Usefulness of Calculation of Cardiovascular Risk Factors to Predict Outcomes in Patients With Acute Myocardial Infarction

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Cardiovascular risk factors contribute differently to short-term prognosis of acute myocardial infarction (AMI); hypertension and diabetes increase adverse outcomes, whereas hyperlipidemia, smoking, and obesity seem to paradoxically decrease these in post-MI patients. We aimed to investigate whether a simple calculation of conventional risk factors, PARADOCS (*P*ressure of *AR*tery elev*A*tion, *D*iabetes, *O*besity, *C*holesterol, *S*moking) score, would improve the ability to predict major adverse cardiac and cerebrovascular events (MACCEs) in post-MI patients. Between November 2011 and December 2015, 13,104 patients with diagnosis of AMI were analyzed in this study from Korean AMI Registry − National Institute of Health database. PARADOCS score was calculated as follows: (number of nonparadoxical risk factors − number of paradoxical risk factors) + 3 where nonparadoxical risk factors are hypertension and diabetes, and paradoxical risk factors are hyperlipidemia, smoking, and obesity. PARADOCS score was significantly greater in patients with 1-year MACCEs compared with those without MACCEs (3.43 ± 1.03 vs 2.88 ± 1.11, p <0.001). In Cox proportional hazards model, PARADOCS score was an independent predictor of 1-year MACCEs (hazards ratio 1.23, 95% confidence interval 1.16 to 1.30; p <0.001) after adjusting for confounding variables. In Kaplan-Meier survival curve, patients with greater PARADOCS score had worse clinical outcome. In conclusion, although it needs more validation, a simple calculation of risk factors, PARADOCS score, could provide useful prognostic information of MI patients to clinicians. **(Am J Cardiol 2019;124:857−863)**

Hypertension, diabetes mellitus (DM), hyperlipidemia, obesity, and smoking are strongly associated with development of coronary artery disease. However, these conventional risk factors seem to differently contribute to prognosis of acute myocardial infarction (AMI). In the previous studies, although hypertension and DM increased adverse outcomes in post-MI patients,[1−3] somewhat surprising, hyperlipidemia, smoking, and obesity paradoxically decreased adverse events.[1,4−7] It would be great if a clinician could estimate AMI patient's prognosis with a simple calculation of these traditional risk factors. There is no such a simple and effective tool to satisfy the clinician's need. Therefore, we developed PARADOCS (*P*ressure of *AR*tery elev*A*tion, *D*iabetes, *O*besity, *C*holesterol, *S*moking) score to predict outcomes in post-MI patients with a very simple method. Accordingly, the aim of this study is to evaluate whether PARADOCS score would improve the ability to predict major adverse cardiac and cerebrovascular events (MACCEs) in patients with AMI.

Methods

The Korean AMI Registry is a prospective, open, observational, multicenter, on-line registry of Korean AMI patients established with support of the National Institute of Health since November 2011. Between November 2011 and December 2015, 13,104 patients diagnosed with AMI at admission were recruited into Korean AMI registry − National Institute of Health database. AMI was diagnosed

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Funding: This research was supported by fund 2013-E63005-02 by Research of Korea Centers for Disease Control and Prevention Cheongju/Chungcheongbuk-do.

See page 862 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.06.010

on the basis of characteristic clinical presentation, serial changes on electrocardiography suggesting infarction, and increase in cardiac enzymes.[8] Patient and procedural details were recorded at the time of admission. All data are collected prospectively at each hospital, electronically encrypted, and recorded on an electronic web page-based case report form in National Institute of Health database. This research was supported by a fund (2013-E63005-02) by Research of Korea Centers for Disease Control and Prevention. The protocol was approved by the ethics committee of each participating institution, and all patients gave written informed consent to participate.

