A Predictive Study of the Dynamic Development of the P-Wave Terminal Force in Lead V₁ in the Electrocardiogram in Relation to Long-Term Prognosis in Non-ST-Segment Elevation Acute Coronary Syndrome Patients during Hospitalization

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Background: Changes in the ECG indicator PtfV₁ reflect left atrial pressure and left ventricular diastolic function in NSTEMI-ACS patients during hospitalization. The value of PtfV₁ in the evaluation of long-term prognosis in NSTEMI-ACS is still not clear. The purpose of this study was to investigate the relationship between the dynamic changes in P-wave terminal force in lead V₁(PtfV₁) in the ECG of non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) patients during hospitalization and the long-term major adverse cardiovascular events (MACEs) of patients.

Methods: A total of 595 patients who received coronary angiography and were confirmed as NSTEMI-ACS in the coronary heart disease database of Department of Cardiology of West China Hospital were continuously included. The PtfV₁ and other clinical data at admission and discharge were collected and dynamically observed. The end events of follow-up observation were MACEs.

Results: Follow-up was performed on 595 patients for 24.71 ± 1.95 months. There were 127 PtfV₁(+) and 468 PtfV₁(-) at admission, and the incidences of MACEs were 14.2% and 11.1%, respectively ($P = 0.731$). Compared with patients with persistent PtfV₁(-) ECG at admission and discharge, 53 patients with persistent PtfV₁(+) ECG at admission and discharge had increased risk for MACEs (HR: 2.221, 95% CI: 1.072–4.601, $P = 0.032$); 94 patients with new PtfV₁(+) ECG at discharge also had significantly increased risk for MACEs (HR: 2.993, 95% CI: 1.660–5.397, $P = 0.000$).

Conclusions: NSTEMI-ACS patients with persistent PtfV₁(+) ECG indicators at admission and discharge and new PtfV₁(+) at discharge had significantly increased risk of MACEs.

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non-ST-segment elevation acute coronary syndrome; electrocardiogram; P-wave terminal force in lead V₁; major adverse cardiac events

Previous studies have considered the possibility that abnormalities in P-wave terminal force in lead

V₁ (PtfV₁), an electrocardiogram (ECG) indicator, suggest left atrial enlargement and left ventricular

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systolic dysfunction. Abnormalities in PtfVI could also be present in patients with increased left atrial pressure and left ventricular diastolic dysfunction, caused by left ventricular hemodynamic failure, even in the absence of left heart enlargement. Therefore, PtfVI has been used extensively for the early diagnosis of chronic heart failure and evaluation of its prognosis.¹⁻⁵ In non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients, myocardial ischemia is always accompanied by hemodynamic changes in heart chambers;^{6,7} therefore, they could also have abnormal PtfV₁. The dynamic change of PtfV₁ in NSTE-ACS patients during hospitalization may indicate the degree of influence of myocardial ischemia on hemodynamics of the all heart chambers. Therefore, it is associated with dynamic factors of patients such as clinical conditions, the range of myocardial ischemia, and the severity of coronary artery disease. It is also associated with whether the treatment is reversible, and it can further suggest the long-term clinical prognosis of patients. However, currently, there are no relevant reports confirming the relationship between the dynamic change of the PtfV₁ ECG indicator in NSTE-ACS patients during hospitalization and their long-term prognosis.

We conducted a prospective observational study to investigate the dynamic change in the PtfV₁ ECG indicator in NSTE-ACS patients during hospitalization and the long-term prognosis of these patients. This study preliminarily investigated the meanings of dynamic changes in relevant clinical indicators accompanied by dynamic changes in PtfV₁.

MATERIALS AND METHODS

Study Subjects and Their Management during Hospitalization

NSTE-ACS patients (including those with unstable angina pectoris [UA] and those with NSTE-myocardial infarction [MI]) hospitalized in West China Hospital of Sichuan University from July 2008 to January 2011 were continuously enrolled into our study. The ages of the enrolled patients were ≥ 18 years, and all received coronary angiography diagnosis. The diagnostic criteria of UA⁸ included (1) coronary angiography showing $\geq 50\%$ stenosis of at least one of the major

epicardial coronary arteries (anterior descending artery, circumflex artery, or right coronary artery); (2) increasing frequency of ischemic chest pain or resting attacks; and (3) no two continuous precordial leads in ECG or the ST segment of two limb leads was continuously elevated by ≥ 0.1 mv. Patients who met the above diagnostic criteria and had (1) at least one typical episode of angina while resting for >20 min and (2) elevated myocardial damage markers (the levels of myocardial damage markers such as serum troponin I or T, high-sensitive troponin T, or creatinine kinase (CK)-MB were ≥ 2 -fold the upper limit of normal levels) were diagnosed as NSTE-MI.⁸

Pregnant patients and patients with malignant tumors, active bleeding, hypokalemia (blood potassium <3.5 mmol/L), diseases of the blood, or severe liver or kidney disease were excluded from the study. Patients with abnormal ventricular rhythm (ventricular fibrillation or flutter, ventricular tachycardia, ventricular escape), atrial rhythm (atrial fibrillation or flutter, atrial tachycardia), pacemaker rhythm, or junctional rhythm were also excluded, and patients who died during hospitalization were excluded.

