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Clinical impact of estimated plasma volume status and its additive effect with the GRACE risk score on in-hospital and long-term mortality for acute myocardial infarction

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ABSTRACT

Background: Estimated plasma volume status (ePVS) is a well-validated prognostic indicator in heart failure. However, it remains unclear whether ePVS has prognostic significance in patients with acute myocardial infarction (AMI). Moreover, there is no available information on its additive effect with the Global Registry of Acute Coronary Events (GRACE) risk score in AMI patients.
Methods: Data were obtained from the Osaka Acute Coronary Insufficiency Study (OACIS) registry database. Patients whose data were available for ePVS derived from Hakim's formula and the GRACE risk score were studied. The primary endpoints were in-hospital and 5-year mortality.
Results: Of 3930 patients, 206 and 200 patients died during hospitalization and 5 years after discharge, respectively. After adjustment, ePVS remained an independent predictor of in-hospital death (OR:1.02, 95% CI: 1.00–1.04, p = 0.036), and 5-year mortality(HR:1.03, 95% CI: 1.01–1.04, p < 0.001). An additive effect of ePVS with the GRACE risk score was observed in predicting the 5-year mortality with an area under the receiver operating characteristic curve (AUC) from 0.744 to 0.763 (p = 0.026), but not in-hospital mortality (the AUC changed from 0.875 to 0.875, p = 0.529). The incremental predictive value of combining ePVS and the GRACE risk score for 5-year mortality was significantly improved, as shown by the net reclassification improvement (NRI:0.378, p < 0.001) and integrated discrimination improvement (IDI:0.014, p < 0.001).
Conclusions: In patients with AMI, ePVS independently predicted in-hospital and long-term mortality. In addition, ePVS had an additive effect with the GRACE risk score on long-term mortality. Therefore, ePVS may be useful for identifying high-risk subjects for intensive treatment.

1. Introduction

Despite the advances in treatment (such as reperfusion therapy in the acute phase and administering evidence-based medications for secondary prevention with statins, renin-angiotensin system blockers and beta-blockers), acute myocardial infarction (AMI) is still associated with significant mortality. Hence, identifying high-risk patients and those who would benefit from more aggressive treatment, is essential for the management of AMI. The Global Registry of Acute Coronary Events (GRACE) risk score is a powerful predictor of prognosis after AMI [1–3]. However, this system

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reflects only certain pathophysiological dimensions related to outcomes in AMI.

Congestion is one of the factors associated with worse outcomes and therefore could be a therapeutic target for improving the prognosis of patients with AMI. However, congestion can be difficult to quantify noninvasively. The total volume of blood plasma in the intravascular compartment is known as the plasma volume (PV), and the estimated plasma volume status (ePVS) could be simply calculated using a weight- and hematocrit-based formula. ePVS has been shown to be a well-validated prognostic indicator associated with morbidity and mortality in heart failure [4–8]. On the other hand, it remains unclear whether ePVS has prognostic significance in patients with AMI. Therefore, we studied the prognostic significance of ePVS in AMI patients, and to the best of our knowledge, this is the first study to investigate this. However, the predictive value of ePVS was expected to be insufficient because it only reflects a certain aspect related to outcomes in AMI. We also demonstrated the clinical significance of ePVS by assessing whether it has an incremental prognostic information to the GRACE risk score.

Therefore, the purpose of this study was to investigate the prognostic significance of ePVS and additional prognostic value of ePVS to the GRACE risk score in AMI patients.

2. Methods

2.1. The OACIS registry and study patients

The Osaka Acute Coronary Insufficiency Study (OACIS) is a prospective, multicenter, observational study in which 25 collaborating hospitals (1 university hospital, 24 regional core centers) in the Osaka region of Japan recorded demographic, procedural, and outcome data, and collected blood samples from patients with AMI (UMIN-CTR ID: UMIN000004575). A detailed description of the OACIS has been published [9–12]. Briefly, patients hospitalized within 1 week of AMI onset were prospectively registered and followed-up for 5 years. AMI was diagnosed if $\geq$2 of the following 3 criteria were met: (1) clinical history of central chest pressure, pain, or tightness lasting $\geq$30 min, (2) ST-segment elevation >0.1 mV in at least 1 standard or 2 precordial leads, and (3) a rise in serum creatine phosphokinase concentration to more than twice the normal laboratory value.

This registry complied with the Declaration of Helsinki, and the study protocol was approved by the ethics committee of each participating hospital.

In this present study, 11,072 consecutive patients registered in the OACIS between April 1998 and September 2012 were included. All patients provided written informed consent to participate in this study.