Conventional risk factors were defined as follows: hypertension, DM, and hyperlipidemia were defined as previously diagnosed by a physician or receiving medications; obesity was defined as body mass index of ≥ 25; current smoker was defined as active smoker, neither never- nor exsmoker. We classified conventional risk factors into 2 groups: nonparadoxical risk factors (NRFs) and paradoxical risk factors (PRFs). The NRFs are hypertension and DM, and PRFs are hyperlipidemia, obesity, and smoker. PARADOCS score was calculated as follows: (number of NRF − number of PRF) + 3 (Supplementary Figure 1).

The Global Registry of Acute Coronary Events (GRACE) score is well-known risk scoring model for patients across the entire spectrum of acute coronary syndrome and is available for download at the site of GRACE project, and was used to calculate each patient's score.[9]

The 1-year MACCEs were defined as composite of death, nonfatal MI, repeat revascularization, cerebrovascular accident, and rehospitalizations. During the follow-up period, clinical outcome data were obtained by reviewing medical records and interviewing patients by telephone.

Data are expressed as mean ± standard deviation for continuous variables and percentages for categorical variables. All comparisons between the baseline variables were assessed using the Student's *t* test for continuous variables and the Pearson's chi-square test for categorical variables. Univariate analyses were performed to determine the predictors for 1-year MACCEs. Kaplan-Meier survival curve analysis was performed to compare 1-year MACCEs according to PARADOCS groups. Cox proportional hazards model was used to determine the independent predictors of 1-year MACCEs. Variables with p values <0.05 on univariate analysis were selected and entered into Cox proportional hazards analyses to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of 1-year MACCEs. The Hosmer-Lemeshow chi-square—a measure of deviation between observed and predicted outcomes in deciles of predicted risk—was used to evaluate the calibration of the model. For all analyses, a 2-sided p <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics are presented in Table 1. Mean age of the study population was 64.0 ± 12.6 years old. The 1-year MACCEs occurred in 1,422 patients (10.9%) including 815 deaths (6.2%), 218 nonfatal MIs (1.7%), 252 revascularizations (1.9%), 42 cerebrovascular accidents (0.3%), and 324 rehospitalizations (2.5%). Patients with MACCEs were older (p <0.001), and had worse clinical and hemodynamic features. Patients without MACCEs were more likely to be prescribed the guideline-recommended medications.

Among NRFs, hypertension (n = 6,689; 51%) was the most common risk factor, followed by DM (n = 3,751; 28.6%), whereas smoking (n = 5,111; 39.0%) was the most common risk factor among PRFs, followed by obesity (n = 4,413; 34.8%), and the least common conventional risk factor, hyperlipidemia (n = 1,474; 11.2%). NRFs were more prevalent in those with MACCEs, whereas PRFs were more prevalent in patients without MACCEs. The prevalence of number of conventional risk factors and PARADOCS score was presented in Figure 1. Only 12.9% (n = 1,693) had no risk factors identified at the time of index hospitalization. Patients who had 1 or 2 risk factors accounted for more than 2/3 of the patients. The prevalence of PARADOCS score was similar to a normal distribution.

GRACE score was significantly correlated with PARADOCS score (r = 0.438, p <0.001, Figure 2). Patients with more PRF had greater GRACE score than those with NRF or no RF in Figure 2 (p for trend <0.001). Patients were categorized into 3 groups according to the PARADOCS score: $PARADOCS_{Low}$ (0 to 1, n = 1,226), $PARADOCS_{Mid}$ (2 to 3, n = 7,405), and $PARADOCS_{High}$ (4 to 5, n = 4,033). GRACE score significantly increased according to PARADOCS score group in Figure 2 (p for trend <0.001).