Patient management during hospitalization was conducted according to the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction by conventional treatment.⁸ All samples were prepared and analyzed in accordance with the ethical recommendations of the hospital's committee on human research. The written informed consents were obtained from all subjects and the treatment process was not interfered with by this study.

Measurement of P-Wave Terminal Force in Lead V₁ (PtfV₁)

A standard 12-lead ECG (25 mm/s and 1 mv) (GE Medical Systems, Milwaukee, WI, USA) was performed on all enrolled patients. PtfV₁ was measured based on the measurement method proposed by Morris et al.³ The measurement of the ECG indicators of all patients was conducted by two researchers, and the average values were calculated. The depth of the negative wave (it was a negative value; units: mm) and the width of the negative wave (units: sec) of three continuous P waves in lead V₁ were measured. The average of these two values was obtained, and the multiplication of these two values yielded the PtfV₁

value (units: mm•s). The criterion for an abnormal PtfV₁ value was PtfV₁ ≤ -0.03 mm•s; in this study, abnormal values were designated PtfV₁(+).

The ECG of each patient was measured at admission and discharge. The study subjects were divided into four groups based on the change in PtfV₁ of the ECG at admission and discharge. Patients with conversion of PtfV₁(+) ECG indicators at admission into PtfV₁(-) at discharge made up the "normalized" group; patients with conversion of PtfV₁(-) ECG at admission into PtfV₁(+) were the "new positive" group; patients with PtfV₁(+) ECG indicators at both admission and discharge were the "persistent positive" group; and patients with PtfV₁(-) ECG indicators at both admission and discharge were the "persistent negative" group.

Collection of Other Clinical Data

A clinical medical history was obtained and a physical examination and clinical laboratory tests were performed prior to enrollment of each patient in the study. History of hypertension was defined as blood pressure higher than 140/90 mmHg suggested by at least two independent tests or previous history of hypertension and current use of antihypertensive medication.⁹ History of diabetes was defined as patients who were taking oral hypoglycemic agents or using insulin to control blood sugar or two new fasting glucose levels >7.0 mmol/L.¹⁰ Hypercholesterolemia was defined as a past history of hypercholesterolemia, currently receiving treatment for hypercholesterolemia, or total cholesterol ≥ 5.18 mmol/L. Global registry scoring of acute coronary events (GRACE)¹¹ was performed on patients at admission and discharge.

Follow-Up and Study Endpoint

Patient follow-up was performed after discharge, and the occurrence of clinical events and the use of major medication were recorded. The sources of follow-up data were the medical personnel who conducted follow-up, the patients themselves, and family members of the patients. All data were consistent with hospital records. The agreement and implementation of this study was in compliance with the Declaration of Helsinki, and the study was approved by the local Review Committee. Informed consent was obtained from all patients before inclusion.

The primary endpoint events were composite endpoint events composed of components of MACEs, including cardiovascular death, nonfatal MI, nonfatal stroke, and recurrent coronary vascularization. The secondary endpoint events included all causes of death and all components of the primary endpoint events.

Statistical Analysis

The statistical analysis of all data was performed using SPSS 18.0 software for Windows (IBM, Armonk, NY, U.S.A.). Categorical variables were presented as ratios or percentages. If continuous variables followed a normal distribution or close to a normal distribution, they were presented as the mean ± standard deviation. The Kaplan-Meier method was used to estimate the incidence of endpoint events during the comparison of endpoint events between groups, and the log-rank test was used for survival analysis between groups. The Cox proportional hazards model was used for survival analysis. In addition, possible confounding factors such as gender, smoking history, old myocardial infarction, history of recurrent vascularization, history of hypertension, history of diabetes, history of stroke, history of hypercholesterolemia, GRACE scores at admission and discharge, current ACS type, and medications (aspirin, clopidogrel, beta-blockers, statins, and angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin II receptor antagonists [ARBs]) were included. Hazard ratio (HR) and 95% confidence intervals (CIs) were calculated by multivariate analysis that included these factors. All tests with $P < 0.05$ were considered statistically significant.

The receiver operating characteristic (ROC) curve was plotted based on the logistic regression analysis. The area under the ROC curve and 95% CIs were calculated. The areas under the curve were compared using the Z-test.

RESULTS

A total of 595 patients were enrolled in this study; 77.0% were males, 12.9% were patients with NSTEMI, and 75.6% received percutaneous coronary intervention treatment. The average age was 65.06 ± 9.78 years. Follow-up with an average duration of 24.72 ± 1.95 months was conducted on all patients after discharge (Table 1). The baseline data of patients in the

