Relative value of serum pregnancy-associated plasma protein A (PAPP-A) and GRACE score for a 1-year prognostication: A complement to calculation in patients with suspected acute coronary syndrome

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Abstract

Background. The Global Registry of Acute Coronary Events (GRACE) study produced a scale for risk stratification in acute coronary syndromes (ACSs). Pregnancy-associated plasma protein A (PAPP-A) serum concentration was implicated as a marker of unstable atherosclerotic plaques.

Objectives. We hypothesized that the measurement of the concentration of PAPP-A on admission may improve the stratification of cardiovascular risk in suspected ACS patients.

Material and methods. We studied 70 patients with chest pain suggesting ACS diagnosis on admission. Serum cardiac biomarkers and PAPP-A were measured on top of the standard biochemical panel, and the GRACE risk score was calculated. A 12-month follow-up was completed to major adverse cardiac events (MACE): death, myocardial infarction (MI), need for percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG), unplanned cardiovascular hospitalization.

Results. In hospital/6-month GRACE, low risk was found in 35 patients (50%)/37 patients (53%), intermediate risk in 23 patients (33%)/21 patients (30%) and high risk in 12 patients (17%)/12 patients (17%). Mean PAPP-A was 39.64 mIU/L (standard deviation – SD = 24.2), and median PAPP-A values for in hospital/6-month GRACE were 21.49 mIU/L (quartile 1st; 3rd – 13.41; 32.65) and 22.61 mIU/L (14.03; 34.1) for low risk patients, 51.76 mIU/L (35.18; 59.99) and 51.76 mIU/L (28.9; 62.1) for intermediate risk patients, and 68.82 mIU/L (58.54; 83.76) for high risk patients. The PAAP-A concentration with specific cut-off points had 66.7% positive predictive value (PPV) and 95.5% negative predictive value (NPV) for death, 33.3% PPV and 80.6% NPV for MI, and 71.4% PPV and 57.1% NPV for any event. Intermediate and high in hospital/6-months GRACE had 14.3%/15.2% PPV and 100%/100% NPV for death, 34.3%/33.3% PPV and 94.3%/91.9% NPV for MI, 74.3%/72.7% PPV and 65.7%/62.2% NPV for any event.

Conclusions. The PAPP-A serum concentration represents a promising prognostic biomarker with significantly improved PPV. The GRACE score is superior to stratification based on PAPP-A with regard to combined cut-off point for 1-year mortality.

Key words: biomarkers, acute coronary syndrome, pregnancy-associated plasma protein A, Global Registry of Acute Coronary Events risk score

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Introduction

Acute coronary syndromes (ACSs), which include myocardial infarction (MI), with or without ST elevation and unstable angina amongst others, are a substantial cause of morbidity and mortality. Presently, diagnosis of ACS is made on the basis of patient history, clinical examination, electrocardiographic findings, biochemical markers, and changes noted on cardiac imaging. Confirmation of diagnosis is often made using plasma biomarkers, such as troponins and myocardial fraction of creatine kinase. A critical clinical point is the effective prediction of ACS risk, which may help prevent these events and optimize pharmacologic therapy. Such a prognostication may involve novel biomarkers or imaging, preferably performed in an outpatient setting.

Global Registry of Acute Coronary Events risk score

The Global Registry of Acute Coronary Events (GRACE) risk score is the current standard for risk assessment in ACS. Global Registry of Acute Coronary Events created a risk stratification tool that may be useful in everyday cardiology practice.[1] It is used for evaluating risk of death during hospitalization and within 6 months from discharge in patients admitted to hospital with a diagnosis of ACS.[2] This kind of evaluation is important in order to implement adequate inpatient therapy and to sustain the best long-term treatment. The tool was created to make this evaluation quick and easy. The GRACE risk score calculator is an online calculator with free access, which analyzes 8 factors: age, pulse rate, systolic blood pressure, renal function, congestive heart failure, ST-segment deviation, cardiac arrest, and elevated biomarkers. The score is a percentage risk of death during hospitalization and within 6-months after discharge – such score was calculated for all subjects in the following study.