PARADOCS score was significantly greater in patients with 1-year MACCEs than without (3.43 ± 1.03 vs 2.88 ± 1.11, p <0.001). In Cox proportional hazards model, PARADOCS score was an independent predictor of 1-year MACCEs (HR 1.23, 95% CI 1.16 to 1.30; p <0.001) after adjusting for confounding variables (Table 2). In Kaplan-Meier survival curve, patients with greater PARADCOS score had significantly greater MACCEs during the follow-up: PARADCOS score 0 = 0%, PARADCOS score 1 = 3.1%, PARADCOS score 2 = 6.4%, PARADCOS score 3 = 9.6%, PARADCOS score 4 = 14.3%, and PARADCOS score 5 = 19.4% (log-rank p <0.001; Figure 3). However, there was no significant relation between the sum of conventional risk factors and 1-year MACCEs: 0 conventional risk factor = 10.6%, 1 conventional risk factor = 10.6%, 2 conventional risk factors = 11.0%, 3 conventional risk factors = 11.6%, 4 conventional risk factors = 9.9%, and 5 conventional risk factors = 7.6% (log-rank p = 0.709; Figure 3). Moreover, patients with more PRF had better clinical outcome than those with NRF or no RF, whereas patients with more NRF had worse clinical outcome than those with PRF or no RF: 2.8% for PRFs ≥2, 6.4% for 1 PRF, 10.6% for no risk factors, 15.4% for 1 NRF, and 20.5% for 2 NRFs (p <0.001). In Cox proportional hazards model, PRF was independently associated with less 1-year MACCEs, whereas NRF was an independent predictor of 1-year MACCEs (Figure 4). Adjusted HRs for 1-year MACCEs were 1 for no risk factors (reference), 0.44 (95% CI 0.29 to 0.65, p <0.001) for PRFs ≥2, 0.79 (95% CI 0.63 to 0.99, p = 0.043) for 1 PRF, 1.23 (95% CI 1.02 to 1.48, p = 0.024) for 1 NRF, and 1.41 (95% CI 1.15 to 1.73, p = 0.001) for 2 NRFs, respectively.

In the Kaplan-Meier survival curves, 1-year MACCEs significantly increased as the PARADOCS score increased: 2.9% in $PARADOCS_{Low}$, 8.2% in $PARADOCS_{Mid}$, and

Table 1
Baseline characteristics of study subject

Variable	Major adverse cardiac and cerebrovascular accident		p value
	No (n = 11,682)	Yes (n = 1,422)	
Age (year)	63.1 ± 12.5	70.8 ± 11.8	<0.001
Men	8796 (75.3%)	890 (62.6%)	<0.001
Body mass index (kg/m^2)	24.1 ± 3.3	23.1 ± 3.5	<0.001
Initial presentation			
Systolic blood pressure (mm Hg)	131.4 ± 28.8	119.7 ± 37.7	<0.001
Heart rate (beats/min)	78.0 ± 18.7	84.4 ± 25.0	0.183
Chest pain	10273 (87.9%)	1022 (71.9%)	<0.001
Dyspnea	2560 (21.9%)	545 (38.3%)	<0.001
ST-elevation myocardial infarction	5602 (48.0%)	698 (49.1%)	0.408
Killip class >1	2178 (18.6%)	704 (49.5%)	<0.001
Previous myocardial infarction	859 (7.4%)	170 (12.0%)	<0.001
Previous angina pectoris	1068 (9.1%)	211 (14.8%)	<0.001
Hypertension*	5776 (49.4%)	913 (64.2%)	<0.001
Diabetes mellitus	3171 (27.1%)	580 (40.8%)	<0.001
Hyperlipidemia†	1357 (11.6%)	117 (8.2%)	<0.001
Current smoker	4720 (40.4%)	391 (27.5%)	<0.001
Obesity‡	4072 (35.7%)	341 (26.9%)	<0.001
PARADOCS score	2.88 ± 1.10	3.43 ± 1.03	<0.001
Left ventricular ejection fraction by volume (%)	52.6 ± 10.7	44.9 ± 13.6	<0.001
Percutaneous coronary intervention	10573 (90.5%)	1158 (81.4%)	<0.001
Multivessel disease	5574 (50.2%)	845 (65.7%)	<0.001
Serum glucose (mg/dl)	165.7 ± 77.7	204.9 ± 110.7	<0.001
Estimated glomerular fraction rate (mL/min)	84.6 ± 38.5	62.0 ± 34.9	<0.001
Peak CK-MB (mg/dl)	108.9 ± 159.8	124.6 ± 198.2	0.004
Total cholesterol (mg/dl)	179.4 ± 45.7	164.3 ± 49.7	<0.001
Low-density lipoprotein cholesterol (mg/dl)	112.9 ± 39.8	101.8 ± 46.0	<0.001
Medical therapy			
Antiplatelet agent	11665 (99.9%)	1394 (98.0%)	<0.001
Beta-blockers	9800 (83.9%)	793 (55.8%)	<0.001
Angiotensin converting enzyme inhibitors/angiotensinogen type II receptor blockers	9290 (79.5%)	756 (53.2%)	<0.001
Statins	10927 (93.5%)	912 (64.1%)	<0.001

