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Predicting no-reflow phenomenon prior to primary percutaneous coronary intervention using a novel probability risk score derived from clinical and angiographic parameters

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Abstract. – OBJECTIVE: We aimed to create a clinically usable probability risk score for prediction of no-reflow (NRF) phenomenon prior to primary percutaneous coronary intervention (PPCI).

PATIENTS AND METHODS: This single-center and retrospective study included 1254 patients with acute ST-segment elevation myocardial infarction (STEMI) who underwent PPCI. Patients were randomly assigned into two groups in the ratio 2:1, the derivation dataset (n=840) and validation dataset (n=414). Independent predictors of NRF were identified and combined to create a prediction model using univariate and multivariate regression analysis in the derivation dataset. The risk score was tested and validated by calculating area under the receiver operating characteristic (ROC) curves in the derivation and validation datasets, respectively.

RESULTS: Five significant, independent predictors of NRF were identified: age ≥ 65 years (odds ratio [OR]: 2.473, 95% confidence interval [CI]: 0.389-1.484, $p < 0.01$), heart rate ≥ 89 bpm (odds ratio [OR]: 1.622, 95% confidence interval [CI]: 0.024-0.945, $p < 0.05$), Killip class ≥ II (odds ratio [OR]: 1.914, 95% confidence interval [CI]: 0.024-1.306, $p < 0.01$), total ischemic time ≥ 268 min (odds ratio [OR]: 2.652, 95% confidence interval [CI]: 0.493-1.565, $p < 0.01$), and thrombus burden G≥4 (odds ratio [OR]: 8.351, 95% confidence interval [CI]: 0.344-15.901, $p < 0.01$). The risk score was created combining these predictors with assigned points. The overall score ranged from 0 to 17 points. The optimal cutoff value of the risk score was 11 points (area under curve [AUC]: 0.772, 95% confidence interval [CI]: 0.729-0.815, sensitivity 71.21%, specificity 70.34%, positive predictive value 30.92%, negative predictive value 92.91%, $p < 0.001$). The ROC curve for the validation group showed good discriminant power.

CONCLUSIONS: We developed a novel risk score based on five clinical and angiographic parameters, which might be a useful clinical tool for prediction of NRF in STEMI patients prior to PPCI with an acceptable accuracy.

Key Words:
STEMI, Primary PCI, No-reflow, Risk score.

Introduction

Primary percutaneous coronary intervention (PPCI) is the most effective treatment for patients with acute myocardial infarction with ST-elevation (STEMI) with success rate of approximately 95%[1]. Rapid restoration of normal blood flow following PPCI in a previously occluded infarct-related artery is associated with improved clinical outcomes[2]. However, in a significant number of patients, restoration of normal blood, namely optimal myocardial reperfusion, cannot be achieved due to no-reflow (NRF) phenomenon[3,4]. NRF occurs in spite of having an opened and patent epicardial coronary artery without angiographic evidence of mechanical vessel obstruction[5].

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The incidence of NRF in patients with STEMI remained relatively high and largely unchanged[5] since its first description in 1992 by Ito et al[6], quoted in the literature to be from 11% to 45%[7-9], despite developments in the technique and technology used for PPCI as well as supporting pharmacological therapy. Furthermore, all previous studies[10-12] consistently showed that NRF after PPCI is an independent predictor of the morbidity as well as the short term and long term mortality. At the same time, the pathogenic mechanisms of NRF are considered complex and multifactorial and still only partially understood[13]. The following pathogenic mechanisms have been proposed: (1) pre-existing microvascular dysfunction, (2) distal micro-thrombo-embolization, (3) ischemic injury, (4) reperfusion injury, and (5) individual susceptibility[14].

Having in mind the importance of NRF and its complex pathophysiology, a number of studies and registries have aimed to identify risk factors and predictors of NRF[15]. Identifying predictors of NRF may help interventional cardiologist to guide and modify interventional strategy in order to reduce the risk of NRF and improve outcome[16]. Most of the previous studies have been focusing on biochemical and inflammatory biomarkers as potential predictors of NRF. Indeed, several biomarkers, including glucose, c-reactive protein, fibrinogen, albumin level, neutrophil/lymphocyte count, and some others have been linked with the occurrence of NRF[17-20]. Nevertheless, they are not a useful clinical tool for predicting no-reflow prior to PPCI since they are typically not available at the time of intervention. Therefore, there is an evident need to have effective predictive tool that will help interventional cardiologist to identify patients at high-risk for NRF prior to PPCI.

In this study, firstly, we sought to determine commonly available clinical and angiographic parameters as independent predictors of NRF, and thereafter, by using and combining these to create a clinically usable risk score for prediction of NRF prior to PPCI.

