

How to improve prognostic value of popular risk scores used in acute coronary syndrome – A single center experience in a long term follow-up

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BACKGROUND: Despite the availability of several acute coronary syndrome (ACS) prognostic risk scores (RSs), there is no appropriate score for post-discharge risk stratification for patients after ACS. The aim of this study was to improve traditional RSs designed for predicting short-term outcome after ACS through the inclusion of additional prognostic factors critical for long-term prognosis.

METHODS: Observational prospective single-center study included 672 consecutive patients admitted for ACS and discharged alive between 2002 and 2004. Multivariate analysis identified additional independent risk factors for long-term mortality, primarily not included in the RSs. Prognostic value of each RS (SIMPLE, TIMI-STEMI, TIMI-UA/NSTEMI, GRACE in-hospital, GRACE post-discharge, ZWOLLE, LLOYD-JONES) with additional risk

factors was evaluated with the area under receiver operating characteristics (ROC) curve.

RESULTS: Multivariate analysis identified following independent risk factors improving prognostic value of each RS: supraventricular or ventricular arrhythmias during hospitalization (for all six scales), peripheral artery disease, male gender, recurrence of angina pectoris with ischemia on ECG (in the case of five scales), diabetes, heart failure (for four scales), multi-vessel coronary disease, impaired renal function (in three scales) and less frequent indicators: hospital discharge, coronary artery disease, dyslipidemia, resuscitated sudden cardiac arrest.

CONCLUSION: Additional clinical parameters initially not included in the description of the ACS risk scores provided independent prognostic value, whereby improved global risk assessment. Taking these factors into consideration may improve risk stratification of ACS patients.

Key Words: Acute coronary syndrome; Long term risk; Prognosis after discharge

INTRODUCTION

Long-term clinical outcomes in patients with acute coronary syndromes (ACS) are dependent on various factors such as the demographic profile of the patient, the extent of myocyte necrosis, and the development of arrhythmic and hemodynamic complications (1). Despite the availability of several acute coronary syndrome (ACS) prognostic risk scores, the majority of them have mostly been validated with respect to in-hospital and short-term (30-day) use (2-8). However, data on long-term prediction differs depending on the duration of the follow-up periods in the clinical trials and registries and there is no appropriate score for post-discharge risk stratification for patients after ACS. The aim of this study was to improve traditional risk scores designed for predicting short-term outcome after ACS through the inclusion of additional prognostic factors critical for long-term prognosis.

RESEARCH METHODOLOGY

We performed a single-center, prospective study of consecutive patients hospitalized for ACS between 2002 and 2004 in our Department with a 24-hour catheter laboratory. All patients underwent coronarography and if indicated percutaneous cardiac angioplasty (PCI). In total, 672 patients with non-fatal ACS who survived until hospital discharge were enrolled and all of them were followed until 2009. The Third Universal Definition of Myocardial Infarction was used in our publication. The patients were classified as having ST-elevated myocardial infarction (STEMI) or unstable angina/non-STEMI (UA/NSTEMI) according to current guidelines:

STEMI

Presence of ST-segment elevation of ≥ 0.2 mV in men ≥ 40 years, ≥ 0.25 mV in men <40 years, ≥ 0.15 mV in women in V2-V3 leads and/or ST-segment elevation of ≥ 0.1 mV in two or more standard leads or new left bundle branch block (LBBB) and positive cardiac necrosis markers

UA/NSTEMI

Presence of ST-segment depression of ≥ 0.05 mV in two or more standard leads or T-wave flattening or inversion and positive (in case of NSTEMI) and negative (in case of UA) cardiac necrosis markers.

The ethical approval before initiation of the study was obtained and all patients provided informed consent.

Risk scores

The obtained data from the admission, in-hospital stay and discharge letters, were entered into a database created by the author in the database management system – MS-Access. The program based on the data automatically calculated the number of points according to the risk scores for stratification of ACS: SIMPLE, TIMI STEMI, TIMI UA/NSTEMI, GRACE, ZWOLLE, LLOYD-JONES.

ACS risk scores (RSs) differ in terms of their predictive values, variables and time frames. Below, we present a brief characteristic of each RS.

The TIMI RS is based on seven predictor variables including age 65 years or older, at least three risk factors for coronary artery disease, prior coronary stenosis of 50% or more, ST-segment deviation on electrocardiogram (ECG) at presentation, at least two angina events in prior 24 h, the use of aspirin in the prior seven days, and elevated serum cardiac markers (6).

The SIMPLE RS is a simplified model that originated from the registry of the fibrinolytic InTime II study (9). This scale has only three parameters, but at the same time is characterized by low prognostic value, especially in patients with other concomitant ailments.