PARADOCS = *P*ressure of *AR*tery elev*A*tion, *D*iabetes, *O*besity, *C*holesterol, *S*moking.
Data expressed as mean ± SD or number (percent).
* Defined as previously diagnosed by a physician and/or receiving medication to lower blood pressure.
† Defined as previously diagnosed by a physician and/or receiving lipid-lowering drugs.
‡ Defined as body mass index of 25 or greater.

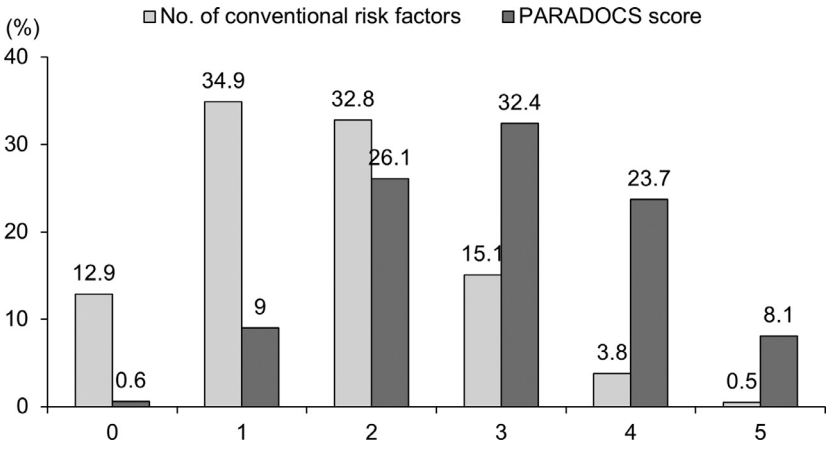

Figure 1. Distribution of number of conventional risk factors and PARADOCS score. PARADOCS = *P*ressure of *AR*tery elev*A*tion, *D*iabetes, *O*besity, *C*holesterol, *S*moking.