Table 1. Baseline Data of Study Subjects

Characteristic	Dynamic Changes in Discharge ECG Compared with Admission ECG									
	Overall (N = 595)	Admission ECG			PtfV ₁ (+)(N = 147)			PtfV ₁ (-)(N = 448)		
		PtfV ₁ (-) (N = 468)	PtfV ₁ (+) (N = 127)	P Value	Positive Group n = 53	New Positive Group n = 94	Normalized Group n = 74	Negative Group n = 374	P Value	
Age-yr	65.06 ± 9.78	64.82 ± 9.91	65.92 ± 9.27	0.262	67.58 ± 7.90	67.06 ± 8.94	64.73 ± 10.03	64.26 ± 10.08	0.018	
Male-no (%)	458(77.0)	362(77.4)	96(75.6)	0.676	40(75.5)	78(83.0)	56(75.7)	284(75.9)	0.517	
Hypertension, no. (%)	365(61.3)	286(61.1)	79(62.2)	0.822	34(64.2)	65(69.1)	45(60.8)	221(59.1)	0.334	
Diabetes-no. (%)	157(26.4)	121(25.9)	36(28.3)	0.572	18(34.0)	34(36.2)	18(24.3)	87(23.3)	0.041	
Smoking history, no. (%)	304(51.1)	246(52.6)	58(45.7)	0.168	25(47.2)	53(56.4)	33(44.6)	304(51.1)	0.446	
Hypercholesterolemia, no. (%)	72(12.1)	63(13.5)	9(7.1)	0.051	3(5.7)	9(9.6)	6(8.1)	54(14.4)	0.129	
Stroke history, no. (%)	24(4.0)	21(4.5)	3(2.4)	0.280	1(1.9)	6(6.4)	2(2.7)	15(4.0)	0.511	
Previous PCI or CABG, no. (%)	59(9.9)	48(10.3)	11(8.7)	0.594	3(5.7)	13(13.8)	8(10.8)	35(9.4)	0.410	
Myocardial infarction history, no. (%)	97(16.3)	66(14.1)	31(24.4)	0.005	16(30.2)	14(14.9)	15(20.3)	52(13.9)	0.018	
GRACE score at admission	115.55 ± 28.15	113.68 ± 25.97	122.46 ± 34.29	0.002	131.92 ± 33.00	121.03 ± 27.63	115.69 ± 33.80	111.83 ± 25.23	0.000	
GRACE score at discharge	117.31 ± 24.50	115.89 ± 23.70	122.54 ± 26.68	0.007	132.04 ± 26.83	123.37 ± 24.68	115.73 ± 24.56	114.01 ± 23.10	0.000	
BP at admission, mmHg										
Systolic	131.13±20.42	131.18±20.13	130.94±21.53	0.908	127.68±21.28	133.85±21.21	133.28±21.54	130.51±19.82	0.226	
Diastolic	74.85±11.51	75.06±11.44	74.08±11.77	0.396	72.66±12.21	74.98±10.84	75.09±11.41	75.08±11.60	0.551	
BP at discharge, mmHg										
Systolic	120.62±13.29	120.81±13.11	119.93±13.97	0.508	120.72±15.57	122.40±12.53	119.36±12.77	120.41±13.24	0.485	
Diastolic	69.77±9.01	70.29±8.92	67.88±9.13	0.008	66.38±8.99	69.82±8.84	68.96±9.14	70.40±8.94	0.018	
HR at admission, beats/min	71.66±13.18	70.86±12.59	74.62±14.85	0.004	75.25±17.02	71.10±11.96	74.16±13.17	70.80±12.75	0.039	
HR at discharge, beats/min	72.95±11.17	72.20±10.77	75.74±12.18	0.001	77.79±13.93	75.22±12.08	74.27±10.61	71.44±10.29	0.000	
Creatinine at admission, μ mol/L	84.79±21.88	84.21±18.64	86.92±31.05	0.216	87.50±34.98	84.31±21.00	86.51±28.15	84.19±18.02	0.661	
Creatinine at discharge, μ mol/L	83.91±19.22	83.62±17.16	84.98±25.45	0.478	85.96±27.33	82.60±17.36	84.28±24.19	83.87±17.13	0.785	
ST depression at admission, no. (%)	164(27.6)	115(24.6)	49(38.6)	0.002	23(43.4)	30(31.9)	26(35.1)	85(22.7)	0.003	

(Continued)

Table 1. Continued

Characteristic	Overall (N = 595)	Admission ECG		Dynamic Changes in Discharge ECG Compared with Admission ECG								P Value
		PtfV ₁ (-) (N = 468)	PtfV ₁ (+) (N = 127)	PtfV ₁ (+)(N = 147)				PtfV ₁ (-)(N = 448)				
				(+) (+) Persistent	(-) (+) New Positive	(+) (-) Normalized	(-) (-) Persistent	Group n = 53	Group n = 94	Group n = 74	Negative Group n = 374	
ST depression at discharge, no.(%)	108(18.2)	76(16.2)	32(25.2)	0.020	23(43.4)	27(28.7)	9(12.2)	49(13.1)	0.000			
Killip> 1 at admission, no.(%)	37(6.2)	21(4.5)	16(12.6)	0.002	9(17.0)	7(7.4)	7(9.5)	4(3.7)	0.004			
Killip> 1 at discharge, no.(%)	23(3.9)	13(2.8)	10(7.9)	0.017	7(13.2)	7(7.4)	3(4.1)	6(1.6)	0.001			
UA, no.(%)	518(87.1)	417(89.1)	101(79.5)	0.004	39(73.6)	79(84.0)	62(83.8)	338(90.4)	0.003			
PCI during hospitalization, no.(%)	450(75.6)	350(74.8)	100(78.7)	0.357	41(77.4)	77(81.9)	63(85.1)	293(78.3)	0.524			
Follow-up time, months	24.72 ± 1.95	24.74±1.93	24.65±2.03	0.502	24.58±2.11	24.86±1.73	24.70±1.98	24.71±1.98	0.857			
Drug treatment in hospital and during follow-up-no.(%)												
Aspirin	579(97.3)	458(97.9)	121(95.3)	0.110	49(92.5)	93(98.9)	72(97.3)	365(97.6)	0.119			
Clopidogrel	575(96.6)	453(96.8)	122(96.1)	0.685	51(96.2)	88(93.6)	71(95.9)	365(97.6)	0.281			
Statin	560(94.1)	440(94.0)	120(94.5)	0.841	50(94.3)	88(93.6)	70(94.6)	352(94.1)	0.994			
Betablocker	438(73.6)	343(73.3)	95(74.8)	0.732	38(71.7)	78(83.0)	57(77.0)	265(70.9)	0.100			
ACEI or ARB	387(65.0)	303(64.7)	84(66.1)	0.769	35(66.0)	60(63.8)	49(66.2)	243(65.0)	0.988			