Management, accessibility and expeditious obtaining results of laboratory testing strongly facilitate ongoing research on biomarkers in cardiology, especially on those that may be utilized in acute situations. The overall aim is to identify a biomarker that conclusively has better sensitivity and specificity as compared to those that are currently in use. In lieu of investigating and determining novel biomarkers, some biomarkers commonly used in other specialties may be transposed and considered for new purposes. However, their clinical utility is yet to be determined, pending further studies.

Pregnancy-associated plasma protein A

Pregnancy-associated plasma protein A (PAPP-A) is a biomarker that is routinely, used in the field of obstetrics. It is often part of a screening test used to estimate the risk of congenital abnormalities such as Down (sensitivity 90%),[3] Edwards, and Patau syndromes. It may also help in assessing complications with the placenta or intrauterine growth restriction. The test is composed of blood sample analysis in conjugate with ultrasound examination to determine fetal measurements and parameters.[4] A positive test result warrants a subsequent amniocentesis to definitely exclude or confirm a diagnosis. The use of PAPP-A in the field of cardiology has been observed in a few small studies.[5,8] These studies have shown that elevated levels of PAPP-A correlate with the occurrence of ACSs. Due to the abovementioned findings, PAPP-A has become synonymous with a biomarker of vulnerable atheromatous plaque.[6,7]

It has been proven that PAPP-A is involved in the pathogenesis of atherosclerotic plaques and its blood concentration is elevated in the setting of MI or unstable angina.[8,9] However, there is no evidence that PAPP-A can provide any diagnostic utility in a group of patients with suspected ACS.[10]

The aim of this study was to evaluate whether the measurement of the serum concentration of PAPP-A on admission may improve the stratification of cardiovascular mortality risk (early and delayed) in patients with suspected ACS.

Material and methods

We studied 70 consecutive patients admitted to tertiary cardiology center due to a suspicion of ACS. Definition of ACS was typical, anginal chest pain lasting for a maximum of 12 h with electrocardiography (ECG) abnormalities characteristic of myocardial ischemia in accordance with European Society of Cardiology. All patients underwent coronary angiography and confirmation of coronary artery disease; including 59 patients who required percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). The demographic and clinical characteristics based on the interviews and hospital records are summarized in Table 1.

Cardiac biomarkers and PAPP-A were added to the standard biochemical panel on admission. Measurements of PAPP-A were made using Cobas Elecsys 2010 analyzer manufactured by Roche Diagnostics Ltd. (Basel, Switzerland) and with reagent PAPP-A manufactured by Roche Diagnostics Polska sp. z o.o. (Warszawa, Poland). The GRACE risk score was calculated using online tool available at www.gracecsore.org.

The follow-up consisted of outpatient office visit 4–8 weeks after discharge, phone interviews conducted at 6 months and another office visit after 12 months. Visits included a detailed medical interview focused on cardiovascular events (death, MI, need for PCI/CABG, and unplanned hospitalization from cardiovascular events), laboratory tests, cardiac stress testing, and echocardiography. The study endpoint was the occurrence of major

Table 1. Demographic and clinical characteristics of study subjects

Parameter	Value
Age [years], mean ±SD	60.90 ±9.4
Sex (male/female), n (%)	58 (82.9)/12 (17.1)
TnT [ng/mL], mean ±SD	0.148 ±0.139
Hypertension, n (%)*	29 (41.4)
Diabetes, n (%)**	12 (17.1)
Obesity (BMI >30), n (%)	24 (34.3)
Current smokers, n (%)***	49 (70.0)
Past smokers, n (%)****	12 (17.1)
Pain onset to open artery (average time) [min]	380.9
Admission to open artery (average time) [min]	38.9
Pharmacotherapy on admission/at discharge, n (%)	
Acetylsalicylic acid	20 (28.6)/70 (100)
Short-acting nitrates	8 (11.4)/61 (87.1)
Long-acting nitrates	2 (2.9)/0
β-adrenolytics	18 (25.7)/70 (100)
Converting enzyme inhibitor	19 (27.1)/70 (100)
Other antihypertensives	11 (15.7)/0
Statins	24 (34.3)/70 (100)
Oral antidiabetic medications	16 (22.9)/11 (15.7)
Insulin	2 (2.9)/6 (8.6)