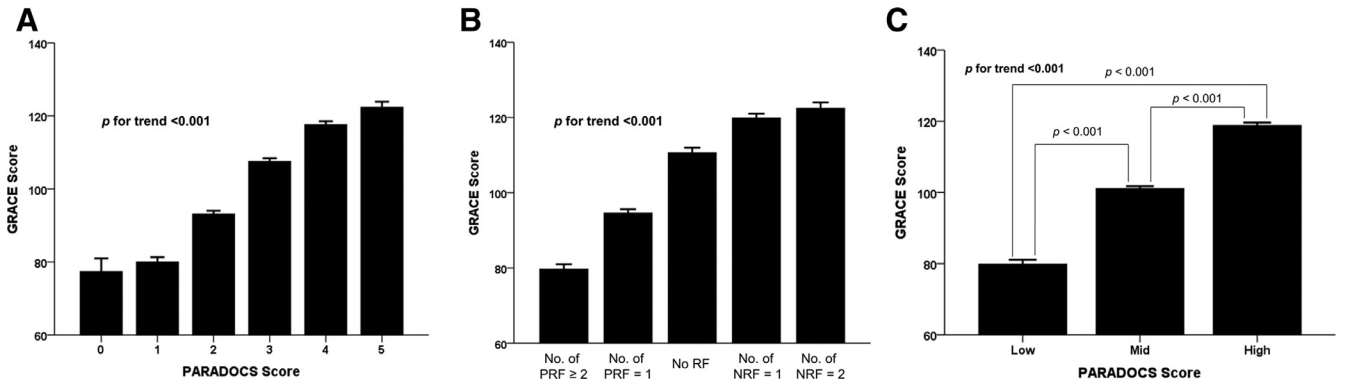

Figure 2. GRACE score according to *(A)* PARADOCS score, *(B)* PRF and NRF, and *(C)* 3 risk groups categorized by PARADOCS score. GRACE = Global Registry of Acute Coronary Events; NRF = nonparadoxical risk factor; PARADOCS = *P*ressure of *AR*tery elev*A*tion, *D*iabetes, *O*besity, *C*holesterol, *S*moking; PRF = paradoxical risk factor.

15.6% in $PARADOCS_{High}$ (long-rank p <0.001; Figure 5). Adjusted HRs for 1-year MACCEs were 1 for $PARADOCS_{Low}$ (reference), 1.94 (95% CI 1.38 to 2.72, p <0.001) for $PARADOCS_{Mid}$, and 2.63 (95% CI 1.85 to 3.72; p <0.001) for $PARADOCS_{High}$, respectively (Figure 6).

Discussion

This observational study clearly demonstrated that PARADOCS score is closely related to 1-year MACCEs in patients with AMI. However, a simple sum of conventional risk factors failed to show any power to predict MACCEs.

There are 3 noteworthy findings in our study. First, to our knowledge, this is the first risk prediction model incorporating PRF and NRF for patients with AMI. Among conventional risk factors, current smoking, hyperlipidemia, and obesity were more prevalent in patients without clinical events after MI. Although they were associated with the development of coronary artery disease, they did not seem to be related to poor prognosis in AMI patients. Many

Table 2
Multivariate predictors of major adverse cardiac and cerebrovascular events during the follow-up

Variables	Hazard ratio	95% confidence interval	p value
Age >70	1.85	1.64 – 2.10	<0.001
Male	1.13	0.99 – 1.27	0.055
Killip class >1	2.72	2.43 – 3.05	<0.001
Previous myocardial infarction	1.27	1.07 – 1.51	0.005
Previous angina pectoris	1.40	1.20 – 1.63	<0.001
Serum creatinine	1.11	1.09 – 1.14	<0.001
Percutaneous coronary intervention	0.68	0.58 – 0.79	<0.001
PARADOCS score	1.23	1.16 – 1.30	<0.001

PARADOCS = *P*ressure of *AR*tery elev*A*tion, *D*iabetes, *O*besity, *C*holesterol, *S*moking.