2.2. Data collection

All the collaborating hospitals were encouraged to enroll consecutive patients with AMI. We prospectively collected data from research cardiologists and trained research nurses using a specific reporting form, including demographic and procedural data. Peripheral blood was sampled on the admission day. Venous plasma concentrations of glucose, lipids, lipoproteins, serum creatinine, HbA1c, red blood cell counts were determined in the clinical laboratory department using standard biochemical techniques. The patient variables presented in the tables were extracted from the OACIS registry database in this study.

2.3. Estimated plasma volume status

The actual PV was calculated using data on admission with the following equation, which has been previously validated [13]:

$$\text{aPV} = (1 - \text{hematocrit}) \times [\text{a} + (\text{b} \times \text{weight (kg)})]$$

where hematocrit is a fraction, a = 1,530 in male patients and a = 864 in female patients, and b = 41 in males and b = 47.9 in females.

The ideal PV (iPV) was calculated from the following well-established formula based solely on weight [14]:

$$\text{iPV} = \text{c} \times \text{weight(kg)}$$

where c = 39 in male patients and c = 40 in female patients.

ePVS, an index of the degree to which patients have deviated from their iPV, was subsequently calculated from the following equation [4]:

$$\text{ePVS} = [(\text{aPV} - \text{iPV})/\text{iPV}] \times 100\%$$

PV expansion was defined as ePVS of >0% [7].

2.4. Calculation of the GRACE risk score

The GRACE risk prediction tool has been described elsewhere [1]. The GRACE score was derived from eight variables that were recorded upon hospital admission (age, heart rate, systolic blood pressure, serum creatinine concentration, Killip classification, cardiac arrest, presence of ST-segment deviation, and elevated cardiac enzymes/markers) and was calculated for each patient.

2.5. Outcomes and follow-up

Clinical events were obtained 3 and 12 months after discharge for AMI and annually thereafter for up to 5 years. Survival data were obtained by dedicated coordinators and investigators through direct contact between patients and their physicians at the hospital in outpatient settings, or by telephone interview of their family, or by mail. In-hospital mortality and 5-year mortality were the primary endpoint of the study.

2.6. Statistical analysis

Continuous variables are expressed as the mean ± SD with a normal distribution and otherwise the median values and interquartile ranges (25–75 percentiles). Categorical data are presented as absolute values and/or frequencies. The baseline group characteristics were compared using a *t*-test, and the chi-square or Fisher's exact test was used for categorical variables. The impact of ePVS on in-hospital and 5-year mortality was assessed as odds ratios (ORs) and their 95% confidence intervals (CIs) using a logistic regression analysis, and the hazard ratios (HRs) and 95% CI using Cox regression analysis, respectively. To reduce the confounding effects of variations in patient backgrounds, the variables examined in these analyses were age, sex, presence of STEMI, Killip classification, systolic blood pressure, heart rate, coronary risk factors (diabetes, hypertension, dyslipidemia, smoking, previous myocardial infarction, prior intervention, and prior coronary artery bypass grafting (CABG)), history of atrial fibrillation, multivessel disease, emergency percutaneous coronary intervention (PCI), laboratory data (blood sugar, serum creatinine, low-density lipoprotein (LDL) cholesterol, HbA1c, hematocrit, and peak creatinine phosphokinase levels), and GRACE risk score. Among the patients who were discharged, the use of the following drugs was also incorporated into the models: antiplatelets, anticoagulants, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II-receptor blockers, statins, and diuretics. The Kaplan-Meier

method was used to estimate the event rates; the differences between patients with and without PV expansion were assessed using the log-rank test. In order to assess the predictive ability of ePVS, we performed subgroup analysis and developed a forest plot. P value for interaction was calculated using the interaction term for ePVS and each subgroup based on Cox regression for in-hospital and 5-year mortality. Missing data were not complemented, and patients with missing data were automatically excluded in the multivariable analyses. The predictive values of ePVS and a combination of ePVS and the GRACE risk score were estimated by comparing the areas under the receiver operating characteristic (ROC) curve. A binary logistic regression model was used to calculate a probability of ePVS + GRACE risk score. Then area under the curve of the variable was calculated using receiver operating characteristic (ROC) curve analysis. DeLong's test was used to compare the area under the curve (AUC) from each model. Moreover, the increased discriminatory value of ePVS was further examined by the net reclassification improvement (NRI) and integrated discrimination improvement (IDI). The NRI evaluates changes in estimated prediction probabilities that imply a change from one category to another between different models. In this analysis, we classified the probability of mortality for 5 years into three categories of < 4%, 4 to 11%, and > 11%, referring to the GRACE-predicted risk of mortality among the study patients. Statistical significance was set as $p < 0.05$. All statistical analyses were carried out using the EZR, version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [15].

