-risk populations included patients with relatively advanced age. Third, although previous studies demonstrated that renal replacement therapy following AKI has been shown to be associated with poorer patient outcomes, we did not include renal replacement therapy in the multivariate model to predict WRF and MACE due to its low incidence in the present study. However, the rate of renal replacement therapy in the present study was similar to the previous reports [33]. Fourth, although many studies have evaluated WRF by an absolute or relative increase of serum creatinine over baseline levels [8, 12, 14, 16, 18], we used WRF definition based on eGFR. However, recent evidence supports the evaluation of eGFR rather than the serum creatinine to predict adverse outcome [11, 19, 34]. Future prospective study is necessary to investigate the association of eGFR decline with patient outcomes. Fifth, we found baseline renal function before hospitalization only in 46% of the study patients. Although it is difficult to evaluate true renal function at baseline in ACS patients treated with emergent PCI, the missing data for baseline renal function may affect the classification of CKD, AKI and WRF. However, the strength of the present study is that we defined the WRF on the basis of baseline eGFR determined from different time points of data collection. Finally, for the retrospective study nature, the present study did not include analysis to determine the association of medical therapies and renovascular protection strategies, including discontinuation of nephrotoxic medications and effects of renal protective drugs with outcomes [19, 35, 36]. Future well-designed study is needed to investigate the associations of the effects

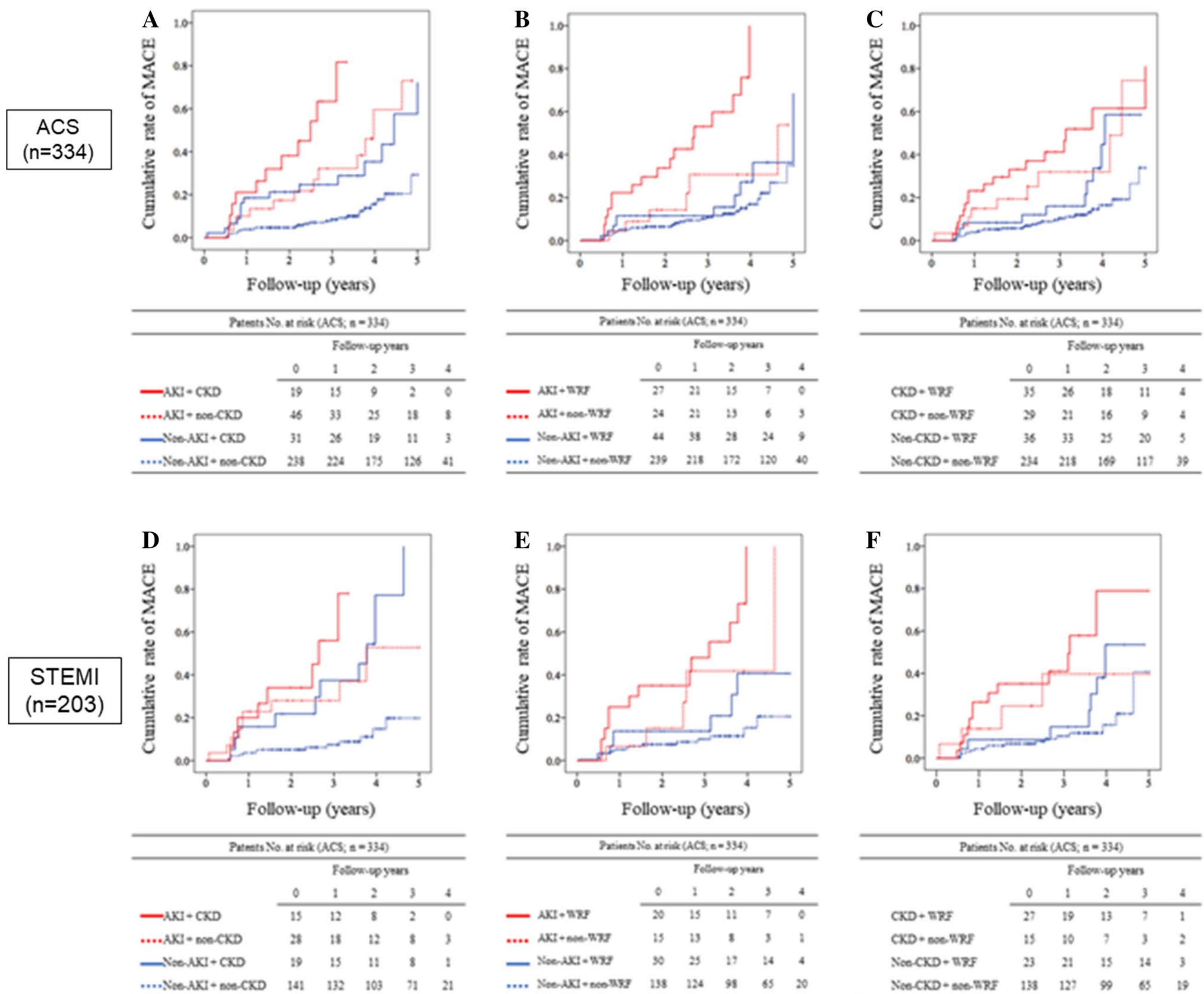

Fig. 3 Time-to-event curves for MACE during follow-up in patients with ACS and STEMI. The cumulative rates of MACE are shown as Kaplan–Meier estimates according to the presence or absence of AKI and CKD (**a**), AKI and WRF (**b**), CKD and WRF (**c**) for patients with ACS; and AKI and CKD (**d**), AKI and WRF (**e**), CKD and WRF (**f**) for patients with STEMI. *AKI* acute kidney injury, *CKD* chronic kidney disease, *MACE* major adverse cardiovascular event, *STEMI* ST-segment elevation myocardial infarction, and *WRF* worsening renal function

of medical therapies on WRF with patient prognosis in the ACS population.

Conclusions

Our data provide practical insights into change pattern of renal dysfunction and long-term outcomes in ACS patients treated with PCI. The baseline renal dysfunction and AKI were strong predictors of outcome in this population. Future studies are necessary to assess whether WRF is associated with outcome in ACS patients treated with PCI.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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