Prediction of SYNTAX score ≥ improvement by temporal heart rate changes between discharge and fist preceding visit on long-term clinical outcomes in patients with acute myocardial infarction

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Research Article

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Abstract

Background: Studies of the prognostic ability of the temporal changes in resting heart rate (ΔHR) regarding cardiovascular (CV) mortality and clinical outcomes in patients with acute myocardial infarction (AMI) are scarce. The aim of this study was to investigate the predictive value of ΔHR using models including the SYNTAX score Ⅱ (SxS-Ⅱ) on the long-term prognosis of patients with AMI.

Methods: A total of 605 AMI subjects with vital signs recorded at the first outpatient visit (2–4 weeks after discharge) was retrospectively recruited into this study. The changes between discharge and outpatient resting heart rate (D-O ΔHR) were calculated by subtracting the HR at first post-discharge visit from the value recorded at discharge. The major adverse cardiovascular events (MACE) were cardiovascular death, recurrent myocardial infarction, revascularization, and nonfatal stroke. The predictive values and reclassification ability of the different models were assessed using a likelihood ratio test, Akaike's information criteria (AIC), receiver operating characteristic (ROC) curves, net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

Results: During the follow-up period, the D-O ΔHR was independently associated with CV mortality [hazards ratio (HR) = 0.97, 95% CI = 0.958–0.985, $P < 0.001$] and MACE (HR = 1.02, 95% CI = 1.011–1.039, p = 0.001). The likelihood test indicated that the combined model of SxS-Ⅱ and D-O ΔHR yielded the lowest AIC regarding MACE and CV death ($P < 0.001$). Moreover, D-O ΔHR alone significantly improved the net reclassification and integrated discrimination of the models containing SxS-Ⅱ regarding both CV mortality and MACE (CV mortality: NRI = 0.5600, $P = 0.001$ and IDI = 0.0759, $P = 0.03$; MACE: NRI = 0.2231, $P < 0.05$ and IDI = 0.0107, $P < 0.05$).

Conclusions: The D-O ΔHR was an independent predictor of long-term CV mortality and MACE. The additive value of D-O ΔHR combined with SxS-Ⅱ could significantly enhance its predictive probability.

Introduction

An elevated resting heart rate (RHR) is a known risk factor for cardiovascular morbidity and mortality in the general population and is associated with various clinical scenarios, such as chronic heart failure, myocardial infarction, cancer, etc.[1–4]. In fact, RHR reduction is associated with clinical benefits after myocardial infarction[5], regardless of the use of beta-blockers and calcium channel blockers. Recently, a series of large-scale trials indicated that the short-term temporal changes in resting HR (ΔHR) occurring within 3 months or less of myocardial infarction showed a better correlation with cardiovascular (CV) mortality and adverse outcomes of HF compared with RHR[2, 6, 7]. However, there is limited evidence regarding the association of the ΔHR recorded between discharge and the first outpatient visit and the long-term prognosis of patients with AMI.

The Synergy between percutaneous coronary intervention (PCI) with Taxus and Cardiac Surgery (SYNTAX) score (SxS) Ⅱ (SxS-Ⅱ) is an update of the anatomical SxS risk system via the incorporation of relevant clinical risk factors. SxS-II has been recommended for the identification of patients with a high

cardiovascular risk among a population with multivessel or left main coronary artery disease (CAD) and for aiding in decision making regarding different coronary revascularization strategies[8]. SxS-□ is a better predictor of major adverse cardiovascular events (MACE) and mortality among patients with acute coronary syndrome (AMI) undergoing primary PCI compared with the conventional SxS and GRACE risk scores (Global Registry of Acute Coronary Event)[9–12]. However, the SxS-□ system is not the optimal risk score compared with other clinical risk scores[11, 13].

The relationship between cardiovascular benefits and RHR reduction has been generally acknowledged[5]. However, the impact of the temporal changes in RHR recorded over the acute phase of AMI on cardiovascular mortality and other events has not been adequately studied. Therefore, the aim of this study was to assess the predictive performance of the ΔHR recorded between discharge and the first outpatient visit regarding the prognosis of patients with AMI undergoing PCI, and to explore the prognostic value of a combined model including ΔHR and the SxS-□ system to reclassify the risk of further CV events.

Methods

Patient selection

A total of 635 consecutive cases with records of vital signs at the first post-discharge visit (2–4 weeks) were retrospectively screened out of 6592 patients with a confirmed diagnosis of AMI undergoing primary PCI at the Beijing Chaoyang Hospital Heart Center between January 2014 and June 2019. The diagnostic criteria of AMI were in accordance with the fourth universal definition of myocardial infarction (MI)[14]: (1) a significant cTnI increment above at least the 99th percentile upper reference limit; (2) typical ischemic symptoms; and (3) a newly developed left bundle branch block pattern or a new ST-segment elevation or depression in two or more contiguous leads, with readings of at least 0.2 mV in leads V1, V2, and V3 or of at least 0.1 mV in the remaining leads. The exclusion criteria were arrhythmia; atrial fibrillation; pacemakers; a life expectancy of less than 6 months; and a history of coronary artery bypass, dialysis, or cirrhosis.