TnT – troponin T; BMI – body mass index; * systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or hypotensive therapy; ** by history/active treatment; *** patients who used any kind of tobacco within 1 year; **** patients who did not use any kind of tobacco for at least 1 year.

adverse cardiovascular events (MACE) defined as at least one of the following:

– cardiac death;
– (another) non-fatal MI;
– necessity of (another) revascularization (PCI in an ACS-related artery or CABG over 30 days from index hospitalization);
– necessity of CABG;
– (another) hospitalization from unstable angina/non-ST elevation MI (NSTEMI) or ST elevation MI (STEMI);
– non-fatal cardiac arrest.

Statistical analysis

Quantitative data was compared to the standardized bell curve with the Lilliefors test (based on the Kolmogorov-Smirnov test). When the data was compatible to normal distribution, a mean and standard deviation (SD) were used (mean ±SD). In other cases, we used a median with the presentation of the 1st and 3rd quartile (Me (Q_{25}; Q_{75})). In most cases, a variance analysis was made with the ANOVA test in the Kruskal-Wallis modification because of the inequality of groups and absence of normal distribution. Verification of the hypothesis and the evaluation of predictive values were made with contingency tables. The hypothesis was analyzed with Fisher's exact test, necessary because of significant differences in quantity of some groups. Cut-off points for serum concentration of biomarkers were assigned. The calculations were made with MedCalc V. 9.5.2.0 (MedCalc Software, Ostend, Belgium). Institutional Review Board approval was obtained for this study.

Results

A follow-up period that lasted 12 months was completed by 100% of patients – 38 (54.3%) of them required another hospitalization for cardiovascular reasons (ACS/PCI), 14 (20%) were diagnosed with MI and 5 (7.1%) died (all from cardiovascular reasons, including sudden cardiac death).

The occurrence of the events is specified in Table 2.

Table 2. Occurrence of events in specified time periods

Occurence of the event	Death (n = 5)	MI (n = 14)	MACE (n = 38)
During hospitalization	3	0	6
From discharge to 6 months	1	6	20
6–12 months	1	8	12

MI – myocardial infarction; MACE – major adverse cardiovascular event.

Pregnancy-associated plasma protein A concentration

The normal range of PAPP-A concentration is <7.15 mlU/L.[11] Mean PAPP-A concentration in our study group was 39.64 mlU/L and there was a significant difference of this parameter in subgroups of patients divided according to the hospital and 6-month GRACE score ($p < 0.001$). The median values were as follows: 21.49 mlU/L (quartile 1st; 3rd – 13.41; 32.65) and 22.61 mlU/L (14.03; 34.1) among patients with low risk in GRACE score, 51.76 mlU/L (35.18; 59.99) and 51.76 mlU/L (28.9; 62.1) among those with intermediate risk, and 68.82 mlU/L (58.54; 83.76) among those with high risk according to GRACE score. When the PAPP-A concentration was assessed in subgroups with 12-month events, the highest mean value was in the group of patients who died (Table 3).

The statistical analysis of PAPP-A concentrations in subgroups specified according to the occurrence of events with receiver operating characteristic (ROC) curve gave cut-off points: 88.63 mIU/L for death (risk of death: 4.5%, 66.7% for patients below and above the threshold, respectively), 88.63 mIU/L for MI (risk of MI: 19.4%, 33.3% for patients below and above the threshold, respectively) and 47.15 mlU/L for MACE (risk of MACE: 42.9%, 71.4% for patients below and above the threshold, respectively). A quantitative analysis of study subjects that exceeded the cut-off PAPP-A concentration and the division into

Table 3. Mean PAPP-A concentration in subgroups with 12-month events (death, infarction, combined endpoint)

Parameter	Dead (n = 5)	Alive (n = 65)	MI (n = 14)	No MI (n = 56)	MACE (n = 38)	No MACE (n = 32)
PAPP-A [mIU/L], mean ±SD	69.47 ±24.48	37.34 ±22.78	49.3 ±22.26	37.61 ±24.29	43.58 ±26.52	34.95 ±20.54
p-value (ANOVA K-W)	0.018		NS (0.073)		NS (0.234)	

MI – myocardial infarction; MACE – major adverse cardiovascular event; PAPP-A – pregnancy-associated plasma protein A; ANOVA K-W – Kruskal-Wallis ANOVA analysis; NS – not significant.