Patients and Methods

Study Population

In this retrospective study, we analyzed a total of 1254 consecutive patients with STEMI who underwent PPCI at the Clinical Hospital Center Zemun, between January 2012 and December 2017, who met following inclusion criteria: (1) patients of both sex, aged > 18 years with a new persistent ST-segment elevation in at least two contiguous leads, with elevation defined as ≥ 2 mV in men or ≥ 0.15 mV in women in leads V2 to V3, or ≥ 0.1 mV in the other leads; (2) duration of symptoms ≤ 12 hours from the onset of pain; (3) rise and fall of the level of myocardial injury markers (creatine kinase-myocardial band [CK-MB] and cardiac troponin I [cTnI]); (4) successfully completed PPCI with stent(s) deployment. The exclusion criteria were as follows: (1) left bundle branch block; (2) duration of symptoms >12 hours from onset until admission; (3) administered thrombolytic therapy; (4) mechanical complications requiring urgent cardiac surgery during index hospitalization; (5) previous PCI; (6) previous coronary artery bypass grafts; (7) pregnancy; (8) known malignancies; (9) previous bleeding disorders.

Patient data, including demographic, clinical, electrocardiographic, and angiographic characteristics, were obtained from the hospital records. The study was approved by the Ethics Committee of the Clinical Hospital Center Zemun decision number 303/1, dated June 14, 2018. Informed consent from patients was waived due to the study's retrospective design.

Coronary Angiography and Primary PCI

Coronary angiography and primary PCI were performed through standard femoral or radial artery approach. All patients received a loading dose of 300 mg acetylsalicylic acid and either 600 mg clopidogrel or 180 mg ticagrelor before invasive procedure. Unfractionated heparin (UFH) was administered in a total dose of 100 IU/kg. Manual thrombus aspiration, tirofiban infusion and intra-aortic balloon pump (IABP) insertion was applied according to the operator's choice. All PPCIs were performed for the culprit vessel only, although in exceptional cases like cardiogenic shock PCI was performed on non-culprit coronary arteries as well. All coronary angiograms were analyzed and the following parameters were evaluated: TIMI flow grade before and after PPCI, infarct-related artery (IRA), the length of the culprit lesion, coronary anatomy, lesion complexity, degree of coronary stenosis, thrombus burden, coronary ectasia and collateral circulation. The diameter of the culprit vessel was measured by quantitative coronary angiography (QCA).

Study Definitions

The NRF was defined by angiographic criteria of final TIMI flow grade ≤ 2 in the infarct-related coronary artery at the completion of PPCI.

Total ischemic time was defined as a time from the onset of cardiac symptoms until PPCI, and it was expressed in minutes.

The Killip-Kimball classification defines heart failure severity in acute myocardial infarction and is graded from class I to IV, based on clinical features[21]. Killip class I indicates no evidence of heart failure, i.e., the absence of rales over the lung fields; Killip class II indicates rales in less than 50% of the lung fields; Class III indicates acute pulmonary edema, i.e., rales in over 50% of the lung fields; Class IV indicates cardiogenic shock or arterial hypotension, defined as systolic blood pressure <90 mmHg and the evidence of peripheral vasoconstriction (oliguria, cyanosis, and diaphoresis).

The lesion complexity of the infarct-related artery was classified according to ACC/AHA classification[22] into types A, B1, B2, and C.

The TIMI flow[23] was graded from 0 to 3, based on angiographic assessment as follows: TIMI-0 indicates the absence of anterograde flow beyond the occlusion site; TIMI-1 indicates a faint anterograde flow beyond the culprit lesion, with an incomplete filling of the distal vessel; TIMI-2 indicates slow or delayed anterograde flow, with complete filling of the distal vessel; TIMI-3 indicates normal brisk flow, with rapid and complete filling of the distal vessel.

The thrombus burden was defined from grade 0 to 5, based on angiographic assessment of the presence of a thrombus and its relative size[24]. The thrombus burden classification is graded as follows: G0 indicates no angiographic evidence of thrombus; G1 indicates a possible thrombus; G2 indicates a definite presence of a small thrombus, with the greatest dimensions of less than 1/2 of the vessel's diameter; G3 indicates a moderate thrombus with the greatest linear dimensions of ½ but is <2 vessel's diameter; G4 indicates a large thrombus with the greatest linear dimension of >2 vessel's diameter; G5 indicates very large thrombus that completely blocks vessel flow.

Statistical Analysis

Patients were randomly assigned in the ratio 2:1 into two datasets, using a computer-generated random number: the derivation dataset (n=840) for model development and the validation dataset (n=414) for validation of the developed NRF risk score. Continuous variables were presented as a mean ± SD, and categorical variables were expresses as percentages. Variables were compared by a two-tailed Student's *t*-test for continuous variables of normal distribution or by the Mann-Whitney U test for continuous variables of non-normal distribution. χ^2-test was used for categorical variables.

In the derivation dataset, association between each variable and NRF were first tested using univariate analysis. The following demographic (age, male sex, smoking history), clinical (heart rate, systolic blood pressure, diastolic blood pressure, Killip class, history of diabetes, total ischemic time), electrocardiographic (maximal amplitude of ST-segment elevation, atrial fibrillation on admitting ECG), and angiographic variables (LAD as infarct-related artery, initial TIMI flow, thrombus burden G≥4, type C coronary lesion, collaterals, coronary ectasia) were considered for entry into the multivariate predictive model. Then, all significant variables were used to establish the predictive scoring system. The variables tested included age, heart rate, Killip class, total ischemic time, and thrombus burden. Each variable's contribution in the predictive screening model was based on its regression coefficient. The risk score was then created using the integer of the odds ratio (OR) for all significant independent predictors of NRF. Bootstrapping (n = 1000) was then performed to calculate all the 95% Confidence Interval [CI] estimates in the multivariable regression model for NRF. All predictors retained their statistical significance after bootstrapping, confirming the validity of the score.

