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Original article

The prognostic impact of worsening renal function in Japanese patients undergoing percutaneous coronary intervention with acute coronary syndrome

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ABSTRACT

Background: The prognostic impact of worsening renal function (WRF) in acute coronary syndrome (ACS) patients is not fully understood in Japanese clinical practice, and clinical implication of persistent versus transient WRF in ACS patients is also unclear.
Methods: With a single hospital-based cohort in the Shinken database 2004–2012 (n = 19,994), we followed 604 ACS patients who underwent percutaneous coronary intervention (PCI). WRF was defined as an increase in creatinine during hospitalization of ≥0.3 mg/dl above admission value. Persistent WRF was defined as an increase in creatinine during hospitalization of ≥0.3 mg/dl above admission value and maintained until discharge, whereas transient WRF was defined as that WRF resolved at hospital discharge.
Results: WRF occurred in 78 patients (13%), persistent WRF 35 patients (6%) and transient WRF 43 patients (7%). WRF patients were older and had a higher prevalence of chronic kidney disease, history of myocardial infarction (MI), and ST elevation MI. WRF was associated with elevated inflammatory markers and reduced left ventricular (LV) ejection fraction in acute, chronic phase. Incidence of all-cause death and major adverse cardiac events (MACE: all-cause death, MI, and target lesion revascularization) was significantly higher in patients with WRF. Moreover, in the WRF group, incidences of all-cause death and MACE were higher in patients with persistent WRF than those with transient WRF. A multivariate analysis showed that as well as older age, female gender, and intubation, WRF was an independent determinant of the all-cause death in ACS patients who underwent PCI.
Conclusions: In conclusion, WRF might have a prognostic impact among Japanese ACS patients who underwent PCI in association with enhanced inflammatory response and LV remodeling. Persistent WRF might portend increased events, while transient WRF might have association with favorable outcomes compared with persistent WRF.

Introduction

The association between cardiovascular disease and chronic kidney disease (CKD) has been extensively explored all over the world [1–3] including Japan [4,5]. Similarly it was reported that worsening renal function (WRF) in acute coronary syndrome (ACS) also has a prognostic impact and WRF is an independent predictor of all-cause death from baseline renal function [6,7]. However, the prognostic impact of WRF in Japanese ACS patients is not fully understood, and the clinical implication of improvement in renal function by the time of discharge in ACS patients is also unclear. Therefore, our primary aim was to explore the prognostic impact of WRF that developed during hospitalization in Japanese ACS patients who underwent percutaneous coronary intervention (PCI), and secondary aim was to explore the clinical implications of transient versus persistent WRF.

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Methods

Study population

We established a single hospital cohort, called the Shinken database [8–10], which has been including all new patients visiting the Cardiovascular Institute Hospital, Tokyo, Japan, since June 2004. It has excluded patients with known active cancers and travelers. Until March 2013, 19,994 patients had been enrolled, for whom background characteristics, risk factors, diagnosis of cardiovascular diseases, blood laboratory data, physiological test results, medications, and outcomes were available in the cohort database. Patients were thoroughly investigated through routine clinical examinations. Among the Shinken database, all patients diagnosed with ACS [ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA)] and who underwent successful PCI were identified. The diagnosis of ACS was decided by cardiologists in our hospital based on definitions of the joint committee of the American College of Cardiology (ACC)/American Heart Association (AHA) [11–13]. The population in the present study comprised 616 patients who were hospitalized for ACS and underwent successful PCI at the initial visit. We defined successful PCI as less than 50% stenosis and over thrombolysis in myocardial infarction grade 3 flow in final angiography without intervention-related complications [14]. Patients undergoing regular dialysis treatments were excluded (n = 12). Finally, a total of 604 patients were examined in the present study (Fig. 1). The median follow-up period was 1315 ± 903 days.

Renal function

Blood was sampled daily during the ACS hospitalization to monitor serum creatinine (Cr). Glomerular filtration rate (GFR) was estimated from gender, age, and Cr, using established equations for Japanese patients with CKD: GFR = 194 × $Cr^{-1.094}$ × $age^{-0.287}$ (if male), GFR = 194 × $Cr^{-1.094}$ × $age^{-0.287}$ × 0.739 (if female), CKD was defined as eGFR <60 ml/min/1.73 m^2 [15,16]. WRF development was defined as a peak increase in serum Cr by ≥0.3 mg/dl from the admission for ACS [7,17,18]. We defined persistent WRF as an increase in creatinine during hospitalization of ≥0.3 mg/dl above admission value and maintained until discharge, whereas transient WRF as that WRF resolved at hospital discharge [19,20].