Table 4. Prognostic value of specific PAPP-A cut-off values for 12-month events (death, infarction, combined endpoint)

Event	Dead (n = 5)	Alive (n = 65)	MI (n = 14)	No MI (n = 56)	MACE (n = 38)	No MACE (n = 32)
≥PAPP-A cut-off	2	1	1	2	20	8
PAPP-A cut-off [mIU/L]	88.63		88.63		47.15	
p-value (Fisher's exact test)	0.01		NS (0.49)		0.03	
PPV [%]	66.7		33.3		71.4	
NPV [%]	95.5		80.6		57.1	
Accuracy [%]	94.3		78.6		62.9	

MI – myocardial infarction; MACE – major adverse cardiovascular event; PAPP-A – pregnancy-associated plasma protein A; ≥PAPP-A cut-off – number of patients that exceeded cut-off PAPP-A concentration; PPV – positive predictive value; NPV – negative predictive value; NS – not significant.

subgroups specified according to the occurrence of events are presented in Table 4. Additionally, predictive values have been shown.

The median values of troponin T (TnT) serum concentration tested on admission in subgroups with this uniform cut-off of PAPP-A serum concentration were specifically different (p = 0.01) – 0.15 ng/mL (0.1; 0.25) for PAPP-A ≥40 mIU/L and 0.09 ng/mL (0.06; 0.10) for PAPP-A <40 mIU/L.

We also tested the prognostic value of PAPP-A concentration 40 mIU/L (close to the mean value of PAPP-A serum concentration in our study group) as a universal prognostic threshold (Table 5).

Global Registry of Acute Coronary Events risk score

The median value of the estimated mortality risk during hospitalization in a whole study group according to GRACE scale was 1.15 (0.6; 2.0) and 3.5 (2.0; 5.8) in 6 months from discharge. The median values for categorized GRACE risk score are shown in Table 6.

The median values of the estimated mortality risk during hospitalization and in 6 months from discharge according to GRACE scale in subgroups are shown in Table 7. The highest calculated risks were found in a group of patients that died.

We combined patients with intermediate and high GRACE risk score in one group and compared them with patients with low GRACE risk score. The risk of death was 14.3% in the first group and 0% in the other one. The risk of MI was 34.3% and 5.7% and the risk of MACE was 74.3% and 34.3%, respectively. A quantitative analysis of study subjects with intermediate and high risk on GRACE scale in subgroups is shown in Table 8. Additionally, predictive values have been shown and they revealed a high NPV for death and MI.

Combined analysis of PAPP-A concentration and GRACE score

Based on the prognostic analysis of PAPP-A and GRACE score, we decided to test the composite approach to post-ACS risk stratification. A combined analysis of PAPP-A concentration with cut-off points for subgroups and GRACE score showed significant relations with the occurrence of death and MACE. In MACE group, PPV was 74.1% for in hospital GRACE risk score and 73.1% for 6-month

Table 5. Prognostic value of simplified, uniform PAPP-A cut-off value 40 mIU/L for death, infarction, combined endpoint

Event	Dead (n = 5)	Alive (n = 65)	MI (n = 14)	No MI (n = 56)	MACE (n = 38)	No MACE (n = 32)
PAPP-A ≥40 mIU/L	5	27	10	22	21	11
p-value (Fisher's exact test)	0.017		0.039		NS (0.096)	
PPV [%]	15.6		31.3		65.6	
NPV [%]	100.0		89.5		55.3	
Accuracy [%]	61.4		62.9		60.0	

MI – myocardial infarction; MACE – major adverse cardiovascular event; PAPP-A – pregnancy-associated plasma protein A; PAPP-A ≥ 40 mIU/L – number of patients with PAPP-A serum concentration ≥40 mIU/L; PPV – positive predictive value; NPV – negative predictive value; NS – not significant.