Plus-minus values are means ± SD. ECG = electrocardiogram; PtfV₁ = P-wave terminal force-V₁; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; BP = blood pressure; HR = heart rate; UA = unstable angina; ACEI = angiotensin-converting enzyme inhibitors; ARBs = angiotensin-II receptor blockers.

four groups described in section "Measurement of P-wave terminal force in lead V₁ (PtfV₁)," including diabetes history, past history of MI, and GRACE scores at admission and discharge, showed statistically significant differences ($P < 0.05$). Statistically significant differences were also present in the relevant clinical data assessed by GRACE scoring, including age, diastolic blood pressure at discharge, heart rates at admission and discharge, and diagnostic type of ACS at this admission. Gender, history of other risk factors of coronary heart disease, the ratio of patients who received percutaneous coronary intervention treatment during hospitalization, and medication during hospitalization and follow-up did not show statistically significant differences ($P > 0.05$).

The baseline data for parameters that showed significant differences were further compared between groups (Table 2). GRACE scores at admission (131.92 ± 33.00 vs 115.69 ± 33.80 , $P = 0.001$), GRACE scores at discharge (132.04 ± 26.83 vs 115.73 ± 24.56 , $P = 0.000$), and ST segment depression at discharge (43.4% vs 12.2%, $P = 0.000$) showed statistically significant differences between the PtfV₁ persistent positive group ($n = 53$) and the PtfV₁ normalized group ($n = 74$). Age (67.06 ± 8.94 vs 64.26 ± 10.08 , $P = 0.013$), diabetes history (36.2% vs 23.3%, $P = 0.011$), GRACE scores at admission (121.03 ± 27.63 vs 111.83 ± 25.23 , $P = 0.004$), GRACE scores at discharge (123.37 ± 24.68 vs 114.01 , $P = 0.001$), heart rate at discharge (75.22 ± 12.08 vs 71.44 ± 10.29 , $P = 0.003$), ST segment depression at discharge (28.7% vs 13.1%, $P = 0.000$), and Killip class larger than I at discharge (7.4% vs 1.6%, $P = 0.006$) were clinical indicators that showed statistically significant differences between the PtfV₁ new positive group ($n = 94$) and the persistent negative group ($n = 374$).

Of the indicators that showed significant differences in between-group comparisons, those that might be expected to show dynamic changes during hospitalization were used for within-group comparison between discharge and admission. The values of the dynamic changes between discharge and admission within each group were also used for between-group comparisons (Table 2). Compared with the persistent positive group, more patients in the PtfV₁-normalized group with ST segment depression recovered to normal (65.4% vs 0.0%, $P = 0.000$). Compared with the persistent negative group, the increase in heart rate at discharge was greater (4.12 ± 14.91 vs 0.64 ± 13.03 , $P =$

0.025), fewer patients with ST segment depression recovered to normal (10.0 vs 42.4%, $P = 0.001$), and fewer patients with Killip class greater than I recovered to I (0.0% vs 57.1%, $P = 0.018$) in the new PtfV₁ positive group.