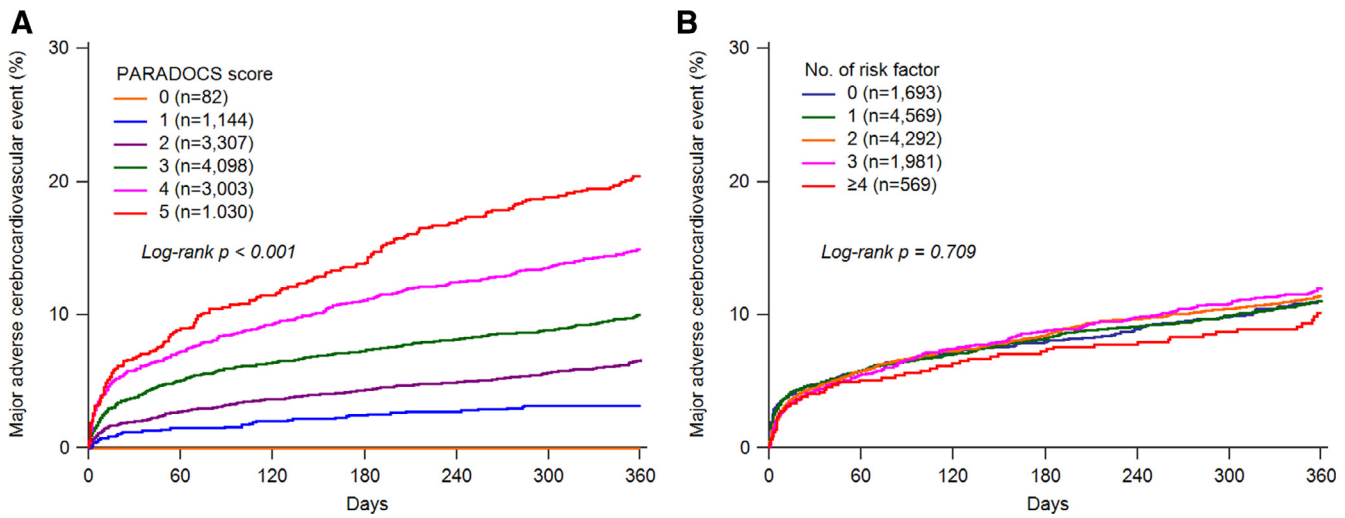

Figure 3. Major adverse cardiac and cerebrovascular events according to *(A)* the PARADOCS score and *(B)* the number of conventional risk factors in Kaplan-Meier survival curve. PARADOCS = *P*ressure of *AR*tery elev*A*tion, *D*iabetes, *O*besity, *C*holesterol, *S*moking.

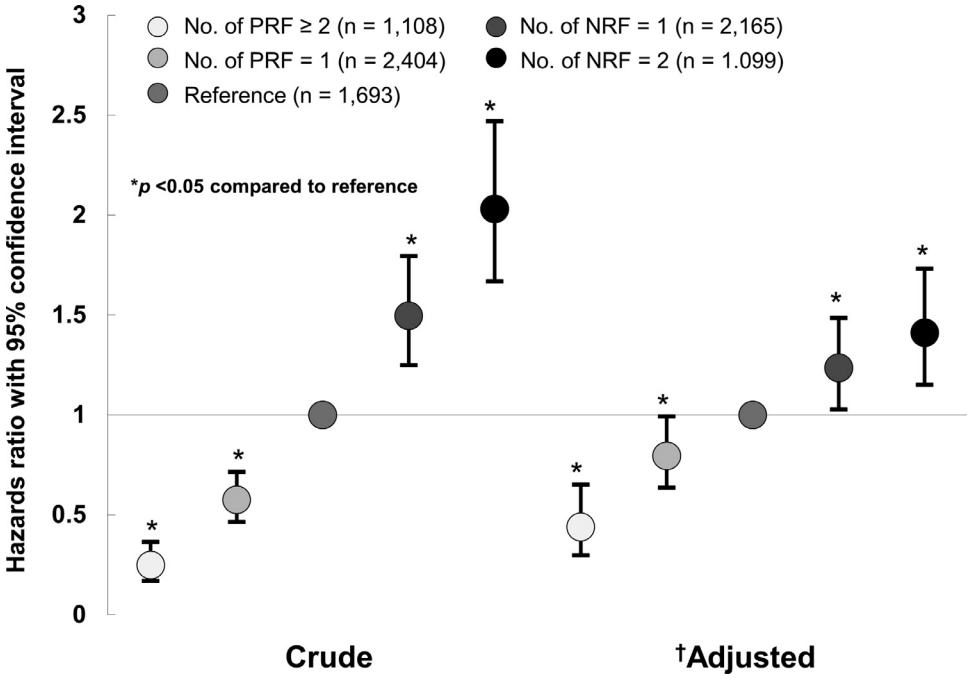

Figure 4. Cox proportional hazard ratio according to the number of PRF and NRF after adjusting for confounding variables. NRF = nonparadoxical risk factor; PRF = paradoxical risk factor. †Adjusted for age, gender, Killip class, previous myocardial infarction, previous angina pectoris, serum creatinine, and percutaneous coronary intervention.

studies attributed the paradoxical phenomenon to confounding effect. Smokers, hyperlipidemic, or obese patients tend to be much younger, have less co-morbidity, and have better hemodynamic condition than non- or exsmokers, people who have low cholesterol levels, and thin people, respectively.[10–13] However, there were conflicting results that showed paradoxical phenomenon did exist even after adjusting baseline characteristics.[6,14–16] Although several plausible interpretations about the paradoxical results have been presented, it is difficult to know the exact reasons for that phenomenon at the moment. Whatever the exact reasons are, paradoxical phenomenon actually exists in our registry.