Table 6. Categorized probability of death during hospitalization and in 6 months from discharge according to GRACE scale

Parameter	Low (n = 35)	Intermediate (n = 23)	High (n = 12)
Medians of categorized mortality risk during hospitalization (Q_{25}; Q_{75})	0.6 (0.5; 0.7)	1.6 (1.5; 2.0)	4.9 (4.6; 5.7)
p-value	<0.001		
Parameter	**Low (n = 37)**	**Intermediate (n = 21)**	**High (n = 12)**
Medians of categorized mortality risk in 6 months from discharge (Q_{25}; Q_{75})	2.1 (1.4; 2.6)	5.3 (4.4; 5.8)	12.0 (9.7; 14.3)
p-value	<0.001		

GRACE – Global Registry of Acute Coronary Events.

Table 7. Probability of death during hospitalization and in 6 months from discharge according to GRACE scale in patients subgroups according to follow up events

Event	Dead (n = 5)	Alive (n = 65)	MI (n = 14)	No MI (n = 56)	MACE (n = 38)	No MACE (n = 32)
Probability of death during hospitalization, median (Q_{25}; Q_{75})	4.7 (4.6; 5.0)	1.0 (0.6; 1.6)	1.7 (1.43; 2.73)	1.0 (0.6; 1.63)	1.6 (0.85; 2.98)	0.7 (0.5; 0.33)
p-value (ANOVA K-W)	0.001		NS (0.052)		0.003	
Probability of death in 6 months from discharge, median (Q_{25}; Q_{75})	12.0 (9.7; 14.0)	2.6 (2.0; 5.3)	5.3 (4.4; 6.75)	2.6 (1.9; 5.35)	4.4 (2.6; 7.0)	2.6 (1.55; 3.73)
p-value (ANOVA K-W)	<0.001		0.046		0.004	

GRACE – Global Registry of Acute Coronary Events; MI – myocardial infarction; MACE – major adverse cardiovascular event; ANOVA K-W – Kruskal-Wallis ANOVA analysis; NS – not significant.

Table 8. Predictive value of intermediate/high GRACE score event probability for actual mortality, MI and MACE occurrence at 12-month follow-up

Event	Dead (n = 5)	Alive (n = 65)	MI (n = 14)	No MI (n = 56)	MACE (n = 38)	No MACE (n = 32)
Number of patients with intermediate and high risk of death during hospitalization (GRACE)	5	30	12	23	26	9
p-value (Fisher's exact test)	NS (0.054)		0.006		0.002	
PPV [%]	14.3		34.3		74.3	
NPV [%]	100		94.3		65.7	
Accuracy [%]	51.1		64.3		70	
Number of patients with intermediate and high risk of death in 6 months from discharge	5	28	11	22	24	9
p-value (Fisher's exact test)	0.019		0.014		0.004	
PPV [%]	15.2		33.3		72.7	
NPV [%]	100		91.9		62.2	
Accuracy [%]	60		64.3		67.1	

GRACE – Global Registry of Acute Coronary Events; MI – myocardial infarction; MACE – major adverse cardiovascular event; PPV – positive predictive value; NPV – negative predictive value; NS – not significant.

GRACE risk score. In a group of patients who died, NPV was 95.5% for both GRACE scores.

A combined analysis of PAPP-A concentration with a cut-off point ≥40 mIU/L for subgroups and GRACE score showed significant relations with the occurrence of death, MI and MACE. In a group of patients that died, NPV was 100% for both GRACE scores. In MI group, NPV was 90.2% for in hospital GRACE risk score and 88.4% for 6-month GRACE risk score. In MACE group, PPV was 72.4% for in hospital GRACE risk score and 70.4% for 6-month GRACE risk score.

The analysis of study subjects that exceeded cut-off PAPP-A concentration as well as those with intermediate and high GRACE risk scores with division into subgroups specified according to the occurrence of events are presented in Table 9 for variable cut-offs and in Table 10 for proposed unified cut-off.