The ZWOLLE scale is a 16-point scale and one of the few that incorporates the coronary flow measure expressed as the post reperfusion TIMI Grade Flow. It has a relatively high predictive value of c-statistics up to 0.91 and assesses the feasibility of early discharge in low-risk patients (10).

The GRACE RS is based on a wide spectrum of ACS patients from a

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prospective, multicenter, global registry and it considers additional risk factors such as sudden cardiac arrest. Initially, it was designed to predict in-hospital mortality or the six-month outcome, but now it is one of the most popular RSs for long-term outcome as well. The components of the GRACE RS (range 2-372) are age, heart rate, systolic blood pressure (SBP), Killip class, cardiac arrest, serum creatinine, ST-segment deviation and cardiac biomarker status (11).

The component of the LLOYD-JONES is: age, prior myocardial infarction, diabetes, BP, Killip class, creatinine, leukocytosis, no percutaneous revascularization during hospitalization and no beta-blocker recommendation at discharge.

Study group

Patients included in the present study were treated according to the hospital protocol compliant with the ESC guidelines presented by the Task Force on the Management of Chest.

Pain published in the 2002 (12). According to the algorithm, patients were referred for an invasive diagnostic with an angiographic imaging at the local 24/7 catheterization laboratory.

The in-hospital medical therapy was compliant with the ESC recommendations with 97.7% of patients receiving acetylsalicylic acid (ASA), 89% clopidogrel, and 60.4% IIb/IIIa inhibitor; 98.2% took either low molecular weight heparin or unfractionated heparin. On discharge from the hospital, patients received ASA (87.2%), clopidogrel or ticlopidine (71.9%), angiotensin converting enzyme inhibitor (89.4%), statin (92.7%) and beta-blocker (92.1%) (13).

Follow up

After discharge from the hospital, the patients were followed-up at 30 days, six months, and one year during visits to the outpatient clinic, by phone, post or home visits. The seven-year follow-up was completed with the use of records from the Government Central Statistical Office (CSO, PESEL database). The incidence of death was chosen as the hard end-point for prediction performance analysis of the seven RSs using the personal identification numbers (PESEL) of the patients; the survival data (which included the incidence and the date of death) were obtained and matched with the hospital registry.

STATISTICAL ANALYSIS

Group comparisons were performed using the t test or the Mann-Whitney U test for continuous variables, and Fisher's or Chi² test for categorical variables. The Shapiro-Wilk test was used to assess the distribution normality of the tested variables. The Kruskal-Wallis test was used for comparing two or more independent samples of equal or different sample sizes. All the tests were performed with the significance level of 0.05.

The relationship between clinical factors and seven-year mortality was analyzed using multivariate logistic regression. The selection of significant factors was based on backward selection procedure, with removal of predictor when 'a' was greater than 0.1.

Statistical analysis was performed using MS Windows XP Professional, MS Office 2003 Professional, Statistical 9 PL i SAS Software 9 (SAS Institute, Cary, NC, USA).

RESULTS

Out of 722 ACS patients who underwent coronarography, 150 patients were excluded from the current analysis because of death during hospitalization. Finally, the study group consisted of 672 patients with median age 61 (52-70) years and 448 (66.7%) males. A total of 417 patients (62.05%) were diagnosed with STEMI and all of them were treated with PCI. The rest of the group i.e., 255 patients (37.95%) presented UA/NSTEMI - 157 (61.57% of all UA/NSTEMI) patients were treated with PCI, 42 (16.47%) with coronary artery bypass grafting (CABG) and 56 (35.67%) were treated conservatively.

During the follow-up 123 (18.3%) of the patients died i.e., 75 STEMI and 48 UA/NSTEMI patients. The overall mortality assessed throughout follow-up until 2009 was comparable in UA/NSTEMI and STEMI patients (18,8% vs. 18%, p=0,7852). Detailed characteristics of patients who survived and died during post-discharge period are presented in Supplementary Table S1.