Outpatient vital sign collection and SYNTAX score □ calculation

The RHR was measured in parallel to the measurement of blood pressure (OMRON HBP-9020 or HEM-7137, Omron, Shandong, China). The HRs were measured at admission and discharge and are presented as a mean value of two RHR values recorded by the inpatient physician. Accordingly, the temporal changes in RHR from admission and discharge resting heart rate (A-D ΔHR) were calculated by subtracting the HR at discharge from the HR at admission. During the routine visit after discharge (2–4 weeks), outpatient vital signs were measured automatically twice with a 1-min interval. The test was started after the participant had rested for 5 min with the arm resting on a table. We calculated temporal changes in resting HR (D-O and A-O ΔHR) by subtracting the HR recorded at the first post-discharge visit (oHR) from the value recorded at admission or discharge. All other baseline information, including clinical

features, demographics, and treatment records, were collected from the medical database of the Beijing Chaoyang Hospital.

In this study, coronary angiography was retrospectively reviewed by two cardiologists. Both investigators were blinded to the outcomes and management of medication during the follow-up. The SYNTAX score was calculated using the initial angiogram based on the SxS calculator. All lesions of stenosis ≥50% in main branch or major side branch (≥1.5 mm in diameter) were scored. Patients with a history of coronary artery bypass grafting were excluded. Subsequently, SxS-□ was calculated based on two anatomical variables (SxS and left main CAD) and six clinical variables (age, gender, COPD, peripheral arterial disease, creatinine clearance, and LVEF) using an automatic online calculation system.

Follow-up and clinical endpoint

All subjects were followed-up via telephone contact, scheduled outpatient visits, or the medical records after clinical adverse cardiovascular events. The primary endpoint was defined as the MACE, which was mainly comprised CV death, recurrent nonfatal MI, repeated coronary revascularization, and nonfatal ischemic stroke.

Statistical analysis

The continuous variables are presented as the mean ± standard deviation (mean ± SD) or median (interquartile range, IQR), and categorical variables are presented as frequency (percentage), as appropriate. Student's *t*-test was conducted for variables with a Gaussian distribution. The Mann–Whitney *U* or Kruskal–Wallis nonparametric tests were used to analyze non-normally distributed variables. The chi-squared test was used to detect differences in categorical variables. The Kaplan–Meier survival curves were implemented to evaluate the incidence of the clinical endpoint, whereas the log-rank test was used to detect intergroup differences. Cox proportional hazard regression analyses were used to identify predictors of MACE and CV mortality. The variance inflation factor (VIF) was calculated for each independent variable. A great collinearity was considered when VIF>10.

Receiver operating characteristic (ROC) curves were generated to assess the predictive value of SxS-□ alone and that of the combined models. Due to the limited ability of classical ROC curve analysis for time-dependent variables, the time-dependent ROC curves methods were performed in this study[15]. Moreover, the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to evaluate the degree to which the different types of ΔHR improved the predictive ability of the SxS-□ model[16]. The event NRI (NRIe) was defined as the net percentage of patients with an event that was correctly assigned a higher predicted risk, whereas the nonevent NRI (NRIne) was defined as the net percentage of patients without an event that was correctly assigned a lower predicted risk. The likelihood ratio test was used to assess whether the combined models could provide a better prognostic value. Akaike's information criteria (AIC) were measured as a parameter to identify the "best-fitting" combined model[17]. Statistical analyses were performed using STATA (version 15.0) and the R

statistical software (version 3.4.0). All statistical tests were two-tailed, and a *P*-value ≤ 0.05 was considered statistically significant.

Results

Clinical information at the baseline and incidence of MACE

After screening the outpatient documents and angiogram, a total of 605 AMI subjects with detailed HR at the first post-discharge visit met the inclusion criteria. Subsequently, all recruited patients were categorized into two groups according to the median of changes in heart rate between discharge and the first post-discharge visit (D-O ΔHR ≤−1 bpm group and ΔHR >−1 bpm group). As presented in Table 1, patients in the D-O ΔHR≤−1 bpm group were older, had a higher proportion of females, presented with a lower admission and discharge diastolic blood pressure (DBP), a lower discharge and outpatient RHR, higher counts of white blood cells, and increased level of hs-CRP. Moreover, their presentation was complicated by a higher prevalence of hypertension and diabetes mellitus and lower proportions of β-blocker and statin therapy. No significant differences in the baseline characteristic were observed between the two ΔHR groups.

Table 1

Baseline characteristic according to the median of temporal change values in heart rate between discharge and first outpatient visit

Factor	Total	D-O ΔHR ≤-1 (beats/min)	D-O ΔHR > -1 (beats/min)	p-value
N	605	314	291	
Age, (year)	62 (54, 71)	63 (54, 72)	62 (51, 69)	0.06
Male, n (%)	463 (76.5%)	229 (72.9%)	234 (80.4%)	0.04
BMI, (kg/m^2)	25.4 (3.68)	25.4 (3.26)	25.4 (4.09)	0.79
Diagnosis, n (%)				0.25
STEMI	592 (97.9%)	308 (98.1%)	284 (97.6%)	
NSTEMI	13 (2.1%)	6 (1.8%)	7 (2.4%)	
Killip, n (%)				0.64
I	283 (46.8%)	145 (46.2%)	138 (47.4%)	
II	262 (43.3%)	140 (44.6%)	122 (41.9%)	
III	33 (5.5%)	18 (5.7%)	15 (5.2%)	
IV	27 (4.5%)	11 (3.5%)	16 (5.5%)	
LVEF, %	61 (52, 67)	61 (51, 66)	61 (52, 67)	0.29
Outpatient SBP, (mmHg)	126 (16.6)	127 (17.6)	125 (15.4)	0.07
Outpatient DBP, (mmHg)	74 (9.8)	74 (11.3)	73 (8.0)	0.96
Admission SBP, (mmHg)	124 (20.4)	123 (18.2)	125 (22.5)	0.27
Admission DBP, (mmHg)	71 (12.7)	70 (11.8)	73 (13.4)	0.03
Discharge SBP, (mmHg)	122 (13.5)	122 (13.0)	122 (14.1)	0.70
Discharge DBP, (mmHg)	71 (9.0)	70 (8.5)	72 (9.5)	0.04
Admission HR, (beat/min)	76 (67, 85)	76 (68, 86)	75 (65, 84)	0.21
Discharge HR, (beat/min)	70 (65, 76)	66 (63, 70)	72 (69, 79)	<0.001
Outpatient HR, (beat/min)	70 (65, 77)	75 (70, 80)	66 (60, 70)	<0.001
A-D ΔHR, (beat/min)	-1 (1, 20)	7 (-1, 16)		<0.001