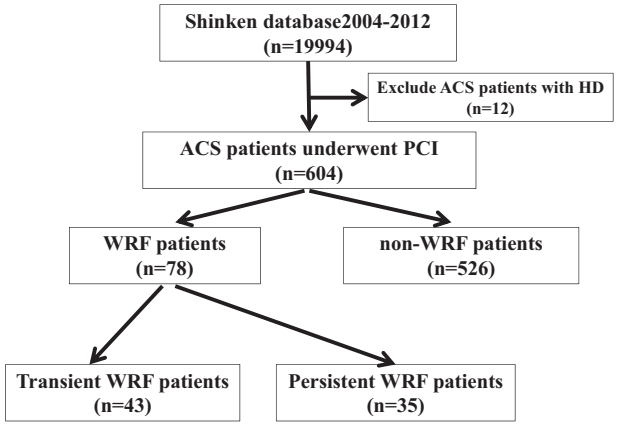

Fig. 1. Patient flow chart of the present study. ACS, acute coronary syndrome; HD, hemodialysis; PCI, percutaneous coronary intervention; WRF, worsening renal function.

Outcomes

The primary outcome was all-cause death. The secondary outcome was major adverse cardiac events (MACE), including all-cause death, myocardial infarction (MI), and target lesion revascularization (TLR). Major adverse cardiac and cerebrovascular events (MACCE) included MACE and stroke. These outcomes were ascertained with medical records or reports on follow-up questionnaires sent to the patients every year. Outcomes were compared with two groups, WRF group and non-WRF group. Similarly in sub-analysis, outcomes were compared with another two groups, persistent WRF group and transient WRF group.

Statistical analysis

All continuous data were expressed as means ± standard deviation and the mean differences between groups were analyzed using Student's t-test. Proportional differences were analyzed using the χ^2 test. Group differences in the temporal change in Cr during the treatment course were assessed using the repeated measures analysis of variance. Kaplan–Meier curves were used to assess the unadjusted all-cause death and MACE and the log-rank test was used to compare these curves. Cox proportional hazards modeling was used to obtain hazard ratios with adjustment for factors potentially associated with patient survival and the risk factors for the WRF development identified in this study. Sub-analysis was examined with similar statistic methods between two groups WRF sustained, or not. A p-value of <0.05 was considered statistically significant. All data were analyzed using SPSS version 19.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics

Baseline characteristics of the study population are shown in Table 1. WRF was observed in 13% (n = 78) of the present population. The WRF group was significantly older (70 ± 12 years vs 63 ± 12 years, $p < 0.001$) and had higher prevalence of CKD (51% vs

Table 1
Baseline characteristics of the study population.

	Non-WRF (n = 526)	WRF (n = 78)	p-value
Age (years)	63 ± 12	70 ± 12	<0.001
BMI (kg/m^2)	25 ± 4	24 ± 4	0.498
Male gender, n (%)	460 (87)	64 (82)	0.189
Diabetes, n (%)	158 (30)	25 (32)	0.718
Hypertension, n (%)	312 (59)	51 (65)	0.307
Dyslipidemia, n (%)	317 (60)	44 (56)	0.517
CKD, n (%)	127 (24)	40 (51)	<0.001
Smoking, n (%)	236 (45)	28 (36)	0.136
Family history, n (%)	77 (15)	8 (10)	0.299
History of MI, n (%)	25 (5)	8 (10)	0.046
History of PCI, n (%)	30 (5)	5 (6)	0.803
History of CABG, n (%)	7 (1)	1 (1)	0.972
LMT disease, n (%)	14 (3)	4 (5)	0.232
Multi-vessel disease, n (%)	133 (25)	26 (33)	0.132
STEMI, n (%)	238 (45)	45 (58)	0.040
Killip more than 2, n (%)	76 (14)	35 (45)	<0.001
IABP, n (%)	38 (7)	24 (31)	<0.001
PCPS, n (%)	4 (1)	6 (8)	<0.001
Intubation, n (%)	13 (2)	10 (13)	<0.001

WRF, worsening renal function; BMI, body mass index; CKD, chronic kidney disease; MI, myocardial ischemia; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LMT, left main trunk; STEMI, ST elevation myocardial ischemia; IABP, intra-aortic balloon pumping; PCPS, percutaneous cardiopulmonary support.