Receiver operating characteristic (ROC) curves were used to identify the best cutoff value of each continuous variable in terms of capability of prediction of NRF. The model was tested for goodness-of-fit (Hosmer-Lemeshow test) and area under the ROC curve. The following values were calculated based on the ROC curve: sensitivity, specificity, positive predictive value, and negative predictive value. The optimal cutoff point selection was based on the Youden index, the maximum sum of sensitivity and specificity. Validation of the risk score was performed using the validation dataset. The discriminating properties of the NRF prediction model were investigated by calculating the area under a ROC

curve. Statistical analyses were performed using statistical software SPSS Statistics 22.0 (SPSS, Inc., Armonk, NY, USA) and R software, version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria). All *p*-values presented were 2-tailed and $p < 0.05$ was considered as statistically significant.

Results

In the derivation dataset, the incidence of NRF was 15.7%. Demographic, clinical and electrocardiographic characteristics of all patients included in the study in the derivation and validation datasets are shown in Table I.

Table I. Demographic, clinical and electrocardiographic characteristics of all patients included in the study in the derivation and validation datasets.

Variable	Derivation dataset (n = 840)			Validation dataset (n = 414)		
	All	No-reflow (n = 132)	Normal flow (n = 708)	All	No-reflow (n = 65)	Normal flow (n = 349)
Demographic characteristics						
Age	61.16±11.77	66.81±11.39**	58.90±11.18	61.46±11.52	64.85±11.28*	60.83±11.47
Age ≥ 65 years	326 (38.8)	78 (59.1)**	248 (35.0)	149 (36.0)	32 (49.2)*	117 (33.5)
Male sex	600 (71.4)	88 (66.7)	512 (72.3)	298 (28.0)	41 (63.1)	257 (73.6)
History of hypertension	586 (69.8)	486 (68.6)	100 (75.8)	306 (74.1)	51 (78.5)	257 (73.3)
History of diabetes	198 (23.5)	42 (31.8)	156 (22.0)	100 (24.2)	21 (32.3)	79 (22.6)
History of hyperlipoproteinemia	301 (35.8)	262 (37.0)	39 (29.5)	168 (40.6)	23 (35.4)	145 (41.5)
Smoking history	427 (50.9)	63 (47.7)	364 (51.4)	207 (50.0)	24 (36.9)*	183 (52.4)
History of cerebrvascular disease	29 (3.5)	7 (5.3)	22 (3.1)	15 (3.6)	1 (1.5)	14 (4.0)
History of chronic kidney disease	27 (3.2)	8 (6.1)*	19 (2.7)	6 (1.4)	1 (1.5)	5 (1.4)
History of myocardial infarction	41 (4.9)	9 (6.8)	32 (4.5)	21 (5.1)	5 (7.7)	16 (4.6)
History of angina	28 (3.3)	21 (3.0)	7 (5.3)	15 (3.6)	1 (1.5)	14 (4.0)
History of atrial fibrillation	37 (4.4)	13 (9.8)*	24 (3.4)	26 (6.3)	4 (6.2)	22 (6.3)
History of peripheral vascular artery disease	37 (4.4)	28 (4.0)	9 (6.8)	12 (2.9)	1 (1.5)	11 (3.2)
Family history of cardiovascular disease	28 (3.3)	21 (3.0)	7 (5.3)	12 (2.9)	1 (1.5)	11 (3.2)
Clinical characteristics						
Body mass index (kg/m^2)	26.25±4.23	26.22±4.24	26.41±4.14	26.07±4.22	25.95±4.18	26.74±4.38
Heart rate (beats per minute)	79.38±19.95	85.39±23.96**	78.26±18.92	78.99±19.55	79.40±23.51	78.92±18.75
Systolic blood pressure (mmHg)	131.26±25.96	123.28±30.31**	132.75±24.81	132.62±25.77	125.23±30.10*	134.00±24.69
Diastolic blood pressure (mmHg)	79.77±14.49	75.57±17.33**	80.5±14.33	80.16±15.19	75.15±19.74*	81.09±14.02
Killip class						
Class I	721 (85.8)	90 (68.2)**	631 (98.1)	352 (85.0)	41 (63.1)**	311 (89.1)
Class II	67 (8.0)	20 (15.5)*	47 (6.6)	38 (9.2)	12 (18.5)*	26 (7.4)
Class III	25 (3.0)	9 (6.8)*	16 (2.3)	9 (2.2)	4 (6.2)*	5 (1.4)
Class IV	27 (3.2)	13 (9.8)*	14 (2.0)	15 (3.6)	8 (12.3)**	7 (2.0)
Total ischemic time	268.20±187.15	363.84±229.07**	250.37±172.68	262.04±175.14	331.83±217.55**	249.04±163.16
Resuscitation before PPCI	31 (3.7)	9 (6.8)*	22 (3.1)	19 (4.6)	5 (7.5)	14 (4.0)
Electrocardiographic characteristics						
Infarction localization						
Anterior	334 (39.8)	65 (49.2)*	269 (38.0)	177 (42.8)	32 (49.2)	145 (41.5)
Inferior	506 (11.0)	67 (50.8)*	439 (62.0)	237 (57.2)	33 (50.8)	204 (58.5)
Heart rhythm						
Sinus rhythm	749 (89.2)	105 (79.5)**	644 (91.0)	367 (88.6)	56 (86.2)	311 (89.1)
Atrial fibrillation	37 (4.4)	13 (9.8)**	24 (3.4)	26 (6.3)	4 (6.2)	22 (6.3)
Nodal rhythm	18 (2.1)	5 (3.8)	13 (1.8)	3 (0.7)	1 (1.5)	2 (0.6)
AV block						
I degree	16 (1.9)	14 (2.0)	2 (1.5)	6 (1.4)	0 (0.0)	6 (1.7)
II degree	9 (1.1)	7 (1.0)	2 (1.5)	6 (1.4)	1 (1.5)	5 (1.4)
III degree	15 (1.8)	11 (1.6)	4 (3.0)	10 (2.4)	3 (4.6)	7 (2.0)
Maximal amplitude of ST- elevation (mm)	2.70±1.56	3.34±1.78**	2.58±1.49	2.75±1.52	3.48±1.57**	2.61±1.47
QS pattern in ECG	247 (29.4)	196 (27.7)*	51 (38.5)	113 (27.3)	20 (30.8)	93 (26.6)
Non-sustained ventricular tachycardia	2 (0.2)	0 (0.0)	2 (0.3)	2 (0.5)	0 (0.0)	2 (0.6)
Ventricular fibrillation	2 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