Univariate Analysis of Endpoint Events

There were 70 patients with primary endpoint events during follow-up (MACEs), including 17 cases of cardiovascular death, 7 cases of nonfatal MI, 6 cases of nonfatal stroke, and 42 cases of recurrent vascularization (including 2 cases of nonfatal MI). Patients with PtfV₁(+) and PtfV₁(-) ECG indicators at admission had similar risk for the occurrence of endpoint events (14.2% vs 11.1%, adjusted HR 1.104, 95%CI 0.627–1.946, $P = 0.731$) (Table 3 and Fig. 1a). Using the PtfV₁ persistent negative group as the control group, the risk for the occurrence of primary endpoint events in the new positive group increased significantly (21.3% vs 8.6%, adjusted HR 2.993, 95%CI 1.660–5.397, $P = 0.000$) with Kaplan–Meier survival analysis $P = 0.000$ (Table 3 and Fig. 1b). The risk for the occurrence of a primary endpoint event in the persistent positive group of patients also increased (22.6% vs 8.6%, adjusted HR 2.221, 95%CI 1.072–4.601, $P = 0.032$) with Kaplan–Meier survival analysis $P = 0.001$ (Table 3 and Fig. 1b). Analysis of the secondary endpoint events showed that the risks of cardiovascular death (7.4% vs 0.8%, adjusted HR 13.757, 95%CI 2.854–66.308, $P = 0.001$), death from any cause (12.8% vs 1.9%, adjusted HR 7.582, 95%CI 2.735–21.018, $P = 0.000$), and recurrent vascularization (13.8% vs 6.1%, adjusted HR 2.856, 95%CI 1.383–5.901, $P = 0.005$) were all significantly higher in the new positive patients than in the persistent negative patients. The risk for the occurrence of cardiovascular death in the persistent positive patients (9.4% vs 0.8%, adjusted HR 6.196, 95%CI 1.220–31.458, $P = 0.028$) was higher than in the persistent negative group, whereas the risks of death from any cause and of recurrent vascularization did not show significant differences. The risks for the primary endpoint events and the secondary endpoint events in the PtfV₁-normalized patients and the persistent negative patients did not show significant differences with Kaplan–Meier survival analysis of the primary endpoint events ($P = 0.924$; Table 3 and Fig. 1b).

Table 2. Comparison of Baseline Data between the PtfV₁ Persistent Positive Group and the Normalized Group and between the PtfV₁ New Positive Group and the Persistent Negative Group: Comparison of the Dynamic Changes in the Baseline Data of Each Group at Admission and at Discharge

Discharge ECG Compared with Admission ECG (Persistent Positive Group vs Normalized Group and New Positive Group vs Persistent Negative Group)						
Characteristic	PtfV ₁ (+) (+) Persistent Positive Group n = 53	PtfV ₁ (+) (-) Normalized Group n = 74	P Value [†]	PtfV ₁ (-) (+) New Positive Group n = 94	PtfV ₁ (-) (-) Persistent Negative Group n = 374	P Value [‡]
Age, yr	67.58 ± 7.90	64.73 ± 10.03	0.103	67.06 ± 8.94	64.26 ± 10.08	0.013
Diabetes, no. (%)	18(34.0)	18(24.3)	0.235	34(36.2)	87(23.3)	0.011
Myocardial infarction history, no.(%)	16(30.2)	15(20.3)	0.199	14(14.9)	52(13.9)	0.805
UA, no. (%)	39(73.6)	62(83.8)	0.160	79(84.0)	338(90.4)	0.078
GRACE score at admission	131.92 ± 33.00	115.69 ± 33.80	0.001	121.03 ± 27.63	111.83 ± 25.23	0.004
GRACE score at discharge	132.04 ± 26.83	115.73 ± 24.56	0.000	123.37 ± 24.68	114.01 ± 23.10	0.001
Dynamic GRACE score change	0.11 ± 24.21	0.04 ± 19.83	0.985	2.34 ± 19.78	2.18 ± 15.21	0.942
P value*	0.973	0.986	–	0.254	0.006	–
Systolic BP at admission, mmHg	127.68 ± 21.28	133.28 ± 21.54	0.127	133.85 ± 21.21	130.51 ± 19.82	0.156
Systolic BP at discharge, mmHg	120.72 ± 15.57	119.36 ± 12.77	0.572	122.40 ± 12.53	120.41 ± 13.24	0.194
Dynamic systolic BP change, mmHg	–6.96 ± 22.47	–13.92 ± 20.33	0.076	–11.45 ± 20.69	–10.10 ± 20.08	0.572
P value*	0.028	0.000	–	0.000	0.000	–
Diastolic BP at admission, mmHg	72.66 ± 12.21	75.09 ± 11.41	0.241	74.98 ± 10.84	75.08 ± 11.60	0.941
Diastolic BP at discharge, mmHg	66.38 ± 8.99	68.96 ± 9.14	0.110	69.82 ± 8.84	70.40 ± 8.94	0.572
Dynamic diastolic BP change, mmHg	–6.28 ± 13.59	–6.14 ± 11.96	0.948	–5.16 ± 12.96	–4.67 ± 11.60	0.723
P value*	0.001	0.000	–	0.000	0.000	–
HR at admission, beats/min	75.25 ± 17.02	74.16 ± 13.17	0.644	71.10 ± 11.96	70.80 ± 12.75	0.842
HR at discharge, beats/min	77.79 ± 13.93	74.27 ± 10.61	0.076	75.22 ± 12.08	71.44 ± 10.29	0.003
Dynamic HR change, beats/min	2.53 ± 12.77	0.11 ± 12.02	0.282	4.12 ± 14.91	0.64 ± 13.03	0.025
P value*	0.155	0.939	–	0.009	0.345	–
Creatinine at admission, μmol/L	87.50 ± 34.98	86.51 ± 28.15	0.803	84.31 ± 21.00	84.19 ± 18.02	0.404
Creatinine at discharge, μmol/L	85.96 ± 27.33	84.28 ± 24.19	0.627	82.60 ± 17.36	83.87 ± 17.13	0.567
Dynamic creatinine chang, μmol/L	–1.54 ± 14.38	–2.23 ± 11.74	0.764	–1.71 ± 9.59	–0.32 ± 4.54	0.173
P value*	0.439	0.106	–	0.087	0.181	–
ST depression at admission, no.(%)	23(43.4)	26(35.1)	0.346	30(31.9)	85(22.7)	0.064
ST depression at discharge, no.(%)	23(43.4)	9(12.2)	0.000	27(28.7)	49(13.1)	0.000
Dynamic ST depression change, no.(%)	0(0.0)	–17(65.4)	0.000	–3(10.0)	–36(42.4)	0.001
P value*	1.000	0.000	–	0.534	0.000	–
Killip> 1 at admission, no.(%)	9(17.0)	7(9.5)	0.208	7(7.4)	14(3.7)	0.203
Killip> 1 at discharge, no.(%)	7(13.2)	3(4.1)	0.653	7(7.4)	6(1.6)	0.006
Dynamic Killip> 1 change, no.(%)	–2(22.2)	–4(57.1)	0.302	0(0.0)	–8(57.1)	0.018
P value*	0.322	0.103	–	1.000	0.011	–