24%, $p < 0.001$), prior history of MI (10% vs 5%, $p = 0.046$), and STEMI (58% vs 45%, $p = 0.040$) than the non-WRF group. There was no significant difference in gender, body mass index, prevalence of classic coronary risk factors, ACS culprit lesion, and past therapeutic history including PCI and coronary artery bypass graft.

Clinical parameters

Clinical parameters of the study population are shown in Table 2. Blood pressure, heart rate at admission, and the volume of contrast medium (WRF: 220 ± 101 ml vs non-WRF: 210 ± 85 ml, $p = 0.456$) at PCI was similar in both groups. Whereas, eGFR (61.1 ± 25.8 ml/min/1.73 m^2 vs 72.7 ± 19.8 ml/min/1.73 m^2, $p < 0.001$), left ventricular (LV) ejection fraction at admission (51 ± 16% vs 60 ± 12%, $p < 0.001$) and one year after discharge (57 ± 13% vs 62 ± 11%, $p = 0.004$) were lower in patients with WRF than non-WRF. In addition, the WRF group had higher blood glucose level (167 ± 78 mg/dl vs 145 ± 60 mg/dl, $p = 0.023$), baseline and peak white blood cell (WBC) count (baseline: 10,891 ± 4701/μl vs 8574 ± 3414/μl, $p < 0.001$; peak: 14,336 ± 6133/μl vs 10,654 ± 3619/μl, $p < 0.001$), baseline and peak C-reactive protein (CRP) (baseline: 2.2 ± 4.2 mg/dl vs 1.0 ± 2.8 mg/dl, $p = 0.024$; peak: 11.9 ± 9.0 mg/dl vs 4.9 ± 5.6 mg/dl, $p < 0.001$), and peak creatine kinase (CK) (2428 ± 2891 IU/L vs 1132 ± 1681 IU/L, $p < 0.001$) than the non-WRF group.

Medications at discharge

Medication use at discharge is presented in Table 2. WRF patients were prescribed more diuretics (33% vs 9%, $p < 0.001$) and fewer statins (59% vs 71%, $p = 0.011$) than non-WRF patients at discharge. Prescription rate of dual antiplatelet therapy (DAPT), beta-blocker, and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) was similar in both groups.

WRF and clinical outcomes

During the follow-up period, there were 32 deaths (cardiac death = 15, non-cardiac death = 17, in-hospital death = 4), 140 MACE, 149 MACCE, 22 MI, 102 TLR, and 37 heart failure admissions among all 604 cohort members. All-cause death, cardiac death, non-cardiac death, MACE, MACCE, MI, and heart failure admission were more commonly observed in WRF group than non-WRF group, while with regard to TLR, there was no significant difference between the two groups (Table 3).

WRF was associated with higher incidence of all-cause death (Fig. 2A) and MACE (Fig. 2B) during the observation period as revealed by Kaplan–Meier curves and log-rank test. Univariate Cox proportional hazards model analysis for all-cause death showed that WRF, age, body mass index, female gender, presence of CKD, LV ejection fraction at admission, blood glucose, the level of inflammatory biomarkers (WBC count, serum CRP level at hospital admission), peak CK, diuretics at discharge, higher Killip level (≥2), and frequency of intra-aortic balloon pumping/percutaneous cardiopulmonary support, intubation were associated with survival (Table 4). Multivariate Cox proportional hazard model analysis revealed that, as well as older age, female gender, and intubation, WRF was an independent determinant of all-cause death (Table 4).