PPCI; primary percutaneous coronary intervention. *No-reflow group *vs*. normal flow group in the derivation and validation dataset, $p < 0.05$. **No-reflow group *vs*. normal flow group in the derivation and validation dataset, $p < 0.01$.

Angiographic characteristics of patients in the derivation and validation datasets are shown in Table II. Multiple stepwise logistic regression analysis revealed five predictors significantly associated with the incidence of NRF: age ≥ 65 years (odds ratio [OR]: 2.473, 95% confidence interval [CI]: 0.389-1.484, $p < 0.01$), heart rate ≥ 89/min (odds ratio [OR]: 1.622, 95% confidence interval [CI]: 0.024-0.945, $p < 0.05$), Killip class ≥ II (odds ratio [OR]: 1.914, 95% confidence interval [CI]: 0.024-1.306, $p < 0.01$), total ischemic time ≥ 268min (odds ratio [OR]: 2.652, 95% confidence interval [CI]: 0.493-1.565, $p < 0.01$), and thrombus burden G≥4 (odds ratio [OR]: 8.351, 95% confidence interval [CI]: 0.344-15.901, $p < 0.01$). Model of multivariate regression analysis for NRF is shown in Table III.

These five identified predictors were used to develop a risk scoring system for prediction of NRF prior to PPCI. The overall score for a patient ranges from 0 to 17 points (except that 16 points is impossible to obtain). We named the developed risk score HAKTT as an acronym consisting of the first letters of words of five predictors included in the score: heart rate, age, Killip class, total ischemic time, and thrombus burden. Sensitivity, specificity, positive predictive value and negative predictive value for each level of the HAKKT risk score

Table II. Angiographic characteristics of all patients included in the study in the derivation and validation datasets.