3. Results

3.1. Clinical characteristics

Among the 11,072 patients registered in the OACIS registry, 7,142 patients were excluded because of the lack of data required for calculating the GRACE risk score or ePVS. As a result, 3,930 patients were included in this study (Fig. 1).

The mean calculated aPV, iPV, and ePVS were 2,390 ± 353 ml, 2,464 ± 510 ml, and 1 ± 13%, respectively. The number of patients with and without PV expansion was 1,697 (43%) and 2,233 (57%) patients, respectively. The distribution of ePVS in the study patients is shown in Fig. 2.

The baseline patient characteristics stratified with and without PV expansion are presented in Table 1. There were significant differences between patients with and without PV expansion in terms of age, sex, patient demographics, presence of STEMI, Killip classification, hypertension, dyslipidemia, smoking, atrial fibrillation and prior CABG, culprit vessel, multivessel disease, and emergency PCI. Laboratory data on admission including blood sugar, serum creatinine, LDL cholesterol, HbA1c, and hematocrit levels differed between the two groups. At discharge, there were also significant differences in the prescribed medication, such as ACE inhibitors and/or angiotensin receptor blockers, statins, antiplatelets, and diuretics, between the two groups. In addition, patients with PV expansion had a higher GRACE risk score than those without PV expansion.

An almost similar trend of baseline characteristics was observed in both groups, when the study patients were divided into two groups according to the tertiles of the GRACE risk score: first and second tertiles $\leq$ 139 (low-risk group) and highest tertile $\geq$ 140 (high-risk group) (Table 1).

3.2. In-hospital and 5-year mortality

Among the 3,930 patients, 206 patients suffered in-hospital death. In-hospital mortality rates were significantly higher in patients with PV expansion (8.2%; 139/1,697) than in those without PV expansion (3.0%; 67/2,283). The multivariate logistic regression analysis showed that each 1% increase in ePVS was linked to a 2.1% estimated risk of in-hospital mortality (OR: 1.02, 95% CI: 1.00–1.04, p = 0.036) in the whole patient population. ePVS was also associated with in-hospital death, but was not considered an independent predictor in the low-risk (OR: 1.03, 95% CI: 0.98–1.12, p = 0.331) and high-risk groups (OR: 1.02, 95% CI: 0.99–1.04, p = 0.087), respectively.

Among the 3,724 patients who were discharged, 200 died during the 5-year follow-up period (138/1,558 in patients with PV expansion, 62/2,166 in those without PV expansion). The time-to-event curves for the 5-year mortality among patients who were discharged alive are shown in Fig. 3. The incidence of 5-year all-cause death was significantly higher in patients with PV expansion

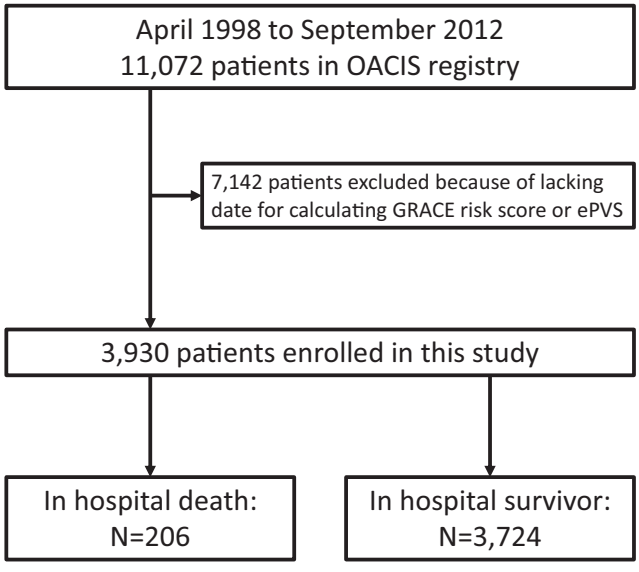

Fig. 1. Patient selection flowchart. OACIS, Osaka Acute Coronary Insufficiency; GRACE, Global Registry of Acute Coronary Events; ePVS, estimated plasma volume status.