Sub-analysis

In sub-analysis, we analyzed outcomes of transient and persistent WRF patients. Persistent WRF occurred in 35 patients (6%) and transient WRF occurred in 43 patients (7%). There were 19 deaths (in-hospital deaths = 3), 30 MACE, 30 MACCE, 6 MI, 13 TLR, and 16 heart failure admissions. All-cause death, cardiac death, MACE, and MACCE were more commonly observed in persistent WRF group than transient WRF group, while there was no significant difference between the two groups with regard to non-cardiac death, MI, TLR, and heart failure admission (Table 3). Incidences of all-cause death (Fig. 3A) and MACE (Fig. 3B) were higher in patients with persistent WRF than those with transient WRF. Patients with transient WRF had worse outcomes than patients with stable renal function; moreover patients with persistent WRF had worst outcomes of three groups compared with stable renal function (Fig. 4). In addition, we investigated two periods and an increase in Cr during

Table 2
Clinical parameters and medication at discharge of the study population.

	Non-WRF ($n = 526$)	WRF ($n = 78$)	p-value
Systolic blood pressure (mmHg)	136 ± 25	138 ± 34	0.498
Diastolic blood pressure (mmHg)	79 ± 16	80 ± 19	0.411
Heart rate (bpm)	80 ± 50	80 ± 20	0.997
LVEF at admission (%)	60 ± 12	51 ± 16	<0.001
LVEF one year after discharge (%)	62 ± 11	57 ± 13	0.004
eGFR (ml/min/1.73 m^2)	72.7 ± 19.8	61.1 ± 25.8	<0.001
Contrast medium (ml)	220 ± 101	210 ± 85	0.456
Glucose (mg/dl)	145 ± 60	167 ± 78	0.023
Baseline WBC (/μ)	8574 ± 3414	10,891 ± 4701	<0.001
Peak WBC (/μ)	10,654 ± 3619	14,336 ± 6133	<0.001
Baseline CRP (mg/dl)	1.0 ± 2.8	2.2 ± 4.2	0.024
Peak CRP (mg/dl)	4.9 ± 5.6	11.9 ± 9.0	<0.001
Peak CK (IU/L)	1132 ± 1681	2428 ± 2891	<0.001
DAPT, n (%)	500 (96)	71 (95)	0.144
OAC, n (%)	37 (7)	6 (8)	0.833
Statin, n (%)	372 (71)	44 (59)	0.011
Beta-blocker, n (%)	223 (43)	41 (55)	0.091
ACEI/ARB, n (%)	345 (66)	51 (68)	0.972
CCB, n (%)	158 (30)	25 (33)	0.718
Vasodilator, n (%)	132 (25)	27 (36)	0.075
Diuretic, n (%)	49 (9)	25 (33)	<0.001

WRF, worsening renal function; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; WBC, white blood cell; CRP, C-reactive protein; CK, creatine kinase; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 3
Clinical outcomes of acute coronary syndrome patients.

	Non-WRF ($n = 526$)	WRF ($n = 78$)	p-value
All-cause death	13 (2)	19 (24)	<0.001
Cardiac death	4 (0.7)	11 (14)	<0.001
Non-cardiac death	9 (2)	8 (10)	<0.001
In-hospital death	1 (0.2)	3 (4)	<0.001
MACE	110 (21)	30 (38)	0.001
MACCE	119 (23)	30 (38)	0.003
MI	16 (3)	6 (8)	0.035
TLR	89 (17)	13 (17)	0.784
Heart failure	21 (4)	16 (20)	<0.001
	Transient WRF ($n = 43$)	Persistent WRF ($n = 35$)	p-value
All-cause death	6 (14)	13 (37)	0.028
Cardiac death	2 (5)	9 (26)	0.011
Non-cardiac death	4 (9)	4 (11)	0.681
In-hospital death	1 (2)	2 (6)	0.421
MACE	10 (23)	20 (57)	0.013
MACCE	10 (23)	20 (57)	0.013
MI	2 (5)	4 (11)	0.265
TLR	7 (16)	6 (17)	0.854
Heart failure	6 (14)	10 (29)	0.123

WRF, worsening renal function; MI, myocardial infarction; TLR, target lesion revascularization; MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events; Data are expressed as counts (percentage).