Second, PARADOCS score is a very simple method that only needs several questions. In the present study, most of high-risk characteristics such as older age, hemodynamic

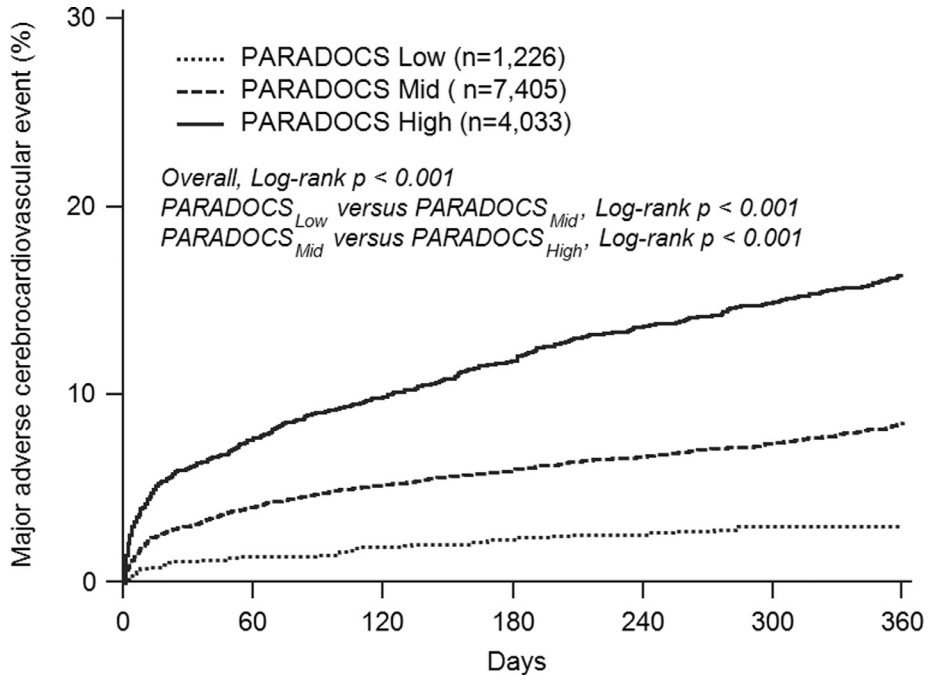

Figure 5. Major adverse cardiac and cerebrovascular events according to the 3 groups categorized by PARADOCS score in Kaplan-Meier survival curve. PARADOCS = *P*ressure of *AR*tery elev*A*tion, *D*iabetes, *O*besity, *C*holesterol, *S*moking.