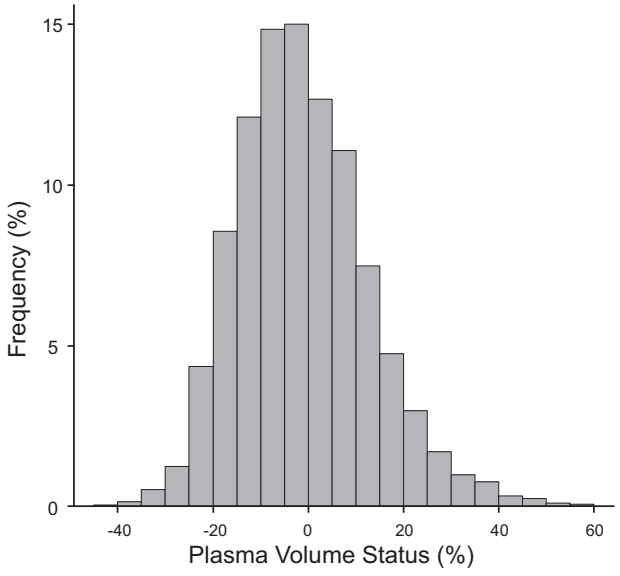

Fig. 2. Distribution of estimated plasma volume status in the study patients.

Table 1
Clinical Characteristics in study patients with and without PV expansion.

	All study patients			Low-risk group			High-risk group		
	PV expansion (+) n = 1697	PV expansion (-) n = 2233	P value	PV expansion (+) n = 861	PV expansion (-) n = 1789	P value	PV expansion (+) n = 836	PV expansion (-) n = 444	P value
Age (years)	73 ± 10	62 ± 12	<0.001	67 ± 9	60 ± 11	<0.001	79 ± 8	73 ± 9	<0.001
Male	68%	82%	<0.001	76%	85%	<0.001	60%	72%	<0.001
Weight (kg)	49.5 ± 6.4	51.2 ± 5.9	0.024	57.2 ± 8.9	69.9 ± 12.2	<0.001	52.1 ± 10.1	66.0 ± 11.3	<0.001
KIllip class (I/II/III/IV)	76%/10%/7%/7%	85%/6%/4%/5%	<0.001	96%/4%/0%/0%	95%/4%/1%/0%	0.67	56%/16%/14%/14%	45%/15%/18%/22%	<0.001
Heart rate (beats/min)	79 ± 22	81 ± 21	0.052	75 ± 18	79 ± 18	0.052	84 ± 25	89 ± 30	0.001
Systolic pressure (mmHg)	132 ± 30	141 ± 31	<0.001	132 ± 30	141 ± 31	<0.001	124 ± 31	124 ± 33	0.89
STEMI	83%	87%	<0.001	84%	87%	0.063	82%	86%	0.054
History									
Hypertension	69%	61%	<0.001	64%	60%	0.112	74%	64%	<0.001
Diabetes Mellitus	32%	31%	0.432	31%	33%	0.314	34%	36%	0.446
Dyslipidemia	36%	48%	<0.001	40%	50%	<0.001	33%	40%	0.01
Smoking	51%	68%	<0.001	51%	68%	<0.001	39%	55%	<0.001
Atrial fibrillation	8%	6%	0.005	4%	4%	0.959	12%	13%	0.638
Myocardial infarction	11%	9%	0.051	8%	8%	0.746	14%	14%	0.878
Prior PCI	10%	9%	0.159	9%	9%	0.738	11%	10%	0.464
Prior CABG	3%	1%	<0.001	2%	1%	0.017	4%	2%	0.059
Medication at discharge	(n = 1558)*	(n = 2166)*							
ACEI or ARB	74%	78%	0.001	76%	80%	0.015	71%	70%	0.768
β-blocker	64%	67%	0.122	64%	67%	0.127	65%	68%	0.647
Statin	55%	69%	<0.001	59%	72%	<0.001	51%	56%	0.121
Antiplatelet	94%	92%	0.029	95%	93%	0.067	94%	91%	0.102
Anticoagulant	14%	17%	0.084	12%	14%	0.143	17%	27%	<0.001
Diuretics	32%	24%	<0.001	22%	19%	0.058	45%	47%	0.552
Coronary angiography	96%	98%	<0.001	99%	99%	0.86	94%	97%	0.008
Culprit artery			0.047			0.047			0.19
LMT	3%	2%		1%	1%		5%	6%	
LAD	44%	48%		44%	48%		42%	45%	
LCx	16%	15%		16%	15%		16%	15%	
RCA	38%	31%		39%	31%		37%	30%	
Multivessel	51%	42%	<0.001	42%	38%	0.058	60%	57%	0.226
Emergent PCI	90%	95%	<0.001	93%	96%	<0.001	87%	92%	0.01
Laboratory data on admission									
Blood sugar (mg/dl)	175 ± 78	180 ± 80	0.033	161 ± 65	172 ± 70	0.033	189 ± 88	215 ± 105	<0.001
Creatinine (mg/dl)	0.9 (0.7–1.2)	0.8 (0.8–1.0)	<0.001	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.537	1.0 (0.8–1.6)	1.0 (0.8–1.3)	0.013
LDL cholesterol (mg/dl)	110 ± 36	134 ± 39	<0.001	115 ± 35	136 ± 39	<0.001	105 ± 35	123 ± 35	<0.001
HbA1c(%)	6.3 ± 1.2	6.6 ± 1.6	<0.001	6.3 ± 1.3	6.6 ± 1.6	<0.001	6.2 ± 1.1	6.6 ± 1.5	<0.001
Hematocrit(%)	35 ± 5	46 ± 12	<0.001	36 ± 4	44 ± 4	<0.001	34 ± 5	43 ± 4	<0.001
Peak CK (U/L)	1592 (807–3229)	2095 (981–4111)	<0.001	1517 (755–3015)	2000 (949–3941)	<0.001	1650 (840–3533)	2313 (080–4953)	<0.001
Length of Hospital stay (days)	19 (15–25)	19 (14–28)	0.571	18 (14–23)	18 (15–23)	0.132	21 (15–36)	25 (16–36)	0.004
GRACE risk score	141 ± 31	116 ± 30	<0.001	117 ± 16	105 ± 21	<0.001	166 ± 22	162 ± 20	0.002