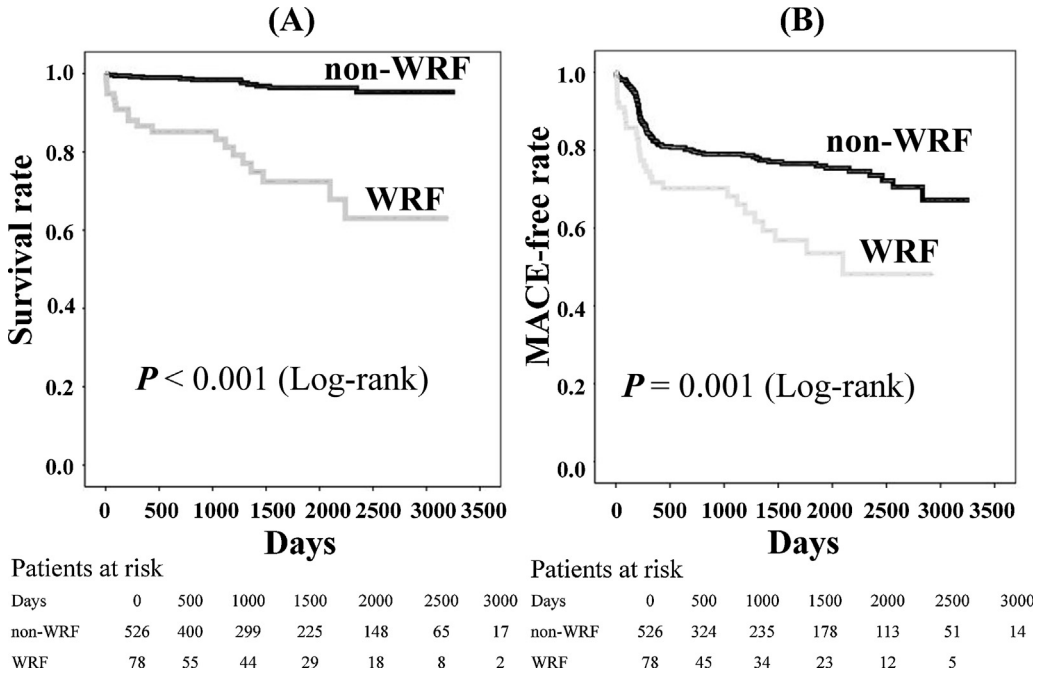

Fig. 2. (A) Kaplan–Meier curves for all-cause death-free survival rate in study population. (B) Kaplan–Meier curves for MACE-free survival rate in study population. MACE, major adverse cardiac events; WRF, worsening renal function.

hospitalization, one period was from admission until peak Cr and another was from peak Cr until discharge. The duration from admission until peak Cr was shorter in transient group than persistent group (4.8 ± 6.3 days vs 11.8 ± 11.7 days, p = 0.001). Whereas, the duration from peak Cr until discharge was longer in the transient group than the persistent group (12.8 ± 13.7 days vs 6.2 ± 7.9 days, p = 0.016). An increase in Cr during hospitalization was lower in the transient group than the persistent group (0.65 ± 0.51 mg/dl vs 0.91 ± 0.72 mg/dl, p = 0.066). Persistent WRF patients had higher peak Cr level at delayed phase in hospitalization than transient WRF patients.

Table 4
Univariate and multivariate analysis for predictors of all-cause mortality.

Univariate	Hazard ratio	95% CI	*p*-value
WRF	10.308	5.090–20.877	<0.001
Age	1.113	1.077–1.150	<0.001
BMI	0.816	0.723–0.922	0.001
Male gender	0.317	0.150–0.669	0.003
CKD	8.12	3.748–17.594	<0.001
LVEF	0.946	0.925–0.968	<0.001
Glucose	1.006	1.001–1.010	0.008
WBC per 1000	1.097	1.012–1.189	0.024
CRP	1.161	1.096–1.229	<0.001
Peak CK per 1000	1.157	1.008–1.327	0.038
Diuretics at discharge	4.964	2.422–10.173	<0.001
Killip more than 2	2.998	1.358–6.618	0.007
IABP/PCPS	4.216	1.995–8.907	<0.001
Intubation	12.414	4.605–33.466	<0.001
Multivariate	**Hazard ratio**	**95% CI**	***p*-value**
WRF	11.663	4.606–29.529	<0.001
Age	1.088	1.044–1.133	<0.001
Male gender	0.337	0.129–0.880	0.026
Intubation	11.725	2.862–48.034	0.001

CI, confidence interval; WRF, worsening renal function; CKD, chronic kidney disease; BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein; CK, creatine kinase; LVEF, left ventricular ejection fraction; IABP, intra-aortic balloon pumping; PCPS, percutaneous cardiopulmonary support.