			-2 (-7, 6)	
A-O ΔHR, (beat/min)	4 (-5, 14)	-1 (-10, 9)	9 (1, 18)	<0.001
Medical history				
Prior MI, n (%)	70 (11.6%)	33 (10.5%)	37 (12.7%)	0.40
Diabetes mellitus, n (%)	199 (32.9%)	119 (37.9%)	80 (27.5%)	<0.01
Hypertension, n (%)	337 (55.7%)	191 (60.8%)	146 (50.2%)	<0.01
Hyperlipoidemia, n (%)	150 (24.8%)	74 (23.6%)	76 (26.1%)	0.47
COPD, n (%)	52 (8.6%)	26 (8.3%)	26 (8.9%)	0.77
PVD, n (%)	4 (0.7%)	4 (1.3%)	0 (0%)	0.12
Smoker, n (%)	358 (59.2%)	188 (59.9%)	170 (58.4%)	0.72
Laboratory test				
White blood cell, (10*9/L)	10.8 (2.86)	11.1 (2.89)	10.6 (2.80)	0.02
Precent of neutral cell, (%)	79.8 (10.07)	79.9 (9.86)	79.7 (10.3)	0.79
Hemoglobin, (10*9/L)	134 (16.9)	135 (15.9)	133 (18.0)	0.23
Platelet count, (10*9/L)	216 (57.3)	219 (57.2)	212 (57.1)	0.11
Cholesterol, (mmol/L)	4.58(1.08)	4.62 (1.03)	4.53 (1.12)	0.11
HDL, (mmol/L)	1.1 (0.29)	1.1 (0.26)	1.1 (0.32)	0.96
LDL, (mmol/L)	2.88 (0.89)	2.91 (0.89)	2.84 (0.88)	0.34
Triglyceride, (mmol/L)	1.32 (0.95, 1.86)	1.34 (0.92, 1.78)	1.3 (0.96, 1.92)	0.72
Fasting glucose, (mmol/L)	6.7 (5.43, 9.01)	6.63 (5.4, 9.06)	6.77 (5.52, 8.96)	0.95
BNP, (pg/ml)	195 (58.6, 642)	245 (64, 656)	145 (55.3, 638)	0.10
CTNI, (ng/ml)	31.28 (9.79, 76.6)	30.4 (10.07, 79.85)	31.99 (9.61, 88.21)	0.65
Hs-CRP, (mg/dl)	4.5	5.3	3.8	0.02

	(2.14, 10.99)	(2.26, 11.3)	(2.0, 10.6)	
Creatinine, (mmol/L)	74.1 (64.4, 87.4)	74.5 (65.6, 87.4)	74.1 (64.3, 87.1)	0.71
Medication at discharge				
Aspirin, n (%)	604 (99.8%)	314 (100.0%)	290 (99.7%)	0.30
Clopidogrel, n (%)	587 (97.0%)	306 (97.5%)	281 (96.6%)	0.52
Ticagrelor, n (%)	18 (3.0%)	8 (2.5%)	10 (3.4%)	0.95
β-blocker, n (%)	380 (62.9%)	180 (57.5%)	200 (68.7%)	<0.01
ACEI/ARB, n (%)	310 (51.2%)	158 (50.3%)	152 (52.2%)	0.64
Statin, n (%)	545 (90.1%)	272 (86.6%)	273 (93.8%)	<0.01
Nitrogen, n (%)	179 (29.6%)	95 (30.3%)	84 (28.9%)	0.71
SYNTAX score	26.32 (9.85)	26.69 (9.68)	25.92 (10.04)	0.34
SYNTAX score II	27.6 (23, 37)	28 (23, 38)	27.6 (22.8, 36)	0.16

Abbreviation: BMI, body mass index; STEMI, ST-segment elevated myocardial infraction; NSTEM, non ST-segment elevated myocardial infraction; LVEF, left ventricular ejection fraction; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; BNP, brain natriuretic peptide; CTNI, cardiac troponin I; HDL, High density lipoprotein; LDL, Low density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery.

During the median follow-up time of 26 months (IQR: 16–38 months), a total of 134 (22.1%) cases exhibited adverse clinical events, which included 34 (5.6%) CV deaths, 32 (5.3%) recurrent MIs, 89 (14.7%) repeat revascularizations, and 4 (0.7%) nonfatal strokes. The overall MACE and CV death values were significantly higher in the D-O ΔHR ≤−1 bpm group compared with the D-O >−1 bpm group (26.4% *vs.* 17.5%, $P < 0.01$; 7.6% *vs.* 3.4%, $P < 0.05$, respectively). Patients in the D-O ΔHR≤−1 bpm group were prone to complications, as they exhibited a higher frequency of repeat revascularizations (17.2% *vs.* 12.0%, $P = 0.07$) and ischemic stroke (1.3% *vs.* 0%, $P = 0.05$) (Figure 1).