Data are presented as the mean value ± SD, the median (25–75 percentiles) or percentage of patients. PV, plasma volume; STEMI, ST elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEI, angiotensin-converting enzyme inhibiter; ARB, angiotensinⅡ receptor blocker; LMT, left mein trunk; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; CK, creatine kinase; GRACE, Global Registry of Acute Coronary Events *patients wth survival discharge.

than in those without PV expansion in all study populations and low-risk and high-risk subgroups. In the multivariable Cox regression analysis, the adjusted HRs of ePVS for 5-year mortality were 1.03 (95% CI: 1.01–1.04, p < 0.001), 1.05 (1.02–1.10, p < 0.001), and 1.03 (1.01–1.05, p = 0.002) in all study populations and the low-risk and high-risk groups, respectively. When ePVS was analyzed as a categorical variable, consistent results were obtained: the adjusted HRs of PV expansion for 5-year mortality were 1.71 (95% CI: 1.16–2.52, p = 0.006), 2.19 (1.22–3.92, p = 0.008), and 1.67 (1.02–2.75, p = 0.04) in all study populations and the low-risk and high-risk groups, respectively.

To evaluate the heterogenecity of ePVS predicting in-hospital and 5-year mortality, we performed subgroup analysis (Fig. S1). There were no significant interactions between each variable and ePVS except for the history of diabetes for 5-year mortality, suggesting that ePVS may have consistent predictive ability for in-hospital and 5-year mortality across various subgroups.

3.3. Effect of combining ePVS and the GRACE risk score

The combined value of ePVS and the GRACE score for predicting the in-hospital and the long-term mortality was assessed. For predicting in-hospital mortality, the AUC of the GRACE risk score alone was 0.875, and ePVS added no additional value to the GRACE risk score (the AUC of the combination of ePVS and the GRACE risk score was 0.875, p = 0.529). On the other hand, for predicting the 5-year mortality, the AUC of the GRACE risk score alone was 0.744 and when ePVS was added to the GRACE risk score, the AUC increased to 0.763 (p = 0.026) (Fig. 4).

Furthermore, the potential for the clinical benefit achieved when ePVS was added to the GRACE risk score was assessed using the category-based NRI. Using 4% and 11% as arbitrary thresholds to define patients at low, intermediate, and high risk, ePVS achieved an NRI of 0.102 (95% CI, 0.031-0.173; p = 0.004). Of 3,524 patients without events, 367 were correctly downgraded