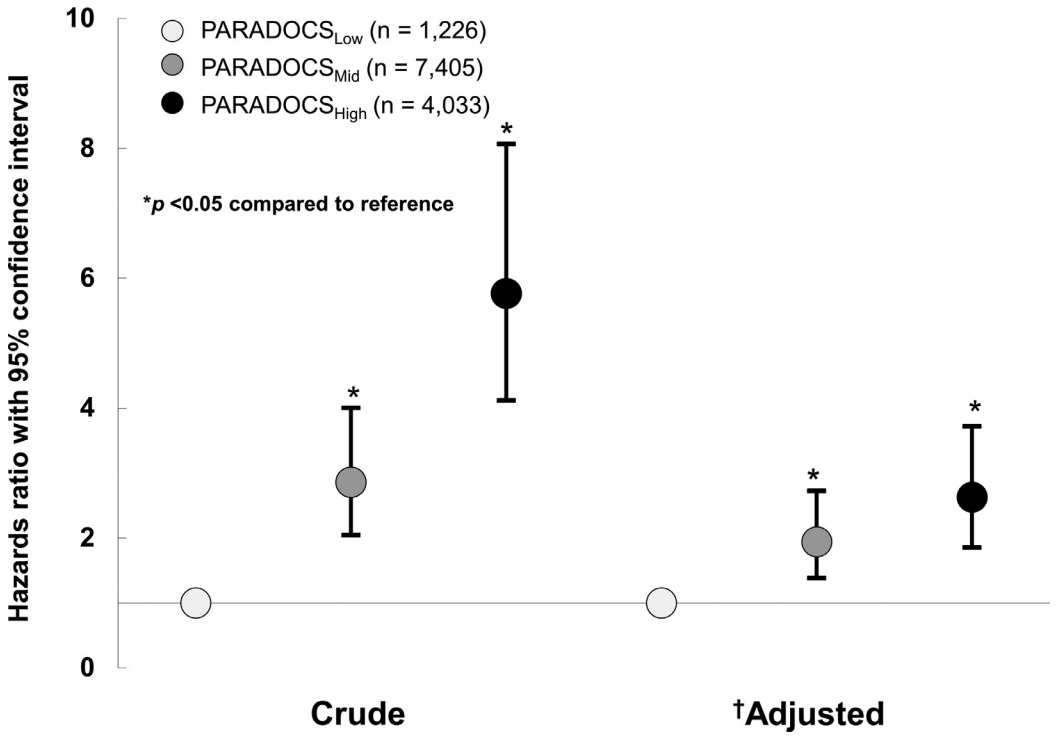

Figure 6. Cox proportional hazard ratio according to 3 groups categorized by PARADOCS score after adjusting for confounding variables. PARADOCS = *P*ressure of *AR*tery elev*A*tion, *D*iabetes, *O*besity, *C*holesterol, *S*moking. †Adjusted for age, gender, Killip class, previous myocardial infarction, previous angina pectoris, serum creatinine, and percutaneous coronary intervention.

instability, low cardiac output, renal dysfunction, and complex lesion subsets were associated with poor prognosis. With these various parameters, it could be possible to create a complex scoring model to predict prognosis for post-MI patients. However, it is not practical to use complex scoring system in emergent setting, because it requires laboratory, echocardiographic and angiographic data.

Finally, PARADOCS score has robust prognostic accuracy in stratifying patients for clinical outcomes in real-world practice. In the present study, survival curves of the patients were so well discriminated according to their PARADOCS scores that the curves did not show any overlapping regions among PARADOCS scores. In contrast, a simple sum of the conventional risk factors a patient had could not show any discriminating power in predicting clinical events. In addition, PARADOCS score showed excellent correlation with GRACE score and MACCEs. Therefore, we believe that PARADOCS score could be an excellent risk prediction model in emergent clinical settings and applied to every AMI patients, because it is basic question to ask at the emergency department whether they have conventional risk factors or not. Accordingly, clinicians can readily estimate patients' prognosis after AMI by simple calculation of PARADOCS scores.

Our study had several potential limitations. First, because our study is not a randomized and controlled study, we cannot completely exclude the possibility of residual confounding factors that were not available in our registry. Therefore, our results should only be regarded as hypothesis generating. Second, although paradoxical phenomenon was observed in our registry, it is not certain that PARADOCS score could be applied to other study populations or other countries. Accordingly, PARADOCS score needs more validation in other registries for widespread use. Despite some limitations of this study, they should not undermine our strength of this study that includes representative of patients encountered in day-to-day clinical practice.

In conclusion, conventional risk factors that were associated with the development of coronary artery disease seemed to differently affect prognosis once AMI developed. A simple calculation of these risk factors, PARADOCS score, could provide useful prognostic information to clinicians.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.06.010.

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