Variable	Derivation dataset (n = 840)			Validation dataset (n = 414)		
	All	No-reflow (n = 132)	Normal flow (n = 708)	All	No-reflow (n = 65)	Normal flow (n = 349)
Infarct-related artery						
Left main	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.6)
LAD	318 (37.9)	64 (48.5)*	254 (35.9)	160 (38.6)	31 (47.7)	129 (37.0)
Diagonal branch	17 (2.0)	2 (1.5)	15 (2.1)	15 (3.6)	2 (3.1)	13 (3.7)
LCX	137 (16.3)	11 (8.3)*	126 (17.8)	64 (15.5)	6 (9.2)	58 (16.6)
RCA	367 (43.7)	55 (41.7)	312 (44.1)	173 (41.8)	26 (40.0)	147 (42.1)
Number of narrowed coronary arteries						
Single vessel disease	409 (48.7)	52 (39.4)*	357 (50.4)	194 (46.9)	25 (38.5)	169 (48.4)
Two vessel diseases	254 (30.2)	42 (31.8)	212 (29.9)	128 (30.9)	18 (27.7)	110 (31.5)
Three vessel diseases	176 (21.0)	38 (28.8) *	138 (19.5)	92 (22.2)	22 (33.8)*	70 (20.1)
Initial TIMI flow						
0	616 (73.3)	114 (86.4)**	502 (70.9)	305 (73.7)	59 (90.8)**	246 (70.5)
1	55 (6.5)	13 (9.8)	42 (5.9)	20 (4.8)	5 (7.7)	15 (4.3)
2	69 (8.2)	3 (2.3)*	66 (9.3)	26 (6.3)	1 (1.5)	25 (7.2)
3	100 (11.9)	2 (1.5)**	98 (13.8)	63 (15.2)	0 (0.0)**	63 (18.1)
Lesion complexity						
A	3 (0.4)	0 (0.0)	3 (0.4)	1 (0.2)	0 (0.0)	1 (0.3)
B1	46 (5.5)	0 (0.0)	46 (6.5)	22 (5.3)	0 (0.0)	22 (6.3)
B2	176 (21.0)	15 (11.4)*	161 (22.7)	84 (20.3)	6 (9.2)	78 (22.3)
C	615 (73.2)	117 (88.6)**	498 (70.3)	307 (74.2)	59 (90.8)**	248 (71.1)
Thrombus burden						
G0	38 (4.5)	0 (0.0)	38 (5.4)	18 (4.3)	0 (0.0)	18 (5.2)
G1	41 (4.9)	0 (0.0)	41 (4.9)	25 (6.0)	1 (1.5)	24 (6.9)
G2	40 (4.8)	0 (0.0)	40 (4.8)	26 (6.3)	1 (1.5)	22 (6.3)
G3	66 (7.9)	5 (3.8)	61 (8.6)	23 (5.6)	4 (6.2)	15 (4.3)
G4	51 (6.1)	16 (12.1)**	35 (4.9)	19 (4.6)	4 (6.2)*	15 (4.3)
G5	604 (71.9)	111 (84.1)**	493 (69.6)	303 (73.2)	59 (90.8)**	244 (69.9)
Collaterals	69 (8.2)	10 (7.6)	59 (8.3)	65 (15.7)	2 (6.7)	63 (16.4)
Coronary ectasia	10 (1.2)	4 (3.0)*	6 (0.8)	7 (1.7)	2 (3.1)	5 (1.4)
Vessel diameter at culprit site (mm)	3.03±0.57	3.02±0.66	3.03±0.55	3.03±0.54	3.04±0.62	3.03±0.52
Vascular access						
Femoral	650 (77.4)	98 (74.2)	552 (78.0)	324 (78.3)	57 (87.7)*	267 (7.5)
Radial	190 (22.6)	34 (25.8)	156 (22.0)	90 (21.7)	8 (12.3*	82 (23.5)

LAD; left anterior descending coronary artery, LCX; left circumflex coronary artery, RCA; right coronary artery. *No-reflow group *vs*. normal flow group in the derivation and validation dataset, $p < 0.05$. **No-reflow group *vs*. normal flow group in the derivation and validation dataset, $p < 0.01$.

Table III. Model of logistic regression analysis of the risk factors for the development of risk scoring system.

Variables	B	S.E.	OR	BCa 95% Confidence Interval		p-value
Age ≥ 65 years	0.905	0.226	2.473	0.389	1.484	< 0.001
Male sex	-0.168	0.240	0.845	-0.657	0.244	0.482
History of diabetes	0.081	0.190	1.084	-0.350	0.518	0.672
Heart rate ≥ 89 bpm	0.484	0.238	1.622	0.024	0.945	0.043
Killip class ≥ II	0.649	0.277	1.914	0.024	1.306	0.019
Systolic blood pressure	-0.011	0.293	0.990	-0.561	0.551	0.971
Diastolic blood pressure	-0.190	0.297	0.827	-0.865	0.418	0.522
Total ischemic time ≥ 268 ms	0.975	0.216	2.652	0.493	1.565	< 0.001
Atrial fibrillation on ECG	0.570	0.447	0.002	-0.320	1.444	0.202
Maximal amplitude of ST- elevation	0.383	0.219	1.466	-0.082	0.873	0.081
LAD as infarct-related artery	0.380	0.232	1.462	-0.123	0.922	0.102
Thrombus burden G≥4	2.122	0.614	8.351	0.344	15.901	0.001
Collaterals	-0.362	0.399	0.696	-1.410	0.427	0.363
Coronary ectasia	1.331	0.753	3.786	-0.850	3.018	0.077
Initial TIMI flow ≤ 2	0.820	0.839	2.271	-0.876	18.559	0.328
Coronary lesion type C	-0.331	0.398	0.718	-1.231	0.802	0.406
Constant	-6.000	0.868	0.002	-23.737	-4.931	< 0.001

ECG; electrocardiogram, LAD; left descending coronary artery. B, unstandardized coefficient; S.E., standard error; OR, odds ratio; BCa 95% CIs, Confidence Interval calculated using bootstrapping technique. Comparison was made using Hosmer-Lemenshow test $p = 0.355$.

obtained from the derivation dataset are shown in Table IV. The optimal cutoff value of the risk score was identified as 11 points (area under the curve [AUC]: 0.772, 95% confidence interval [CI]: 0.729-0.815, sensitivity 71.21%, specificity 70.34%, positive predictive value 30,92%, negative predictive value 92,91%, $p < 0.001$). The receiver operating curve (ROC) for the HAKTT risk score identified by multivariate logistic regression in the derivation dataset is shown in Figure 1. Components and their assigned points in the HAKTT risk score are shown in Table V.