Based on collected data, we recently published the results of our research regarding investigate long-term follow-up of unselected ACS patients (14) and risk factors of mortality during post-discharge period following an ACS hospitalization (15). The final element of the analysis of collected data was multivariate analysis of RSs and clinical parameters, initially not included in

TABLE 1

Multivariate Cox regression analysis of the ZWOLLE score, over the entire follow-up period, diversify by clinical parameters with additional prognostic value, initially not included in the description of the ACS risk scale

Risk factors	HR	95% CI	P
LLOYD-JONES (every 1 point) Components: age, prior MI, diabetes, BP, pulmonary edema, creatinine, leukocytosis, medical therapy without revascularization, no beta-adrenolytic recommendation at discharge	-	-	>0.05
Angina pectoris <i>de novo</i> < 2 months	0.297	0.088-0.998	0.0496
Dyslipidemia	2.551	1.155-5.634	0.0205
Maximum troponin I value (every 1 ng/ml)	1.011	1.006-1.017	0.0001
MDRD (every 1 ml/min/1.73 m ²)	0.947	0.929-0.966	<0.0001
Resuscitated SCA	6.597	2.231-19.511	0.0006
Recurrence of angina pectoris with ischemia on ECG	4.720	1.699-13.117	0.0029
Ventricular arrhythmias during hospitalization	10.662	2.297-49.486	0.0025

ACS: Acute Coronary Syndrome; BP: Blood Pressure; ECG: Electrocardiogram; MDRD: Modification of Diet in Renal Disease; MI: Myocardial Infraction; SCA: Sudden Cardiac Arrest

TABLE 2

Multivariate Cox regression analysis of the SIMPLE score, over the entire follow-up period, diversify by clinical parameters with additional prognostic value, initially not included in the description of the ACS risk scale

Risk factors	HR	95% CI	P
SIMPLE (every 1 point)	1.036	1.016-1.057	0.0005
Components: age, BP, HR			
Male gender	1.946	1.208-3.136	0.0062
Diabetes	2.228	1.377-3.606	0.0011
HF, NYHA class III/IV	3.185	1.484-6.833	0.0029
PAD	3.001	1.745-5.159	<0.0001
Creatinine (every 1 mg/dL)	1.547	1.282-1.868	<0.0001
MVD	1.622	1.059-2.485	0.0263
Recurrence angina pectoris with ischemia on ECG	3.217	1.561-6.630	0.0015
Ventricular arrhythmias	2.348	1.006-5.482	0.0485
Supraventricular arrhythmias	2.735	1.535-4.874	0.0006

ACS: Acute Coronary Syndrome; BP: Blood Pressure; ECG: Echocardiogram; HF: Heart Failure; HR: Heart Rate; MVD: Multi-vessel Coronary Disease; NYHA: New York Heart Association; PAD: Peripheral Artery Disease

TABLE 3

Multivariate Cox regression analysis of the TIMI STEMI score, over the entire follow-up peri-od, diversify by clinical parameters with additional prognostic value, initially not included in the description of the ACS RS

Risk factors	HR	95% CI	P
TIMI STEMI (every 1 point) Components: age, diabetes, hypertension, CAD, BP, time of chest pain, HR, Killip class, weight, LBBB, anterior wall MI	1.257	1.099-1.438	0.0008
Gender male	2.887	1.457-5.721	0.0024
HF	7.535	2.555-22.220	0.0003
PVD	3.923	1.881-8.183	0.0003
Supraventricular arrhythmias	3.335	1.734-6.415	0.0003
Discharge home	0.312	0.144-0.676	0.0032

TABLE 4

Multivariate Cox regression analysis of the GRACE in-hospital score, over the entire follow-up period, diversified by clinical parameters with additional prognostic value, initially not included in the description of the ACS RS

Risk factors	HR	95% CI	P
GRACE in-hospital score (every 1 point) Components: age, SCA, BP, pulse, Killip class, ST-segment changes, creatinine, markers of myocardial necrosis	1.014	1.007-1.021	0.0001
Male gender	1.522	1.008-2.298	0.0456
Diabetes	2.147	1.364-3.379	0.0010
HF NYHA class III/IV	2.993	1.504-5.958	0.0018
PVD	2.901	1.782-4.720	<0.0001
MVD	1.823	1.234-2.695	0.0026
Recurrence of angina pectoris with ischemia on ECG	3.172	1.693-5.943	0.0003
Supraventricular arrhythmias during hospitalization	2.828	1.660-4.817	0.0001

BP: Blood Pressure; HF: Heart Failure; MVD: Multi-vessel Coronary Disease; PVD: Peripheral Vascular Disease; SCA: Sudden Cardiac Arrest

TABLE 5

Multivariate Cox regression analysis of the GRACE post-discharge score, over the entire follow-up period, diversified by clinical parameters with additional prognostic value, initially not included in the description of the ACS RS