Plus-minus values are means ± SD. ECG = electrocardiogram; PtfV₁ = P-wave terminal force-V₁; BP = blood pressure; HR = heart rate. * Comparison of the dynamic changes of baseline data at discharge and admission in each group. † Comparison of baseline data between the PtfV₁ persistent positive group and the normalized group. ‡ Comparison of baseline data between the new positive group and the persistent negative group.

Table 3. Dynamic Observation of Changes in PtfV₁ ECG Indicators at Discharge and Admission and Univariate Analysis of Endpoint Events

	Admission ECG		Dynamic changes in Discharge ECG Compared with Admission ECG			
	PtfV ₁ (–) (N = 468)	PtfV ₁ (+) (N = 127)	PtfV ₁ (+) (N = 147)		PtfV ₁ (–) (N = 448)	
			(+) (+) Persistent Positive Group n = 53	(–) (+) New Positive Group n = 94	(+) (–) Normalized Group n = 74	(–) (–) Persistent Negative Group n = 374
Primary outcome*						
Absolute number of events, no. (%)	52 (11.1)	18 (14.2)	12 (22.6)	20 (21.3)	6 (8.1)	32 (8.6)
Unadjusted HR (95%CI)	1.298 (0.760–2.219)		2.844 (1.465–5.521)	2.758 (1.577–4.823)	0.961 (0.402–2.298)	1.0
P value	0.340		0.002	0.000	0.928	
Adjusted HR(95%CI)	1.104 (0.627–1.946)		2.221 (1.072–4.601)	2.993 (1.660–5.397)	0.984 (0.406–2.386)	1.0
P value	0.731		0.032	0.000	0.971	
Secondary outcome						
Cardiovascular death						
Absolute number of events, no. (%)	10 (2.1)	7 (5.5)	5 (9.4)	7 (7.4)	2 (2.7)	3 (0.8)
Unadjusted HR (95%CI)	2.623 (0.999–6.892)		12.833 (3.066–53.709)	10.530 (2.721–40.749)	3.401 (0.568–20.354)	1.0
P value	0.050		0.000	0.001	0.180	
Adjusted HR (95%CI)	1.298 (0.418–4.034)		6.196 (1.220–31.458)	13.757 (2.854–66.308)	2.594 (0.331–20.313)	1.0
P value	0.652		0.028	0.001	0.364	
All-cause death						
Absolute number of events, no. (%)	19 (4.1)	9 (7.1)	6 (11.3)	12 (12.8)	3 (4.1)	7 (1.9)
Unadjusted HR (95%CI)	1.775 (0.803–3.922)		6.501 (2.184–19.346)	7.556 (2.973–19.203)	2.191 (0.567–8.473)	1.0
P value	0.156		0.001	0.000	0.256	
Adjusted HR (95%CI)	0.792 (0.308–2.032)		2.799 (0.808–9.700)	7.582 (2.735–21.018)	1.081 (0.222–5.262)	1.0
P value	0.627		0.105	0.000	0.923	
Recurrent vascularization						
Absolute number of events, no. (%)	36 (7.7)	6 (4.7)	4 (7.5)	13 (13.8)	2 (2.7)	23 (6.1)
Unadjusted HR (95%CI)	0.626 (0.264–1.485)		1.312 (0.454–3.794)	2.457 (1.244–4.853)	0.446 (0.105–1.891)	1.0
P value	0.288		0.616	0.010	0.273	
Adjusted HR (95%CI)	0.580 (0.235–1.431)		1.169 (0.371–3.685)	2.856 (1.383–5.901)	0.479 (0.111–2.063)	1.0
P value	0.237		0.790	0.005	0.323	

ECG = Electrocardiogram; PtfV₁: P-wave terminal force-V₁; HR, hazard ratio; CI, confidence interval.