Validation of the developed risk scoring system was tested in 414 patients assigned in the validation dataset, of whom 65 patients had NRF; therefore, the incidence of NRF was 15.7% in the validation dataset, the same as in derivation dataset. The ROC curve for the validation group showed good discriminant power as shown in Figure 2. For cutoff value of 11 points, the area under curve [AUC] was 0.718, confidence interval [CI]: 0.654-0.783, sensitivity 60.00%, specificity 69.05%, and positive and negative predictive value of 26.53% and 90.26%, respectively, $p < 0.001$.

Table IV. Sensitivity, specificity, PPV and NPV for each cutoff value of the developed risk score in the derivation dataset.

Cutoff value	No (%)[a]	Sensitivity	Specificity	PPV	NPV
≤ 8	18 (5.0)	97.0	25.1	19.5	97.8
9	1 (33.3)	86.4	48.4	23.8	95.0
10	19 (11.0)	85.6	48.7	23.7	94.8
11[b]	11 (14.5)	71.2	70.3	30.9	92.9
12	14 (29.8)	62.9	79.5	36.4	92.0
13	26 (27.4)	52.3	84.2	38.1	90.4
14	5 (41.7)	32.6	93.9	50.0	88.2
15	25 (45.5)	28.8	94.9	51.4	87.7
16	-	-	-	-	-
17	13 (68.4)	9.8	99.2	68.4	85.5

PPV; positive predictive value, NPV; negative predictive value. [a]Incidence of no-reflow for each level of the score; note that 16 points cannot be obtained. [b]Optimal cutoff value of the developed risk score.

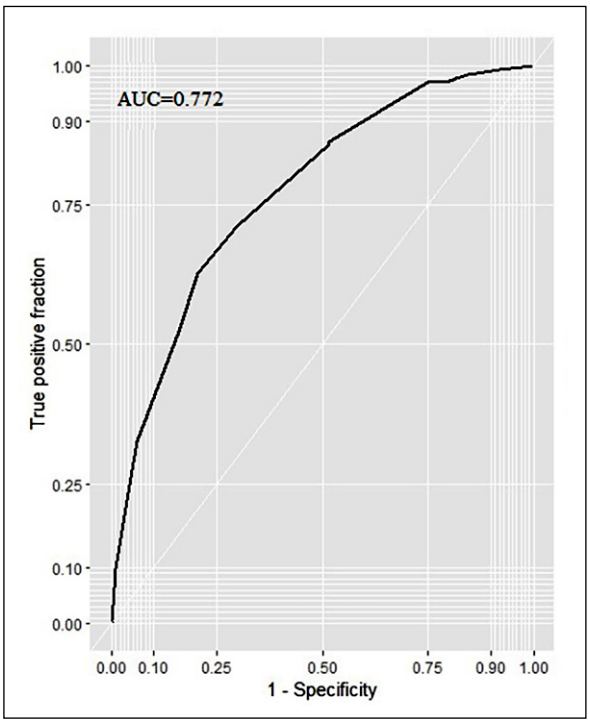

Figure 1. Receiver operating curve (ROC) for the HAKTT risk score identified by multivariate logistic regression in the derivation dataset. For cutoff = 11, area under curve [AUC] 0.772, 95% confidence interval [CI]: 0.729-0.815, sensitivity 71.21%, specificity 70.34%, positive predictive value [PPV] 30.92%, negative predictive value [NPV] 92,91%, $p < 0.001$.

Discussion

This was a retrospective study of the NRF phenomenon in patients presenting with STEMI undergoing PPCI, and its main objective was to build a probability scoring system for prediction of NRF prior to PPCI. We developed the HAKTT risk score, that was named as an acronym for first letters of five components included in the score: heart rate, age, Killip class, total ischemic time, and thrombus burden. This novel risk score was tested internally in the validation dataset, showing sensitivity of 60.00%, specificity of 60.05%, PPV of 26.53%, and NPV of 90.26%, that indicate good performance of the developed scoring system for predicting low risk of NRF.

NRF is an important issue in the management of STEMI patients undergoing PPCI and one of the most serious complications, with major influence on both short[10] and long term outcome[25]. NRF is associated with 10-fold increased risk of early clinical complications, as well as an increased risk of 30-day mortality[26], with persistence of this impact up to 5 years[27]. The poor prognosis with NRF appears to be related to adverse left ventricular remodeling, larger infarct sizes, and reduced global systolic function[12].

Since currently used therapies for NRF have controversial effectiveness and no standard treatment has been established to date[28,29], prevention of NRF is of the utmost importance. Therefore, there is a need for clinically useful scoring system for prediction of NRF for individual patient. Indeed, over the last few years several scoring systems have been proposed[30-34]. However, most

Table V. Components and their assigned points in the HAKTT risk score.

Risk factors	Points
Age ≥ 65 years	Yes +2; No +0
Heart rate ≥ 89 bpm	Yes +2; No +0
Killip Class ≥ II	Yes +2; No +0
Total ischemic time ≥ 268 min	Yes +3; No +0
Thrombus burden G≥4	Yes +8; No +0

HAKKT is an acronym consisting of the first letters of words Heart rate, Age, Killip class, Total ischemic time, and Thrombus burden.