Risk factors	HR	95% CI	P
GRACE post discharge score (every 1 point) Components: age, SCA, BP, pulse, ST-segment changes, creatinine, markers of myocardial necrosis, HF, non-invasive procedure	1.021	1.013-1.029	<0.0001
Male gender	1.634	1.080-2.472	0.0202
Diabetes	1.997	1.288-3.096	0.0020
PVD	2.576	1.575-4.212	0.0002
MVD	1.582	1.067-2.346	0.0226
Recurrence of angina pectoris with ischemia on ECG	2.510	1.327-4.750	0.0047
Supraventricular arrhythmias	3.109	1.868-5.173	<0.0001

HF: Heart Failure; MI: Myocardial Infarction; MVD: Multi-vessel Coronary Disease

TABLE 6

Multivariate Cox regression analysis of the ZWOLLE score, over the entire follow-up period, diversified by clinical parameters with additional prognostic value, initially not included in the description of the ACS RS

Risk factors	HR	95% CI	P
ZWOLLE (every 1 point) Components: age, time of chest pain, Killip class, anterior wall MI, MVD, results of angioplasty	-	-	>0.05
Male gender	2.541	1.270-5.086	0.0084
Diabetes	2.180	1.121-4.242	0.0217
HF NYHA class III/IV	9.275	3.171-27.135	<0.0001
PVD	4.987	2.418-10.286	<0.0001
Creatinine level at admission (every 1 mg/dL)	1.695	1.192-2.411	0.0033
Supraventricular arrhythmias	4.590	2.405-8.760	<0.0001
Discharge home	0.250	0.115-0.543	0.0005

HF: Heart Failure; MI: Myocardial Infarction; MVD: Multi-vessel Coronary Disease

TABLE 7

Multivariate Cox regression analysis of the TIMI UA/NSTEMI score, over the entire follow-up period, diversified by clinical parameters with additional prognostic value, initially not included in the description of the ACS RS

Risk factors	HR	95% CI	P
TIMI UA/NSTEMI (every 1 point) Components: age, hypertension, hypercholesterolemia, Diabetes, smoking, CAD, ASA, angina pectoris, ST-segment depression, markers of myocardial necrosis	1.737	1.312-2.298	0.0001
Male gender	2.348	1.209-4.558	0.0117
TC (every 1 mg/dL)	1.005	1.000-1.010	0.0312
MDRD (every 1 ml/min/1.73 m ²)	0.962	0.946-0.977	<0.0001
Resuscitated SCA	9.478	3.045-29.500	0.0001
Recurrence of angina pectoris with ischemia on ECG	3.362	1.475-7.662	0.0039
Ventricular arrhythmias during hospitalization	7.635	1.747-33.371	0.0069

ASA: Acetylsalicylic Acid; CAD: Coronary Artery Disease; ECG: Electrocardiogram; MDRD: glomerular Filtration Rate using Modification of Diet in Renal Disease; TC: Total Cholesterol; SCA: Sudden Cardiac Arrest

the description of the ACS RSs (Tables 1-7).

In the multivariate analysis, all scales except the ZWOLLE and LLOYD-JONES scale had an independent prognostic value and were included in the final model. The clinical parameters initially not included in the description of the ACS RSs, with independent prognostic value are summarized in Supplementary Table S1. The summary shows that the risk indicators most often attached to the multivariate model were: supraventricular or ventricular arrhythmias during hospitalization (for all six scales), peripheral artery disease, male gender, recurrence of angina pectoris with ischemia on ECG (in the case of five scales), diabetes, heart failure (for four scales), multi-vessel coronary disease, impaired renal function (in three scales) and less frequent indicators: hospital discharge, coronary artery disease, dyslipidemia, resuscitated sudden cardiac arrest.

Although, it is beyond the scope of the present publication, it is worth noting that we evaluated the prognostic value of each risk scales in individual observation periods with the calculation of differences in prognostic values between the analyzed scales (Supplementary Tables S2 and S3).

In the STEMI population, there were no differences in prognostic values between the scales in individual periods of observation, evaluated by the area under the ROC curve (Supplementary Table S4).

In the UA/NSTEMI population, no differences were observed in the early periods of observation, however statistically significant differences were observed in the later periods (Supplementary Table S3). In the multivariate analysis, TIMI STEMI and GRACE scales demonstrated independent prognostic value in STEMI population and TIMI UA/NSTEMI and LLOYD-JONES in the UA/NSTEMI population. The most frequent scale with the highest prognostic values when assessing the field under the ROC curve in individual observation periods was the GRACE scale (for the post-discharge assessment).