Discussion

The present study showed that WRF was related to a poor clinical outcome in Japanese ACS patients who underwent PCI. Poor prognosis was independent from baseline renal function, and did not appear to be related to the initial clinical presentation. The main findings of the present study were the following.

(1) WRF was observed in 13% of ACS patients who underwent PCI.
(2) WRF patients were older and had a higher prevalence of CKD and LV dysfunction. WRF was associated with higher inflammatory markers such as WBC count and CRP, and were prescribed more diuretics and less statins at discharge than the non-WRF group.
(3) As well as older age, female gender, and intubation, presence of WRF was an independent predictor of all-cause death.
(4) Incidences of all-cause death and MACE were higher in patients with persistent WRF than those with transient WRF. Persistent WRF patients had higher peak Cr level at delayed phase in hospitalization than transient WRF patients.

AlFaleh et al. reported that WRF was a powerful predictor for in-hospital death and cardiovascular complications in ACS patients [6]. Amin et al. also reported that there was a linear relationship between the extent of WRF and the risk of long-term mortality [7]. Even a small decline in renal function has been reported to be associated with increased mortality, length of hospital stay, and cost in hospitalized patients [21]. WRF was observed in 13% of ACS patients who underwent PCI in this study. A recent study in Saudi Arabia showed that approximately 6% of ACS patients had WRF within 7 days of hospitalization [6]. In the present study, the incidence of WRF in ACS patients appeared to be relatively high. Compared with the study in Saudi Arabia, of the factors that were associated with WRF, such as age, prevalence of CKD, and STEMI, the severity of CKD on admission was higher in our study. It might affect the difference. In addition, the definition of WRF might affect the difference of the incidence of WRF [22,18]. In fact, another recent study which used

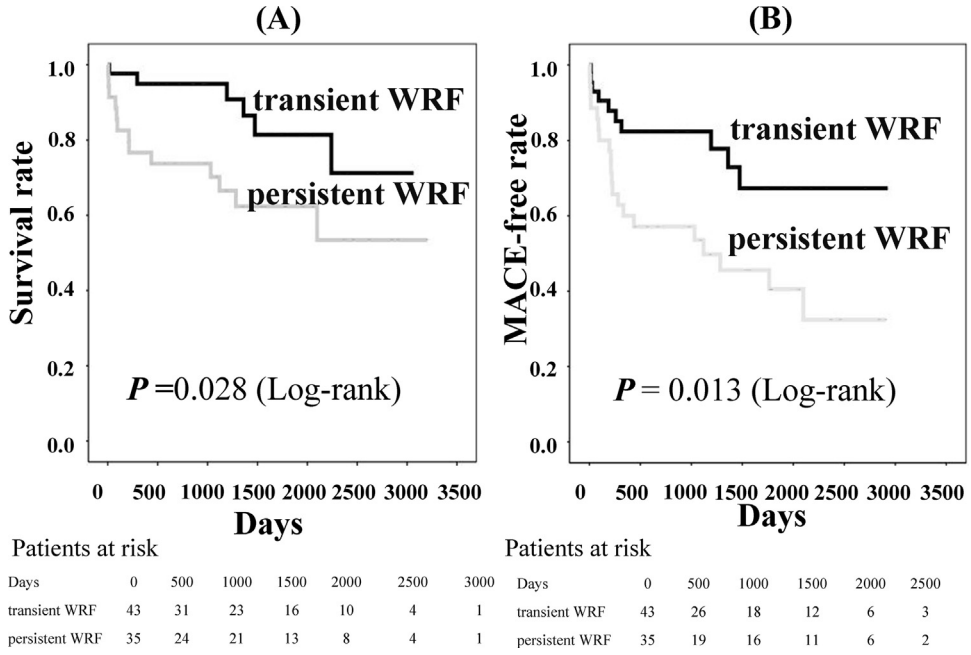

Fig. 3. (A) Kaplan–Meier curves for all-cause death-free survival rate in WRF group. (B) Kaplan–Meier curves for MACE-free survival rate in WRF group. MACE, major adverse cardiac events; WRF, worsening renal function.

the same definition of WRF showed that approximately 19% of AMI patients had WRF [7], which was equivalent with the present study.