Kaplan–Meier survival curves and Cox regression analysis for MACE and CV mortality

The cumulative survival curves for MACE and CV mortality in the two groups, which were divided according to the median D-O ΔHR and the median A-D ΔHR were assessed using a Kaplan–Meier survival curve, respectively (Figure 2). During the observational period, patients with D-O ΔHR >−1 bpm had a

significantly lower incidence of MACE and CV deaths compared with in the D-O ΔHR≤−1 bpm group (log-rank test: $P < 0.01$ and $P = 0.02$, respectively) (Figure 2 A and B). Moreover, a similar phenomenon was observed in the two groups by dividing by the median A-D ΔHR (log-rank test: $P < 0.01$ for MACE and $P < 0.01$ for CV deaths, respectively) (Figure 2 C and D). In contrast, the cumulative survival rates regarding MACE and CV deaths were not significantly different among the two groups that were divided by the median A–O ΔHR (Figure 2 E and F).

The results of the Cox proportional hazard regression analysis are shown in Table 2. The univariate analysis revealed that RHR at the outpatient visit (HR = 1.02, 95% CI = 1.013–1.031, $P < 0.001$; HR = 1.02, 95% CI = 1.013–1.031, $P < 0.001$) and admission (HR = 1.01, 95% CI = 1.002–1.023, $P = 0.02$; HR = 1.02, 95% CI = 1.002–1.040, $P = 0.03$), and A–D ΔHR (HR = 1.01, 95% CI = 1.001–1.021, $P = 0.02$; HR = 1.02, 95% CI = 1.004–1.038, $P = 0.02$) were associated with an increased risk of MACE and CV mortality, respectively. The D–O ΔHR was a protector against MACE and CV mortality (HR = 0.98, 95% CI = 0.969–0.987, $P < 0.001$; HR = 0.96, 95% CI = 0.954–0.976, $P < 0.001$, respectively), whereas an elevated value of A–O ΔHR was exclusively associated with a decrease in CV mortality (HR = 0.97, 95% CI = 0.963–0.991, $P = 0.001$). No multicollinearity between the different types of ΔHR and its continuous parameters (i.e., SS, age, LVEF, and creatinine) was observed based on the VIF. After adjustment for other potential confounders, including sex, age, levels of creatine, ejection fraction, SYNTAX score, level of HGB, history of diabetes mellitus, hypertension, hyperlipidemia, PCI, and prior MI, the multivariate analysis indicated that the D–O ΔHR (HR = 0.97, 95% CI = 0.958–0.985, $P < 0.001$), A–O ΔHR (HR = 0.98, 95% CI = 0.971–0.997, $P = 0.02$), and RHR at the first outpatient visit (HR = 1.02, 95% CI = 1.011–1.039, $P = 0.001$) remained independent powerful predictors of the prevalence of CV morality. Regarding the incidence of MACE, the D–O ΔHR (HR = 1.02, 95% CI = 1.011–1.039, $P = 0.001$), A–D ΔHR (HR = 1.01, 95% CI = 0.997–1.020, $P = 0.05$), and RHR at the first outpatient visit (HR = 1.02, 95% CI = 1.006–1.025, $P < 0.001$) remained independent powerful predictors of outcomes in patients with AMI.

Table 2

Cox proportional hazard regression analyses for major adverse cardiovascular events and CV mortality

Model [a]	Univariate analysis		Multivariable analysis	
MACE	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
Outpatient HR	1.02 (1.013—1.031)	<0.001	1.02 (1.006—1.025)	<0.01
Admission HR	1.01 (1.002—1.023)	0.02	1.01 (0.998—1.020)	0.10
Discharge HR	0.99 (0.974—1.015)	0.63	0.99 (0.969—1.012)	0.38
A-D ΔHR	1.01 (1.001—1.021)	0.02	1.01 (0.997—1.020)	0.05
A-O ΔHR	0.99 (0.984—1.004)	0.25	0.99 (0.985—1.004)	0.31
D-O ΔHR	0.98 (0.969—0.987)	<0.001	0.98 (0.974—0.993)	<0.001
Mortality				
Outpatient HR	1.03 (1.023—1.043)	<0.001	1.02 (1.011—1.039)	0.001
Admission HR	1. 02 (1.002—1.040)	0.03	1.01 (0.991—1.034)	0.24
Discharge HR	0.98 (0.942—1.025)	0.42	0.96 (0.920—1.013)	0.15
A-D ΔHR	1.02 (1.004—1.038)	0.02	1.02 (0.998—1.036)	0.08
A-O ΔHR	0.97 (0.963—0.991)	0.001	0.79 (0.971—0.997)	0.02
D-O ΔHR	0.96 (0.954—0.976)	<0.001	0. 97 (0.958—0.985)	<0.001

a.Model: Adjustment of cofounding factors, including sex, age, creatine, ejection fraction, SYNTAX score, level of HGB, history of diabetes mellitus, hypertension, hyperlipidemia, PCI and prior MI.

Abbreviations: HGB, hemoglobin；PCI，percutaneous coronary intervention；MI，myocardial infarction.