DISCUSSION

Several previous studies, as in the presented paper, made assessments of the prognostic value of popular risk assessment scales and show similar results. In most cases, the scales showed a good prognostic value (ROC>0.7), but some observations show a poor impact of a given scale on the risk assessment of a given group of patients. In Kozieradzka et al. study, out of 505 STEMI patients treated with PCI, prognostic values (c statistics) for predicting 5-year mortality equaled: 0.742 (CI 0.69-0.79) for the GRACE risk score, 0.727 (CI 0.67-0.78) for TIMI, 0.72 (CI 0.67-0.77) for Zwolle, and 0.687 (CI 0.63-0.74) for CADILLAC (the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) (16). Further, in the group of 2,148 patients with NSTEMI from the Korean national registry of KAMIR (Korea Acute Myocardial Infarction Registry), prognostic values (c statistics) for predicting in-hospital mortality equaled: 0.616 for TIMI NSTEMI and 0.75 for GRACE risk score; and 5-year mortality equaled: 0.629 and 0.754, respectively (17).

Interestingly, in Addala et al. study, within group of 855 consecutive STEMI patients treated with PCI, all CADILLAC, TIMI, and PAMI risk scores had relatively high predictive accuracy for 30-day and 1-year mortality (C statistic range 0.72 to 0.82), while GRACE score did not perform as well and had low predictive accuracy for mortality (C statistic 0.47). It was explained by the fact that no patients with features of cardiogenic shock were included in the analysis, besides all patients had biochemical myocardial necrosis and elevation of ST segment in ECG on admission to the hospital (18).

The main purpose of this study was to improve traditional risk scores designed for predicting short-term outcome after ACS through the inclusion of additional prognostic factors critical for long-term prognosis. However, it should be noted that some of these parameters have already been included in individual scales, e.g. markers of myocardial necrosis are included in most scales, diabetes in both TIMI and LLOYD-JONES scales, coronary artery disease in both TIMI scales, creatinine level in both GRACE scales and LLOYD-JONES, a history of heart failure on the GRACE scale from the time of discharge.

Interestingly, in the multivariate model of the LLOYD-JONES scale (comprised creatinine level), the glomerular filtration rate calculated from the MDRD formula was an independent prognostic factor. It can be explained by the fact that the point value of the LLOYD-JONES scale was not in the final model ($p < 0.05$) and thus the concentration of creatinine was not included in the risk assessment. This result strengthens the influence of kidney function on the prognosis of patients after ACS.

The number of publications, that improve existing risk score systems, is growing to increase the prediction for long-term clinical outcomes in patients with ASC. The Kozieradzka et al. study selected few additional parameters to increase the power of the particular risk scores being prognostic of 5-year all-cause mortality in patients with ASC i.e., coronary artery disease and ejection fraction (EF) for GRACE in-hospital score, EF, weight for TIMI STEMI score, age, pulse, weight for ZWOLLE score (16).

Interesting "improvement" of the SIMPLE model proposed Kim et al. study. A new risk score was constructed using the variables related to one-year mortality: TIMI risk index (17.5-30: 1 point, >30: 2 points), Killip class (II: 1 point, >II: 2 points) and serum creatinine (≥ 1.5 mg/dL: 1 point), based on the multivariate-adjusted risk relationship. Compared to SIMPLE score, the new risk score showed good predictive value for in-hospital (ROC curves increase from 0.616 to 0.8 ($p < 0.0001$)) and one-year post-discharge mortality (ROC curves increase from 0.629 to 0.815 ($p < 0.0001$)) (17).

Limitations of the study

As the main purpose of the study was to assess the long-term outcome of patients with ACS hospitalized and discharged from particular referral center with 24-hour catheter laboratory in collaboration with centers without interventional cardiology unit, this was a single-center study. Such analysis may be more appropriate than the use of clinical trial data, which initially represent the population excluding the most-at-risk patients. Furthermore, at the time when the study was performed, percutaneous techniques and intracoronary devices were in an early stage of development. The currently available state-of-the-art technologies, including third and fourth generation drug eluting stents, demonstrate improved results that potentially may also influence the long-term survival analyzed in our study.

Another limitation of the study is the fact that our study encompassed patients hospitalized for ACS between 2002 and 2004 when there were other trends in the treatment of ACS patients, hence the treatment with clopidogrel/ticlopidine instead of ticagrelor/prasugrel.

The next limitation is the single-center location of the study. However, there are also advantages to an unicentric research, including the possibility of following all subjects closely for the duration of the study and gathering considerably detailed information on each study participant. We are considering an extension of this research to other research centers to validate these results.

CONCLUSION

Additional clinical parameters initially not included in the description of the ACS risk scores provided independent prognostic value, whereby improved global risk assessment. Taking these factors into consideration may improve risk stratification of ACS patients.

DISCLOSURE OF INTEREST

The authors report no conflicts of interest.

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