In this study, WRF patients were older and had baseline renal insufficiency, and LV dysfunction. The severity of CKD on admission was higher in WRF patients than in non-WRF patients. WRF was associated with higher inflammatory markers, such as WBC count, serum CRP level, and were prescribed more diuretics and fewer statins at hospital discharge than the non-WRF group. In contrast, there was no significant difference in gender, body mass index, prevalence of classic coronary risk factors, the volume of contrast medium at PCI, and prescription of DAPT, beta-blocker, and ACE-I/ARB. Similar to the present study, older age, CKD and LV dysfunction were associated with WRF in Western countries [6,7]. The volume of contrast medium was not significantly different between patients with WRF and without WRF. Anzai et al. previously reported that acute kidney injury (AKI) after STEMI was not associated with the volume of contrast medium [23]. Goldberg et al. also reported that transient and persistent AKI after acute myocardial infarction was not associated with the volume of contrast medium [24]. On the other hand, other factors such as inflammation and neurohormonal activation induced by ACS might aggravate the renal function and result in poor clinical outcomes.

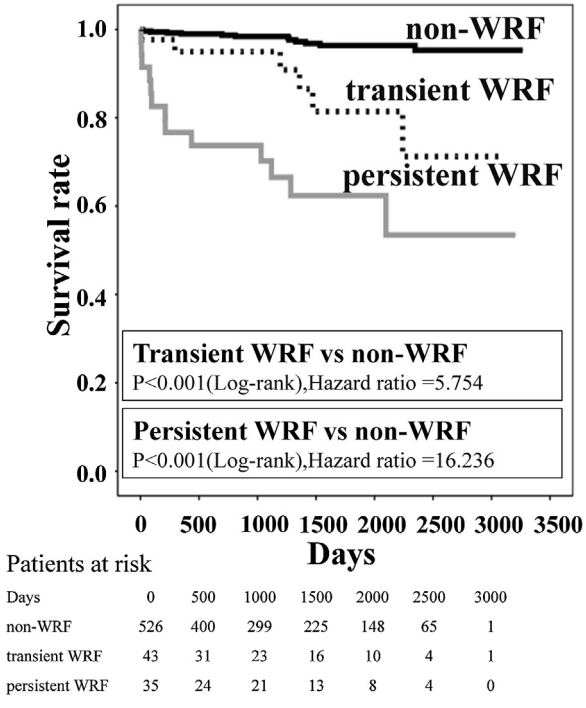

Fig. 4. Kaplan–Meier curves for all-cause death-free survival rate in 3 groups. WRF, worsening renal function.

Multivariate analysis showed that the presence of WRF was an independent predictor of all-cause death, cardiac death, and non-cardiac death. Several potential mechanisms have been proposed to explain the association between WRF and poor prognosis in ACS patients. One mechanism was inflammatory factors, and another mechanism was neurohormonal factors. Both factors might be associated with LV remodeling. Devarajan et al. reported that systemic inflammation was the factor of acute renal dysfunction. Ischemia induces renal endothelial dysfunction followed by intense renal vasoconstriction, overexpression of adhesion molecules, acceleration of inflammatory cells migration, and microvascular congestion. Such inflammatory cascade can be markedly augmented by the generation of pro-inflammatory and chemotactic cytokines, released by inflammatory cells [25]. These findings indicate that activated systemic inflammation after ACS, reflected by higher peripheral WBC count, and serum CRP level in the present study, might be a key player in the induction and even enhancement of WRF. In fact, the relationship between AKI and inflammatory markers was reported previously [23]. The vulnerable myocardium, which consists of necrotic tissue and inflammatory cells, is susceptible to wall stress, resulting in infarct expansion [26]. Systemic inflammation relates to LV remodeling, therefore, inflammation by WRF at ACS may contribute to the poor outcomes at chronic phase. There is the possibility that anti-inflammatory drugs such as statins might prevent WRF by controlling inflammatory cascade. In our study, WRF patients