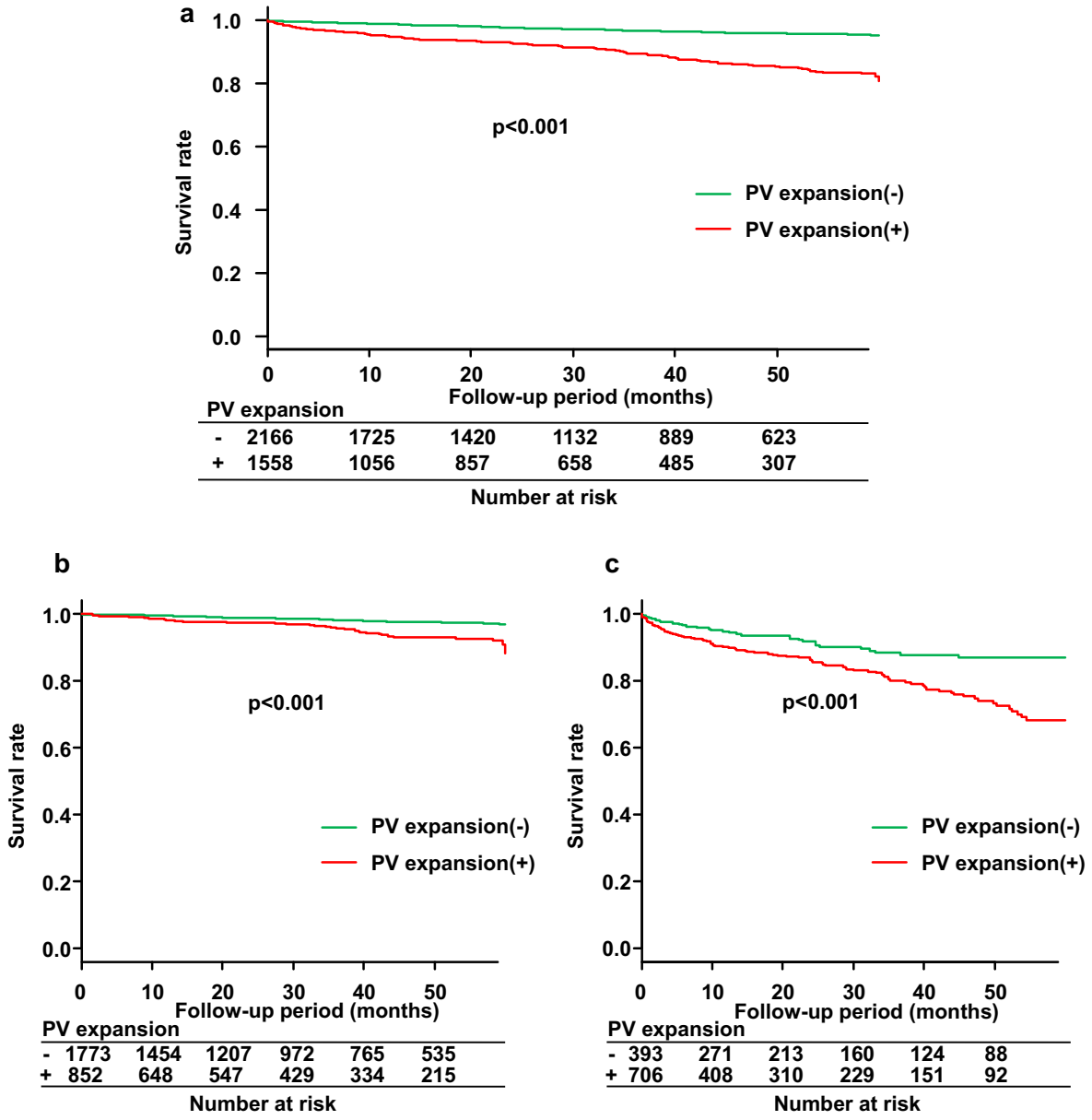

Fig. 3. Kaplan-Meier survival estimates in (a) all study patients and (b) low-risk group and (c) high-risk group. The numbers of patients at risk are summarized below the figures PV, plasma volume.

and 289 were wrongly upgraded by at least one category by ePVS, whereas of 200 patients with an event, 34 were correctly upgraded, and 18 were wrongly downgraded (Table 2). Additionally, the continuous NRI was 0.378 (95% CI, 0.236–0.519; $p < 0.001$), and the IDI was calculated as 0.014 (95% CI, 0.008–0.021; $p < 0.0001$).

4. Discussion

In this study, we investigated the impact of ePVS on in-hospital and long-term (5-year) mortality of all-comer AMI patients. To the best our knowledge, no previous study has investigated the prognostic impact of ePVS on AMI. We observed that ePVS measured on admission was associated with in-hospital mortality and 5-year mortality. In addition, ePVS also added discriminatory predictive value to the GRACE risk score for predicting long-term mortality, whereas it had no additional value to the GRACE risk score for predicting in-hospital death.