Adjusted for gender, GRACE score at admission and discharge, history of smoking, history of myocardial infarction, previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), hypertension, diabetes, history of stroke, hypercholesterolemia, exposure to drugs (aspirin, clopidogrel, beta-blocker, statin, angiotensin-converting enzyme inhibitors [ACEI]/angiotensin II receptor blockers [ARBs]), PCI during hospitalization, and clinical presentation (non-ST-segment elevation acute myocardial infarction [NSTEMI] or unstable angina [UA]).

* Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and recurrent vascularization.

Figure 1. Kaplan-Meier estimation of the primary outcome measure (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and recurrent vascularization) during the follow-up. (a) PtfV₁(+) group versus PtfV₁(-) group of admission electrocardiogram. (b) Normalized PtfV₁ group, new PtfV₁(+) group, and persistent PtfV₁(+) group versus persistent PtfV₁(-) group of dynamic changed electrocardiogram.

Table 4. Results of Cox Proportional Hazards Regression Analysis of Primary Endpoint Events

Variable	Adjusted Hazard Ratio (95% Confidence Interval)	P Value
Admission ECG		
GRACE score at admission	1.012 (1.004–1.020)	0.004
PCI during hospitalization	0.538 (0.320–0.905)	0.020
Exposure to aspirin	0.365 (0.153–0.874)	0.024
Discharge ECG compared with admission ECG		
GRACE score at admission	1.009 (1.001–1.018)	0.027
PtfV ₁ (-) (+)	2.785 (1.586–4.892)	0.000
PtfV ₁ (+) (+)	2.160 (1.081–4.315)	0.029
PCI during hospitalization	0.530 (0.312–0.901)	0.019
Exposure to aspirin	0.368 (0.150–0.905)	0.029

ECG = electrocardiogram; PtfV₁ = P-wave terminal force-V₁; PCI = percutaneous coronary intervention; UA = unstable angina.

Multivariate Analysis of Endpoint Events

The primary endpoint events (MACEs) were analyzed using the Cox proportional hazards model. After adjusting for possible confounding factors, the results showed that new positive PtfV₁, persistent positive PtfV₁, and increase in GRACE scores at admission were independent risk factors for MACEs (cardiovascular death, nonfatal MI, nonfatal stroke, and recurrent coronary vascularization) (Table 4).

Analysis of Dynamic Changes in PtfV₁ Combined with GRACE Scores

To analyze whether the assessment of dynamic changes in PtfV₁ increased the predictive value of

GRACE scores on long-term prognosis, the new PtfV₁(+) and persistent PtfV₁(+) were combined with the GRACE scores at admission and discharge and ROC curves based on the logistic regression analysis were plotted.

The area under the ROC curve of prediction of long-term primary endpoint events by the GRACE score at discharge was 0.579, with 95%CI 0.504–0.654. After combination with the new PtfV₁(+), the area under the ROC curve was similar (0.630, 95%CI 0.555–0.706, P = 0.349; Fig. 2a). After combination with the persistent PtfV₁(+), the area under the ROC curve was also similar (0.600, 95%CI 0.526–0.675, P = 0.696; Fig. 2b). The area under the ROC curve of prediction of long-term primary endpoint events by

Figure 2. ROC curve of the GRACE score compared with the GRACE score-dynamic changed PtfV₁ based on logistic regression analysis. (a and c) New PtfV₁(+) added to discharge and admission GRACE score. (b and d) Persist PtfV₁(+) added to discharge and admission GRACE score.

GRACE score at admission was 0.581 with a 95%CI of 0.503–0.659. After combination with the new PtfV₁(+), the area under the ROC curve was similar (0.614, 95%CI 0.536–0.693, $P = 0.560$; Fig. 2c). After combination with the persistent PtfV₁(+), the area under the ROC curve was also similar (0.598, 95%CI 0.519–0.677, $P = 0.764$; Fig. 2d). These results suggest that although the combination of dynamic PtfV₁ and the GRACE scores had predictive values for prognosis, the predictive value of the GRACE scores was not increased.

DISCUSSION

This study included an analysis of the ECG indicator PtfV₁. This indicator was previously

used primarily to reflect left ventricular diastolic function and left atrial pressure, and it was also a sign of abnormal atrial conduction and was considered important in the diagnosis of patients with chronic heart failure,^{2,12,13} suggesting that dynamic observation of NSTEMI-ACS patients during hospitalization is clinically useful. The results of the current study suggest that persistent PtfV₁(+) during hospitalization and new PtfV₁(+) at discharge were significantly associated with an increased risk of long-term MACEs in these patients.

In 1964, Morris et al.³ proposed the concept of PtfV₁ and investigated its mechanism of occurrence. Current research has shown that PtfV₁ is associated with left atrial enlargement, elevated