Combination of SxS-Ⅹ with different types of ΔHR values for predicting clinical outcomes

Based on the likelihood ratio test, models of SxS-Ⅹ and D－O ΔHR exhibited the best fit with the lowest AIC compared with the remaining four models regarding both MACE (AIC: 1553.823, $P < 0.001$) and CV death (AIC: 390.9558, $P < 0.001$) (Table 3).

Table 3

Akaike's information criteria and likelihood ratio test to determine the best fitting model for predicting MACE and cardiovascular death.

		AIC	Likelihood ratio test		
Clinical outcomes	Model	AIC	χ^2	df	P-value
MACE	SxS-□	1561.39			
	SxS-II + oHR	1555.927	7.46	1	<0.01
	SxS-II + D-OΔHR	1553.823	9.57	1	<0.01
	SxS-II + A-DΔHR	1557.27	4.29	1	0.04
	SxS-II + A-OΔHR	1562.754	0.64	1	0.43
CV mortality	SxS-□	404.5431			
	SxS-□ + oHR	394.4685	12.07	1	<0.001
	SxS-II + D-OΔHR	390.9558	15.59	1	<0.001
	SxS-II + A-DΔHR	403.2508	2.96	1	0.09
	SxS-II+A-O ΔHR	400.9642	5.58	1	0.02

Abbreviations: AIC, Akaike's information criteria; SxS-□, SYNTAX score □; MACE, major adverse cardiovascular events.

The incremental prognostic value of the incorporation of the different types of ΔHR values into SxS-II regarding MACE and CV mortality was measured based on the increase in the area under the ROC curve (AUC) (Figure 3 A and B). Regarding MACE, no significant difference was observed among the AUC values of the models (SxS-II: 0.6396 *vs.* SxS-II + oHR: 0.6485 *vs.* SxS-II + D–O ΔHR: 0.6517 *vs.* SxS-II + A–D ΔHR: 0.6471 *vs.* SxS-II+ A–O ΔHR: 0.638; $P = 0.82$). Except for the SxS-II and A–O ΔHR models, the AUC of combination of the three remaining models for CV death was 0.7679, 0.7737, and 0.747, respectively, of which all were grossly higher than that recorded for SxS-□ alone ($P = 0.04$). According to the tendency analyzed by time-dependent ROC curve, it indicated that the AUC containing SxS-II and D–O ΔHR could provide a durable and competent predictive ability for MACE and CV deaths (Figure 3 C and D).

According to the results obtained using NRI and IDI, the models of SxS-□ and D–O ΔHR exhibited a significantly better net reclassification improvement in predicting MACE and CV mortality (Table 4). Compared with the other combined models, models of SxS-□ and D–O ΔHR provided a significant improvement of 2.99% in the reclassification of patients with MACE and an improvement of 19.32% in the classification of those without MACE, with a significant ($P < 0.05$). In total, the net reclassification improvement (NRI) of the models of SxS-□ and D–O ΔHR was 22.31% and 56.0% regarding MACE and CV deaths, respectively. In the setting of cardiovascular death, the two combined models of SxS-□ and D–O ΔHR or oHR resulted in a significant discrimination and reclassification improvement in the nonevent and event groups (17.64% and 38.36%, and 29.42% and 46.76%, respectively; $P < 0.001$). However, the IDI analysis indicated that the predictive value of the system

regarding MACE and cardiovascular death was only significantly improved by the incorporation of D–O ΔHR into the SxS-□ model (MACE: 0.0107, $P < 0.05$; cardiovascular death: 0.0759, $P = 0.03$).

Table 4

Net reclassification improvement for model improvement with the addition of different types of heart rate discrepancy to SS□ alone

MACE						
Models	NRIe	NRIne	NRI total	P-value	IDI total	P-value
SxS-□ + oHR	-0.2239	0.3546	0.1307	0.18	0.0096	0.09
SxS-II + D-OΔHR	0.0299	0.1932	0.2231	<0.05	0.0107	<0.05
SxS-II + A-OΔHR	0.00	0.0064	0.0064	0.95	0.0008	0.25
SxS-II + A-DΔHR	0.0149	0.096	0.1109	0.25	0.0058	0.10
Cardiovascular mortality						
Model	NRIe	NRIne	NRI total	P-value	IDI total	P-value
SxS-□ + oHR	0.2942	0.4676	0.7617	<0.001	0.0627	0.07
SxS-II + D-OΔHR	0.1764	0.3836	0.5600	0.001	0.0759	0.03
SxS-II + A-OΔHR	-0.2352	0.1874	-0.0478	0.61	0.0323	0.15
SxS-II + A-DΔHR	0.1764	0.1704	0.3469	0.05	0.0077	0.08

Abbreviations: NRI, net reclassification index; IDI, integrated discrimination improvement; SxS-□, SYNTAX score □; HR, heart rate; MACE, major adverse cardiovascular events.

Discussion

The findings of the present study shed some light on the association between three different types of ΔHR recorded during the acute phase of MI and long-term adverse clinical events in patients with AMI. After adjustment for other relevant confounding factors, the temporal RHR changes recorded between discharge and the first outpatient visit (2–4 weeks) remained an independent predictor of MACE and CV mortality. Moreover, models combining D–O ΔHR and the SxS-□ system efficiently improved the predictive value regarding long-term CV death and MACE. In addition, the calibration, discriminatory capacity, and reclassification of the SxS-□ model were significantly updated by the integration of D–O ΔHR.