Risk stratification is important for AMI patients because of the great variability in individual prognosis. Many models have been proposed to predict the risk of mortality [16–18], of which the GRACE risk score is the most commonly used and recommended by current guidelines [19,20]. However, the original models could only estimate the risk of short- to mid-term prognosis. Although the GRACE risk score was updated to evaluate the short- and long-term risks, the evidence for its long-term prognostic accuracy is relatively weak [21,22]. Thus, the scoring system needs to determine another additional variable to enhance the long-term predictive value.

ePVS is one of the markers for systemic congestion, which is calculated simply using the body weight and hematocrit level. Several studies have shown that ePVS is a well-validated prognostic indicator associated with morbidity and mortality in heart failure [4–8]. Higher ePVS values were also associated with worse outcomes and could help refine risk stratification in patients after CABG [23]. In patients with AMI, heart failure in the acute phase was shown to

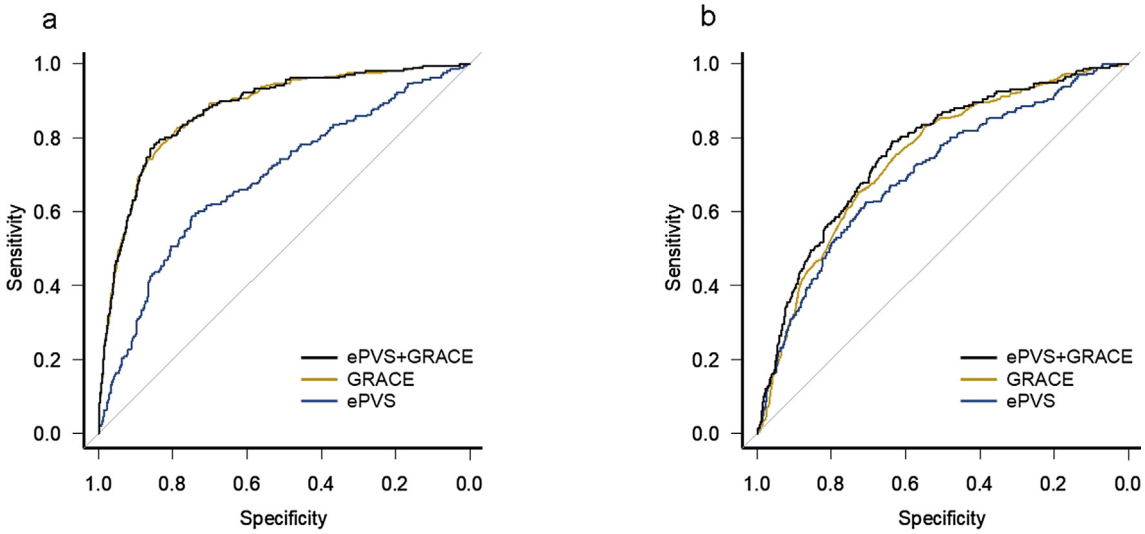

Fig. 4. Receiver operating characteristic (ROC) curve analysis for predicting (a) in-hospital death and (b) 5-year mortality. (a) For predicting in-hospital mortality, the area under the curve (AUC) of the GRACE risk score alone was 0.875. When ePVS was added to the GRACE risk score, the AUC became 0.875 (p = 0.529). (b) For predicting the 5-year mortality, the AUC of the GRACE risk score alone was 0.744. When ePVS was added to the GRACE risk score, the AUC became 0.763 (p = 0.026) with statistical significance. GRACE, Global Registry of Acute Coronary Events; ePVS, estimated plasma volume status.

Table 2
Reclassification for the risk of 5-year mortality when ePVS was added to GRACE risk score.

Non-survivor				
		GRACE risk score adjusted by ePVS		
GRACE risk score	<4%	4–11%	>11%	Total
<4%	1702	154	2	1868
4–11%	284	962	123	1369
>11%	0	83	204	287
Total	1986	1199	329	3524
Survivor				
		GRACE risk score adjusted by ePVS		
GRACE risk score	<4%	4–11%	>11%	Total
<4%	25	7	0	32
4–11%	10	76	27	113
>11%	0	8	47	55
Total	35	91	74	200

GRACE, Global Registry of Acute Coronary Events; ePVS, estimated plasma volume status.

increase long-term mortality [24,25]; the results of the present study were consistent with these studies in this aspect. Furthermore, subgroup analysis showed the consistent prognostic value of ePVS especially for 5-year mortality even in AMI patients without heart failure or high risk. In other words, our data could provide new insights based on the premise that even subclinical congestion, represented by ePVS, could be associated with long-term mortality regardless of patient's severity such as GRACE risk score or Killip classification. In terms of short-term mortality, the prognostic value of ePVS was also consistent in subgroups but relatively week compared to the prognostic value for long-term mortality.