were prescribed fewer statins at discharge than non-WRF patients. There might be a clinical problem for long-term prognosis in our clinical setting. It was usual practice that there was hesitation to prescribe statins to patients with renal dysfunction, but our recent study reported that statin therapy was associated with reduced all-cause mortality in patients with renal dysfunction and coronary artery disease after PCI [16]. In addition to inflammatory factors, neurohormonal factors in association with LV remodeling, including renin-angiotensin-aldosterone systems and the sympathetic nervous systems, are known to be activated after ACS and to be involved in the cardiorenal syndrome [27,28]. Importantly, among ACS patients developing WRF, beta-blockers and ACE-I/ARBs might improve long-term prognosis by attenuating neurohormonal activation. Amin et al. reported that ACS patients developing WRF who used ACE-I/ARBs had a 37% lower hazard for 4-year mortality [7]. WRF following ACS might possibly serve as a marker of cardiac disease severity. On the other hand, WRF might be an active participant in further cardiovascular injury through the activation of neurohormonal- and immune-mediated pathways. Aggressive use of conventional cardiovascular therapies or new therapeutic strategies might be beneficial for patients with coexistent WRF and ACS.

In sub-analysis, incidence of all-cause death and MACE were higher in patients with persistent WRF than those with transient WRF. In particular, with regard to all-cause death, patients with transient WRF had worse outcome than patients with stable renal function, and patients with persistent WRF had worst outcome of these three groups. Latchamsetty et al. reported that the return to baseline renal function during hospitalization does not appear to protect from cardiovascular risk in ACS patients [19]. While, Aronson et al. reported that persistent WRF portended increased mortality, transient WRF appeared to be associated with a better outcome as compared with persistent WRF as well as non-WRF in acute decompensated heart failure [20]. Therefore, the prognostic impact of persistent and transient WRF in ACS patients is still controversial. In our study, recovery of renal function after WRF had important prognostic implications. Furthermore, persistent WRF patients had higher peak Cr level at delayed phase in hospitalization than transient WRF. Peak Cr level and the time when WRF occurred might be associated with poorer outcomes. We will further analyze in the next study about this point. Our study was of a small sample size, so we could not conclude it, but we should prevent WRF, and optimize renal protection after WRF. Importantly many of the factors that promote WRF such as neurohormonal factors, inflammatory factors, diuretic use and dosing [29], and hemodynamic state [30] are potentially reversible, so initiation of anti-neurohormonal, and anti-inflammatory drugs such as beta-blockers, ACE-I/ARBs, statins, or reduction of diuretics dose or stabilization of hemodynamic state may prevent persistent WRF. Although CKD could not be treated after the ACS, an early therapeutic intervention to prevent WRF might be crucial in improving the clinical outcomes of ACS patients undergoing PCI.

Study limitations

The present study has several limitations. First, this study is based on a single-center cohort, so it does not include a large sample of ACS patients. Our database has been including all new inpatients and outpatients visiting our hospital. Half of the patients are not diagnosed with cardiovascular diseases, and our hospital is located in a place where there is a small population at night time. So, the prevalence of ACS is lower than expected. Since our hospital is a single-department cardiovascular facility, ACS patients with unstable hemodynamic state, such as cardiopulmonary arrest and cardiogenic shock are seldom transferred to our hospital. Therefore, the number of ACS patients with unstable and severe hemodyamic state is supposed to be smaller than expected. A multi-center cohort with a large sample is required to confirm our results. Second, we have no data about renovascular events such as induction of dialysis because our hospital is a single-department cardiovascular facility. It is an important factor about renovascular events when the study about renal function is analyzed. Third, we established a comprehensive database with demographic, physiological, and clinical variables that we adjusted for in the analyses. However, as with all observational studies, it is possible that unmeasured confounders may influence the results. In particular, we have no data available about unsuccessful PCI, which is supposed to influence the outcomes. Lastly, there are various definitions of WRF or AKI and different definitions could alter the results. In the present study, we used WRF defined as an absolute increase in serum Cr of $\geq$0.3 mg/dl, because there are several studies demonstrating that this level of Cr increase has an impact on the outcomes and because this cut-off level is endorsed by the Acute Kidney Injury Network.

Conclusion

WRF had a short-term and long-term prognostic impact in Japanese ACS patients undergoing PCI in association with LV remodeling and enhanced inflammatory response. In WRF patients, persistent WRF had further clinical impacts than transient WRF.

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None.

Conflict of interest

We have no conflict of interest to declare.

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