The association between changes in RHR and cardiovascular mortality and other outcomes has been previously assessed in populations without a known CV disease[3, 4, 18]. In the study reported by Vazir[2], individuals with an increase in ΔHR within a median interval of 3 years exhibited a greater risk of CV

mortality and other clinical outcomes in a community-based cohort. A series of recent studies have demonstrated that the predictive value of changes in RHR regarding CV mortality and other clinical events is similar to or better than that of RHR[1, 4, 19]. Although the subjects included in most studies had no history of coronary heart disease (CHD) as the target of primary prevention for the incidence of CHD, few studies have investigated the predictive value of ΔHR for cardiovascular outcomes. To the best of our knowledge, this was the first study to describe an association between long-term cardiovascular deaths and other events and D–O ΔHR in patients AMI undergoing primary PCI. The present study indicated that D–O ΔHR at the early stage of AMI is likely to be a powerful and efficient predictor of cardiovascular outcomes.

As previously demonstrated by the results of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Study)[7], we confirmed that an increase in RHR over a median of 3 months was associated with a higher risk of CV deaths, hospitalization for heart failure, and stroke in patients with heart failure with a preserved ejection fraction, with the exception of the incidence of recurrent MI. Our observations suggest a similar prognostic importance for the changes in RHR that occur between the period from discharge to the first outpatient visit in patients with AMI. In essence, an increase in HR may reflect the higher sympathetic tone triggered by the deterioration of HF or a cascade of inflammatory reactions observed in the pathophysiology of AMI. In the study reported by Paterek *et al.* [20], the cardiac output stimulated by an increased RHR was elevated within 7 days and, after a drop, within 1 to 2 months after MI in a rat model. Further beneficial effects of RHR reduction on the left ventricular diastolic pressure and increased ejection fraction were observed within 1 to 2 months, similarity to our findings. Conversely, our previous study[21] suggested that an impaired heart rate profile at the first post-discharge visit is associated with long-term cardiovascular outcomes. The decreased RHR changes are associated with reduced myocardial oxygen consumption, adequate coronary and myocardial perfusion, and rehabilitation of impaired cardiac function and subendocardial blood flow[1, 22, 23].

The SxS-□ score comprises both coronary anatomy and clinical risk factors and was better than the traditional SYNTAX score in guiding decision making regarding the treatment of left main CAD or complex three-vessel disease in ESC guidelines[8, 24]. Recent studies showed that the predictive ability of the SxS-□ risk system regarding the long-term CV mortality is also excellent in patients with STEMI, and is superior to other risk-scoring systems, including the GRACE and TIMI scores [9, 11, 25, 26]. Although the increase in RHR is independently associated with long-term MACE, cardiovascular mortality, and heart failure in patients with AMI[21, 27, 28], the SxS-II system does not include any vital sign indices as a variable in the model. As presented here, the D–O ΔHR grossly provided a much more significant improvement in risk stratification and reclassification of clinical outcomes, better than the RHR at post-discharge visit. Although a greater improvement in net reclassification was found after adding the RHR at the first outpatient visit to the SxS-II system, the IDI analysis devised by Pencina *et al.*[29] for evaluating reclassification indicated that these matrices improved when the D–O ΔHR is added to the SxS-II. In conclusion, our analysis provided a comprehensive and logical rationale for determining the utility of the temporal changes in HR as a biomarker for optimizing the predictive ability of the SxS-II system.

Limitations

Some of the limitations of this study should be noted and discussed. First, because of the retrospective nature of the study, a selection bias was inevitable and affected our findings. Moreover, the high proportion of STEMI patients included in this study may have caused some selection bias. Therefore, a large prospective study with a subgroup analysis is necessary to address these issues. Second, previous studies indicated that the RHR at discharge is associated with CV mortality and clinical outcomes; however, no similar phenomenon was observed in our study. This may be attributed to the controlled RHR at discharge, with a median of 70 beats/min, which yields a similar risk of CV mortality to that of an RHR of 60 beats/min[27]. Hence, we speculate that the discrepancy between the two RHR values recorded at different time points may increase the predictive ability of the tool. Finally, as RHR or ΔHR is associated with various chronic inflammation disorders, such as asthma, inflammatory bowel disease, and vasculitis, it is uncertain whether ΔHR is potentially influenced by the inflammation status. However, in the context of the hyperactivity of inflammation disorders, the RHR could still evaluate the severity of inflammation activity and predict coronary atherosclerosis and cardiac mortality[30].

Conclusion

According to the results of this retrospective study, it is worth noting that D–O ΔHR was a strong independent predictor of adverse clinical outcomes in patients with AMI undergoing primary PCI after adjusting for conventional cardiovascular risk factors. Moreover, the models that incorporated the ΔHR recorded between discharge and the first outpatient visit into the SxS-II system provided the best predictive ability for patients with AMI after primary PCI.

Declarations

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to the policies of Beijing Chaoyang Hospital on individual confidentiality but are available from the corresponding author upon reasonable request.

Declarations

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Consent to publication

Not applicable.

Competing interests

All authors declare no conflict of interest.

Ethical approval and Consent to Participate

The current study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of Beijing Chaoyang Hospital approved this study (2017-S-187) and informed consent was waived by the Ethics Committee of Beijing Chaoyang Hospital because of the retrospective nature of the study.