The present study shows that a single measurement of ePVS on admission enhances the predictive value of the GRACE risk score for long-term mortality, but not for in-hospital mortality. The GRACE risk score was originally developed for predicting relative short-term prognosis. Because of the robust predicting power, no other factor might enhance the short-term predictive value of the GRACE risk score. On the other hand, the predictive value of the GRACE risk score declined when predicting long-term cardiovascular risk [26]. One of the reasons might be that the GRACE scoring system reflects only certain pathophysiological dimensions related to outcomes in AMI; thus, biomarkers that address the different aspects of AMI pathophysiology are needed. Therefore, combining biochemical indices with the GRACE risk score is superior in predicting long-term cardiovascular events in patients with AMI as compared to the GRACE risk score alone. Indeed, the patients with PV expansion had a doubled risk of 5-year mortality compared with those without PV expansion regardless of the GRACE risk score, suggesting that we should implement careful management of patients with PV expansion, despite their GRACE risk score being low. Consequently, such patients might receive clinical benefits from interventions to their PV.

From the viewpoint of PV management in AMI patients, the usage of diuretics in patients with and without PV expansion is important. In this study cohort, the usage of diuretics was significantly associated with worse long-term outcomes in patients without PV expansion (HR: 2.0, 95% CI: 1.0–3.9, p = 0.04), whereas it was not associated with worse outcomes in those with PV expansion (HR: 1.2, 95% CI: 0.7–1.9, p = 0.52). Theoretically, diuretics can cause activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, leading to poor clinical outcome. Previous studies reported that the use of loop diuretics was associated with higher mortality and an increased risk of hospitalization

in patients with heart failure [27,28]. On the other hand, diuretics play an essential role in reducing the extent of systemic congestion. These negative and positive effects of diuretics would counterbalance each other in patients with PV expansion. This finding might suggest the potential clinical utility of ePVS-guided fluid management in patients with AMI. For example, patients with low GRACE risk score have been recognized as low risk for long-term mortality and tend not to be received careful management so far. However, we found that ePVS could refine risk stratification even in such patients and provide additional treatment plan based on ePVS. In other word, volume reduction therapy may be considered for patients with PV expansion. However, this concept is largely hypothesis generating and prospective studies are needed to evaluate the clinical potential of ePVS-guided therapy.

5. Study limitations

This study has several limitations. First, a large number of patients was excluded from this study, because some variables of ePVS and the GRACE risk score were not mandatory in the OACIS registry. Although there was no significant difference in GRACE risk score between patients who were included and excluded patients in overall patients, there was statistically significant difference in each variable of patients characteristics between the groups (data not shown), suggesting that we cannot exclude the possibility that there was a potential selection bias in the current study. Therefore, our observations are needed to be confirmed in various cohort. Second, the definition of AMI in our registry was derived from WHO criteria [29], because the registry was started in 1998. A new criteria for diagnosis of AMI that was proposed in 2000 with an usage of cardiac troponin [30] have been widely used in recent clinical studies. Therefore, there could be a possibility that we missed AMI patients who have small infarction without CK elevation but with troponin elevation. Third, ePVS on admission, not discharge, was used as a predictor for long-term mortality because it was uncomplicated. The predictive value and additive effect of ePVS on discharge to the GRACE risk score were also analyzed, revealing that it had a similar predictive value to that on admission. Fourth, we had no data on B-type natriuretic peptide (BNP) and only a few data on N-terminal pro-B-type natriuretic peptide (NT-proBNP). These markers reflect ventricular blood volume and were reported to be an independent predictor of mortality in patients with AMI [31,32]. However, several reports showed that ePVS was an independent predictor from BNP and NT-proBNP in patients with heart failure [4–8]. Further investigations are required to examine the relationship between ePVS and these markers in AMI patients. Finally, the left ventricular ejection fraction (LVEF) assessed by echocardiography or left ventriculography during hospitalization, which is known as one of the most important prognostic factors in AMI patients, was not included in the multivariate analyses because of missing data in a substantial number of patients. The data on LVEF of 2748 patients were available, and all the data were accessed by Teichholz method. When the data was added to multivariate analyses, the prognostic significance of ePVS for 5-year mortality could maintain (HR:1.03, 95% CI: 1.01–1.04, p = 0.001), but not for in-hospital mortality (OR:1.02, 95% CI: 0.99–1.05, p = 0.228).

6. Conclusions

ePVS, which is calculated simply form weight and hematocrit and represents intravascular compartment and congestion, could identify poor prognosis in patients with AMI. In addition, ePVS could provide additional long-term prognostic information to the GRACE risk score. ePVS-guided therapy may be considered for improving the prognosis of patients with AMI.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors declare that they have no conflict of interest.

Appendix A

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Appendix B. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100748.

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