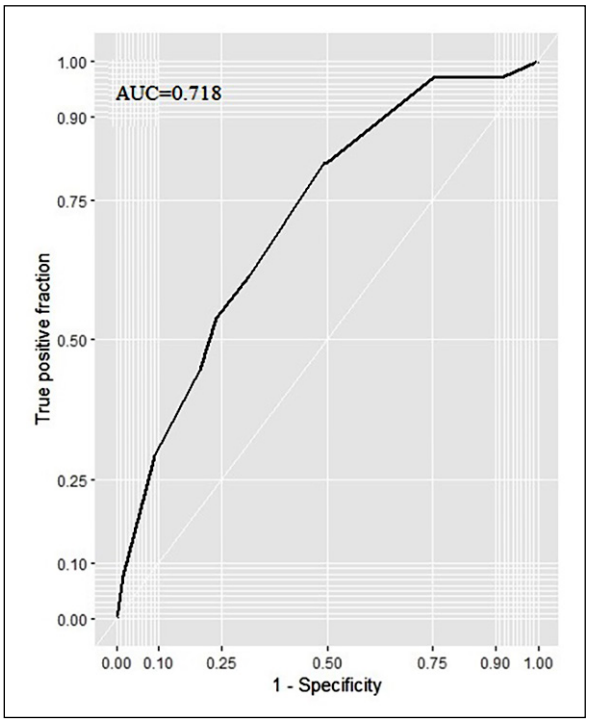

Figure 2. Receiver operating curve (ROC) for the HAKTT risk score identified by multivariate logistic regression in the validation dataset. For cutoff = 11, area under curve [AUC] 0.718 confidence interval [CI]: 0,654-0,783, sensitivity 60.00%, specificity 69.05%, positive predictive value [PPV] 26.53%, negative predictive value [NPV] 90.26%, $p < 0.001$.

of the proposed risk scoring systems included either biochemical or echocardiographic parameters that are time consuming and not suitable for pre-interventional risk assessment, as PPCI should be performed without any delay.

We purposely developed a novel risk score exclusively from widely available clinical and angiographic parameters. To the best of our knowledge this predictive model, besides the one of Rossington et al[31], is the only pre-interventional risk score derived without any laboratory or echocardiographic parameters, but with different clinical and angiographic components.

The results of our study showed that the large thrombus burden had the strongest association with occurrence of NRF. This is consistent with previous studies[35,36] reporting high thrombus burden as an independent predictor of NRF[35] and moreover an independent predictor of mortality in STEMI patients[36]. The strategy of reducing risk of NRF in patients with high thrombus burden with manual thrombus aspiration was shown beneficial in the TAPAS study[37] as well as in other small-scale and single center studies[2]. However, the TASTE study[38] did not confirm benefit of the routine use of this technique. Safety concerns emerged in the large TOTAL study[39], which showed that routine thrombus aspiration in the subgroup of patients with G≥3 was associated with fewer cardiovascular deaths, but with more strokes or transient ischemic attacks. An alternative technique with deferred stenting in DEFER-STEMI trial[40] showed in the beginning promising results, with reducing rate of NRF in high-risk STEMI patients, but large DANAMI 3-DEFER trial[41] showed no beneficial effect with deferred stenting 48 hours after the index procedure. The thrombus burden and TIMI flow are interrelated, with the higher thrombus load associated with lower TIMI flow[14]. Large coronary thrombi along with endothelial cells and lipid matrix are responsible for distal atherothrombotic embolization, migrating downstream from the culprit lesion, leading to microvascular obstruction and further injury[1]. Although the use of GP IIb/IIIa inhibitors has been shown to improve coronary flow, their routine use is associated with an increased risk of bleeding[2]. Furthermore, the current guidelines of the European Society of Cardiology for the management of STEMI patients[2] do not endorse routine use of thrombus aspiration, deferred stenting and GP IIb/IIIa inhibitors. However, these modalities might be beneficial in selected high-risk patients, particularly in those with angiographic evidence of large thrombus burden[2].

Total ischemic time was identified as an independent predictor of NRF in our study and it was the component of HAKTT risk score with the second highest assigned points. Previous studies also identified ischemic time as an important risk factor correlated with NRF, but there was high variability of cutoff values used in each study[42]. Our results revealed that the cutoff value of total ischemic time ≥ 268 minutes was significantly associated with the occurrence of NRF. This is quite similar with the findings of Bayramoglu et al[32] who reported pain-to-balloon time ≥ 4 hours to be independent predictor of NRF. Prolonged myocardial ischemia leads to edema and swelling of the distal capillary bed, blocks myocardial cells and neutrophils and changes the capillary integrity, thus damaging the microcirculation[13,14]. Furthermore, a longer ischemic time causes accumulation of erythrocytes, making the thrombi become more rigid and inclined to distal coronary embolization[9]. Consequently, all of these may lead to the extension of infarct size and occurrence of NRF[4]. Thus, the longer ischemic time is associated with more severe damage of myocardial microcirculation and increased risk of NRF[1,4,9,14].