left atrial pressure, and left heart hemodynamic failure caused by a variety of conditions. Many studies have used a $\text{PtfV}_1 \leq -0.03 \text{ mm}\cdot\text{s}$ as the abnormal standard.^{14,15} However, there are no reports showing that this indicator can predict the long-term prognosis of NSTEMI-ACS patients. During acute MI, the presence of abnormal PtfV_1 in patients was usually associated with left ventricular diastolic dysfunction caused by infarcted myocardia, and its presence was noted earlier than the presence of heart failure symptoms and left ventricular systolic dysfunction.^{4,5} Furthermore, the myocardial tissue of patients had necrosis or ischemia; although blood perfusion in ischemic myocardia was improved to a certain degree after treatment, some myocardia still might exhibit myocardial stunning for an extended period due to the presence of residual ischemia and nonintervention vessels. In addition, combined with the loss of normal function in infarcted myocardia, cardiac insufficiency would occur.⁶ Especially in cases in which left ventricular volume and left atrial pressure were affected, the presentation in the ECG included persistent or new $\text{PtfV}_1(+)$. Therefore, dynamic changes in PtfV_1 may have to some extent reflected the dynamic condition of patients such as degree of myocardial damage, residual ischemia, hemodynamic changes, and changes in heart function. In NSTEMI-ACS patients, PtfV_1 may also have similar values and may be associated with long-term prognosis. Williamson et al.⁷ reported that the presentation of myocardial stunning could be improved within a short time after reperfusion treatment in acute MI patients. Therefore, ECGs showing persistent $\text{PtfV}_1(+)$ during hospitalization or new $\text{PtfV}_1(+)$ at discharge suggest the presence of increased left atrial pressure or left ventricular diastolic dysfunction caused by irreversible left heart hemodynamic disorders. This may be associated with the presence of irreversible myocardial damage or residual ischemia of nonintervention vessels. Win et al.¹⁶ reported that left ventricular fibrosis is a cause of abnormal PtfV_1 . It may be also a mechanism behind our NSTEMI-ACS patients who had left ventricular fibrosis caused by long and repeated myocardial ischemia¹⁷ and persistent $\text{PtfV}_1(+)$ during hospitalization.

Tereshchenko et al.¹⁸ reported that electrocardiographic deep terminal negativity of the PtfV_1 were independently associated with increased risk of death due to cardiovascular disease. Our study observed the dynamic changes of PtfV_1 and also

showed that the incidence of long-term MACEs increased significantly in patients with persistent $\text{PtfV}_1(+)$ ECG or new $\text{PtfV}_1(+)$ at discharge as measured over more than 2 years of follow-up. In addition, these patients were at higher risk for cardiovascular death, recurrent vascularization, and death from all causes, and these indicators were independent risk factors for MACEs. Patients with normalized ECG indicators at discharge or persistent $\text{PtfV}_1(-)$ during hospitalization had significantly lower risk of long-term MACEs. This observation suggests that intracardiac hemodynamic changes caused by acute ischemia may be reversed to a certain degree through intervention measures in some patients. The results also confirm the finding that dynamic observation of the ECG indicator PtfV_1 is helpful in determining the long-term prognosis of NSTEMI-ACS patients.

In addition to dynamic observation of the PtfV_1 ECG indicator, this study also included dynamic observation of clinical data that reflects the natural course of cardiac disease under conventional treatment during hospitalization, especially GRACE scoring of related clinical indicators that were easy to collect and observe. Although the combination of new $\text{PtfV}_1(+)$ at discharge or persistent $\text{PtfV}_1(+)$ with GRACE scores at admission or discharge had predictive value for prognosis, it did not increase the predictive value of the GRACE scores at admission or discharge. The analysis of dynamic changes in between-group and within-group clinical data related to the GRACE scores showed that a higher percentage of patients who had new $\text{PtfV}_1(+)$ at discharge and persistent $\text{PtfV}_1(+)$ than of patients who had persistent $\text{PtfV}_1(-)$ and PtfV_1 normalized patients also had persistent ST segment depression at discharge. Because the ST segment depression clearly reflected the ischemic condition of the coronary artery in patients with NSTEMI-ACS^{19,20} and was clearly associated with long-term prognosis,^{21,22} this phenomenon further suggests that $\text{PtfV}_1(+)$ indeed is associated with severity of coronary artery disease and with ischemic conditions in patients. Intensive coronary ischemia therapy may benefit patients with $\text{PtfV}_1(+)$ ECG at discharge. The dynamic change in heart rate increase in patients with new $\text{PtfV}_1(+)$ at discharge was also higher than in patients with persistent $\text{PtfV}_1(-)$, whereas reduction of the Killip class to class I in the new PtfV_1 positive group was less pronounced than in the persistent $\text{PtfV}_1(-)$ group. This finding suggests that these patients still

presented increased cardiac load and heart failure at discharge. Thus, intensive therapy to prevent heart failure may benefit patients.

This study had some limitations. First, because it was a single center cohort study, factors such as patient treatment were not strictly controlled. In addition, the follow-up time was relatively short, and the sample size was relatively small. However, this study only enrolled patients with NSTE-ACS, the baseline clinical characteristics of study subjects between groups (such as known coronary disease risk factors, stent implantation conditions, follow-up time, and drug exposure) were comparable, the included ECG indicators were dynamically observed, and the incidences of the primary endpoint events differed significantly between the groups. Thus, the results of this study have creditability and indicate the need for further large-scale clinical studies.

CONCLUSION

In NSTE-ACS patients, new PtfV₁(+) at discharge and persistent PtfV₁(+) during hospitalization were independent risk factors for the development of long-term MACEs. Dynamic observation of changes in the ECG indicator PtfV₁ in patients during hospitalization has value for the prediction of long-term prognosis after discharge.

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