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Author contributions

Dr. CL, WJZ, YXY conceived the present study, collected and assembled all data, participated in the design, conducted data analysis and drafted the manuscript. Dr. QZ and KBL commented on the manuscript drafts. Pro. MLC provided material and technical support and commented on the manuscript drafts. Dr. KX and Professor LFW aided interpretation of data, commented on this study design and provided critical review. All authors have read and approved the manuscript.

References

1. Nwabuo CC, Appiah D, Moreira HT, Vasconcellos HD, Aghaji QN, Ambale-Venkatesh B et al. Temporal Changes in Resting Heart Rate, Left Ventricular Dysfunction, Heart Failure and Cardiovascular Disease: CARDIA Study. Am J Med. 2020; 133:946-53.
2. Vazir A, Claggett B, Jhund P, Castagno D, Skali H, Yusuf S et al. Prognostic importance of temporal changes in resting heart rate in heart failure patients: an analysis of the CHARM program. Eur Heart J. 2015; 36:669-75.
3. Nauman J, Janszky I, Vatten LJ, Wisloff U. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA. 2011; 306:2579-87.
4. Seviiri M, Lynch BM, Hodge AM, Yang Y, Liew D, English DR et al. Resting heart rate, temporal changes in resting heart rate, and overall and cause-specific mortality. Heart. 2018; 104:1076-85.

5. Cucherat M. Quantitative relationship between resting heart rate reduction and magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials. Eur Heart J. 2007; 28:3012-9.
6. Kim TH, Kim H, Kim IC, Yoon HJ, Park HS, Cho YK et al. Heart rate at first postdischarge visit and outcomes in patients with heart failure. Heart. 2018; 104:1086-92.
7. Vazir A, Claggett B, Pitt B, Anand I, Sweitzer N, Fang J et al. Prognostic Importance of Temporal Changes in Resting Heart Rate in Heart Failure and Preserved Ejection Fraction: From the TOPCAT Study. JACC Heart Fail. 2017; 5:782-91.
8. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European heart journal. 2014; 35:2541-619.
9. Rencuzogullari I, Cagdas M, Karabag Y, Karakoyun S, Yesin M, Cinar T et al. Value of syntax score II for predicting in-hospital and long-term survival in octogenarians with ST-segment elevation myocardial infarction: A comparison of six different risk scores. Archives of gerontology and geriatrics. 2019; 83:37-43.
10. Obeid S, Frangieh AH, Raber L, Yousif N, Gilhofer T, Yamaji K et al. Prognostic Value of SYNTAX Score II in Patients with Acute Coronary Syndromes Referred for Invasive Management: A Subanalysis from the SPUM and COMFORTABLE AMI Cohorts. Cardiol Res Pract. 2018; 2018:9762176.
11. Cid-Alvarez AB, Gomez-Pena F, Redondo-Dieguez A, Avila A, Lopez D, Sanmartin X et al. Prognostic impact of the SYNTAX score II in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: analysis of a four-year all-comers registry. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2019; 15:E796-+.
12. Li C, Zhang Q, Wang Q, Zhong J, Wang L, Li K et al. Prognostic values of the SYNTAX score II and the erythrocyte sedimentation rate on long-term clinical outcomes in STEMI patients with multivessel disease: a retrospective cohort study. BMC Cardiovasc Disord. 2020; 20:213.
13. Synetos A, Georgiopoulos G, Pylarinou V, Toutouzas K, Maniou K, Drakopoulou M et al. Comparison of prognostic risk scores after successful primary percutaneous coronary intervention. International journal of cardiology. 2017; 230:482-87.
14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018; 72:2231-64.
15. Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: current methods and applications. BMC Med Res Methodol. 2017; 17:53.
16. Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Statistics in medicine.

2008; 27:157-72.

17. Wagenmakers EJ FS. AIC model selection using Akaike weights. Psychonomic Bulletin & Review. 2004; 11:192-96.
18. Chen XJ, Barywani SB, Hansson PO, Ostgard Thunstrom E, Rosengren A, Ergatoudes C et al. Impact of changes in heart rate with age on all-cause death and cardiovascular events in 50-year-old men from the general population. Open Heart. 2019; 6:e000856.
19. Vazir A, Claggett B, Cheng S, Skali H, Shah A, Agulair D et al. Association of Resting Heart Rate and Temporal Changes in Heart Rate With Outcomes in Participants of the Atherosclerosis Risk in Communities Study. JAMA Cardiol. 2018; 3:200-06.
20. Paterek A, Kepska M, Kolodziejczyk J, Leszek P, Mackiewicz U, Maczewski M. Acute Heart Rate-Dependent Hemodynamic Function of the Heart in the Post-Myocardial Infarction Rat Model: Change Over Time. Can J Cardiol. 2018; 34:1341-49.
21. Li C, Zhang Q, Feng D, Wang L, Yang X, Su P et al. First post-discharge heart rate and long-term prognosis in patients with acute myocardial infarction. Rev Cardiovasc Med. 2022; 23:24.
22. Koskela JK, Tahvanainen A, Haring A, Tikkakoski AJ, Ilveskoski E, Viitala J et al. Association of resting heart rate with cardiovascular function: a cross-sectional study in 522 Finnish subjects. BMC Cardiovasc Disord. 2013; 13:102.
23. Fox KM, Ferrari R. Heart rate: a forgotten link in coronary artery disease? Nat Rev Cardiol. 2011; 8:369-79.
24. Serruys PW, Kogame N, Katagiri Y, Modolo R, Buszman PE, Iniguez-Romo A et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with three-vessel disease: 2-year follow-up of the SYNTAX II study. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2019.
25. Magro M, Nauta S, Simsek C, Onuma Y, Garg S, van der Heide E et al. Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: The MI SYNTAXscore study. American heart journal. 2011; 161:771-81.
26. Wang G, Wang C, Zhang Y, Wang P, Ran C, Zhao L et al. Usefulness of the SYNTAX score II to predict 1-year outcome in patients with primary percutaneous coronary intervention. Coron Artery Dis. 2016; 27:483-9.
27. Jensen MT, Kaiser C, Sandsten KE, Alber H, Wanitschek M, Iversen A et al. Heart rate at discharge and long-term prognosis following percutaneous coronary intervention in stable and acute coronary syndromes - results from the BASKET PROVE trial. Int J Cardiol. 2013; 168:3802-06.
28. Antoni ML, Boden H, Delgado V, Boersma E, Fox K, Schalij MJ et al. Relationship between discharge heart rate and mortality in patients after acute myocardial infarction treated with primary percutaneous coronary intervention. Eur Heart J. 2012; 33:96-102.
29. Pencina MJ, D'Agostino RB, Sr., Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. Stat Med. 2012; 31:101-13.