Older age was also predictive of NRF in our study. This is in keeping with the previous report of Yang et al[33], who reported the age of ≥ 65 years as an independent predictor of NRF, while Wang et al[34] reported younger age (≥ 55 years) to be associated with NRF. These differences may relate to the population/ethnicity and/or the way of life. Age is widely known as one of the risk factors for coronary artery disease[43]. The relationship between the age and NRF might be explained by pre-existing microvascular dysfunction[1]. Older age is associated with vascular endothelial dysfunction and stiffening of large elastic arteries[14]. Furthermore, vascular endothelial dysfunction has been shown to impair coronary flow reserve and may increase the vulnerability of myocardium to both ischemic injury and reperfusion injury[44]. In addition, hypertension, diabetes mellitus, atrial fibrillation, chronic kidney disease, diffuse atherosclerosis, severe calcification, and microvascular disease are more prevalent in advanced age, and all of these conditions combined or individually could increase risk of NRF[45].

The Killip class ≥ II was found to be the next independent predictor of NRF in our study. This is in line with a previous report[15], in which either

Killip class ≥ II or Killip class ≥ III were shown to be associated with NRF. It has been postulated that the higher the Killip class, the worse the outcomes in patients with STEMI[2]. Systolic dysfunction in STEMI patients is related with reduced coronary blood flow, increased coronary microcirculation resistance, which leads to poor myocardial perfusion and increased infarct size[13]. In addition, reduction in blood flow can also promote leukocyte aggregation, adhesion, and capture by capillaries and all of these may aggravate NRF[4].

Finally, heart rate ≥ 89 beats per minute was the fifth independent predictor of NRF in our multivariate analysis. In the meta-analysis of Fajar et al[15], increased heart rate was also shown to be an independent predictor of NRF. To date, no study reported relationship between heart rate and NRF. It is possible to hypothesize that heart failure may bridge the association between heart rate and NRF. Higher heart rate, above 70 beats per minute, is known to be an independent risk factor for the development of heart failure[46]. Moreover, reducing heart rate is beneficial for clinical outcomes and better survival of patients with heart failure[47].

Besides the risk factors above that showed to be an independent predictors of NRF, we also carefully explored other potential risk factors and independent predictors highlighted in previous studies. History of chronic kidney disease, previous atrial fibrillation, both systolic and diastolic blood pressure was significantly different between the groups of NRF and normal flow, but not independently predictive. The following electrocardiographic parameters were identified as risk factors in the present study: anterior localization of STEMI, presence of atrial fibrillation on admitting ECG, QS pattern and higher maximal amplitude of ST-elevation. However, multivariate regression analysis showed that none of these electrocardiographic parameters were independent predictors of NRF. Among angiographic parameters, LAD as infarct-related artery, three-vessel coronary disease, initial TIMI flow 0, type-C lesion, and the presence of coronary ectasia were more prevalent in NRF group, but again, the multivariate analysis failed to prove them as independent predictors in the present study. Generally, we believe that older age, which was an independent predictor of NRF in our study, may represent a surrogate marker of all these parameters, as they are more prevalent in the elderly[15].

NRF occurred in the present study in 15.7% of STEMI patients who underwent PPCI, which is consistent with the results from other studies that used the similar angiographic definition of NRF (final TIMI flow ≤ 2)[10]. However, the large discrepancies in the incidence of NRF existing in the literature may be a consequence of: 1) heterogeneous population studied, 2) different methodology used for detecting NRF, and 3) inconsistencies in definition of NRF. We believe that angiography-based diagnosis of NRF used in this study is the most practical and closest to real-world practice. Other imaging methods, such as cardiac MRI or myocardial contrast echocardiography, might be more sensitive for detecting NRF, but they are not widely available and can only be exploited after PPCI. In other words, angiography is the only imaging method that can be used for early prediction of the risk of NRF, before intervention, while other methods can be used in the later course, after PPCI and in stable patients, for risk stratification and prognosis before hospital discharge.

Our novel HAKTT score revealed good sensitivity and specificity and excellent negative predictive value, and it might be a useful tool for interventional cardiologists in planning PPCI. In particular, according to high negative predictive value, HAKTT score can be reliably used in predicting the absence of NRF, and therefore, may be helpful in planning the procedure and interventional team.

Limitations of the Study

Our study has certain limitations. First, although it was a single-center study, done in high volume tertiary PCI center with a relatively large sample, study population was solely Caucasian, which may limit the relevance in all populations. Second, the study has inherent limitations of retrospective design, although data processing and statistical analysis were conducted by independent research personnel. Thirdly, we did not have complete data regarding pharmacological treatment in the period before STEMI, which might also influence the final TIMI flow, so this was not tested as possible risk factors. And finally, the validation of the score was tested on the same population in which the risk score was developed. Therefore, further large-scale multicenter and prospective studies are needed to determine the real-world predictive performance of this newly developed risk score.

Conclusions

Based on five independent clinical and angiographic predictors of NRF (heart rate, age, Killip class, total ischemic time, and thrombus burden), we created a novel, simple, clinically usable HAKTT risk score for prediction of NRF prior to PPCI that revealed good accuracy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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