30. Vargas-Hitos JA, Soriano-Maldonado A, Martinez-Bordonado J, Sanchez-Berna I, Fernandez-Berges D, Sabio JM. Association of Resting Heart Rate With Arterial Stiffness and Low-Grade Inflammation in Women With Systemic Lupus Erythematosus. Angiology. 2018; 69:672-76.

Figures

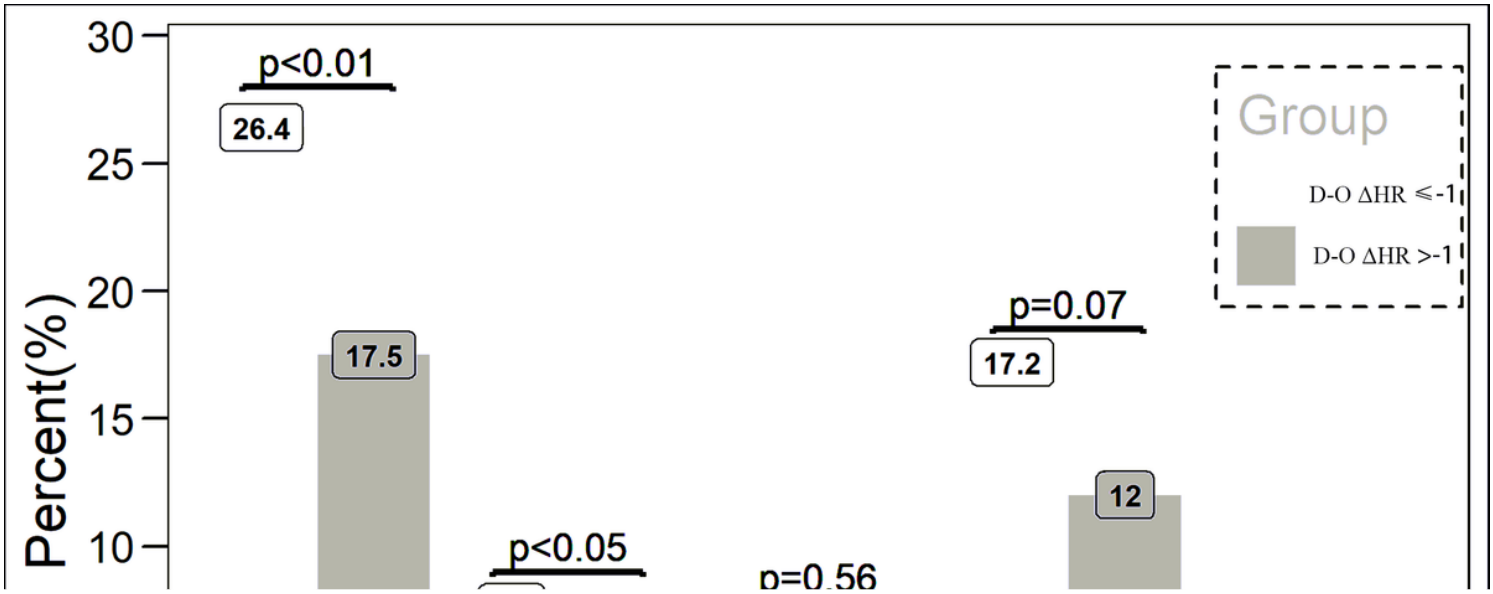

Figure 1

Comparison of clinical endpoints among the two D-O ΔHR groups. Patients with the D-O ΔHR ≤-1 bpm had higher incidence of MACE, CV mortality and non-fatal stroke.

Figure 2

2 Kaplan–Meier failure curve of MACE and CV mortality during the follow-up median of 26 months according to D-O□A-O and A-D ΔHR, respectively. Patients with the D-O ΔHR >-1 bpm were favorable to free MACE (A) and CV mortality (B). Patients with A-D ΔHR>5 bpm were prone to suffer MACE (C) and CV

mortality(D). No significant discrepancy among two group divided by the median of A-O ΔHR was observed on MACE (E) and CV mortality (F).

Figure 3

Conventional and time-dependent receiver operating characteristic (ROC) curve for the combined models and SYNTAX score II (SxS-□) alone in predicting long-term MACE (A, C) and CV mortality (B, D), respectively. Combined models containing SxS-□ and D-O ΔHR provided the best predictive value significantly.