Discussion

The assessment of the complications in ACS patients can strongly influence the therapeutic course and post-hospital management. To our knowledge, this is the first study that shows the correlation of plasma levels of PAPP-A and the risk of ACSs, complicated by cardiac death and/

Table 9. Prognostic value of specific PAPP-A cut-off values and intermediate/high GRACE score for 12-month events (death, infarction, combined endpoint)

Event	Dead (n = 5)	Alive (n = 65)	MI (n = 14)	No MI (n = 56)	MACE (n = 38)	No MACE (n = 32)
GRACE in hospital (intermediate and high risk) + ≥PAPP-A cut-off	2	1	1	2	20	7
PAPP-A cut-off [mIU/L]	88.63		88.63		47.15	
p-value (Fisher's exact test)	0.012		NS (0.494)		0.013	
PPV [%]	66.7		33.3		74.1	
NPV [%]	95.5		80.6		58.1	
Accuracy [%]	94.3		78.6		64.3	
GRACE 6 months (intermediate and high risk) + ≥PAPP-A cut-off	2	1	1	2	19	7
PAPP-A cut-off [mIU/L]	88.63		88.63		47.15	
p-value (Fisher's exact test)	0.012		NS (0.494)		0.025	
PPV [%]	66.7		33.3		73.1	
NPV [%]	95.5		78.6		62.9	
Accuracy [%]	94.3		78.6		62.9	

MI – myocardial infarction; MACE – major adverse cardiovascular event; GRACE – Global Registry of Acute Coronary Events; GRACE in hospital – patients with intermediate and high risk of death during hospitalization according to GRACE scale; PAPP-A – pregnancy-associated plasma protein A; ≥PAPP-A cut-off – number of patients that exceeded cut-off PAPP-A concentration; PPV – positive predictive value; NPV – negative predictive value; GRACE 6 months – patients with intermediate and high risk of death in 6 months from hospitalization according to GRACE scale; NS – not significant.

Table 10. Prognostic value of simplified, uniform PAPP-A cut-off value 40 mIU/L and intermediate/high GRACE score for death, infarction and combined endpoint

Event	Dead (n = 5)	Alive (n = 65)	MI (n = 14)	No MI (n = 56)	MACE (n = 38)	No MACE (n = 32)
GRACE in hospital (intermediate and high risk) + PAPP-A ≥40 mIU/L	5	24	10	19	21	8
p-value (Fisher's exact test)	0.001		0.016		0.015	
PPV [%]	17.2		34.5		72.4	
NPV [%]	100		90.2		58.5	
Accuracy [%]	65.7		67.1		64.3	
GRACE 6 months (intermediate and high risk) + PAPP-A >40 mIU/L	5	22	9	18	19	8
p-value (Fisher's exact test)	0.007		0.035		0.048	
PPV [%]	18.5		33.3		70.4	
NPV [%]	100		88.4		55.8	
Accuracy [%]	68.6		67.1		61.4	

MI – myocardial infarction; MACE – major adverse cardiovascular event; GRACE – Global Registry of Acute Coronary Events; GRACE in hospital – patients with intermediate and high risk of death during hospitalization according to GRACE scale; PAPP-A – pregnancy-associated plasma protein A; PAPP-A ≥40 mIU/L – number of patients with PAPP-A serum concentration ≥40 mIU/L; PPV – positive predictive value; NPV – negative predictive value; GRACE 6 months – patients with intermediate and high risk of death in 6 months from hospitalization according to GRACE scale.

or subsequent cardiac events, which can be treated as complementary to current GRACE risk score.

Pregnancy-associated plasma protein A serum concentration

Our study analyzed the relationship of PAPP-A and GRACE score. We were assessing PAPP-A blood concentration within the first 6 h from admission to hospital in a group of patients with symptoms of ACS. The concentration was compared to the risk of death in hospital and 6 months after ACS calculated with GRACE risk score, and to the concentrations of myocardial necrosis biomarkers. A comparison of these calculations to follow-up results helped to estimate predictive values of PAPP-A blood concentration, GRACE risk score and a combination of them. The necessity of identifying a prognostic biomarker that would help to estimate the probability of cardiac events has been postulated over the years.[12] Pregnancy-associated plasma protein A has promising attributes to fulfill the criteria of a new biomarker in the field of cardiology. It was observed that mean PAPP-A serum concentration was the highest in a subgroup of patients that died throughout

the duration of the study (Table 3). Assigning specific cut-off points for PAPP-A concentration (ROC analysis) in subgroups showed that it can provide a strong NPV for the occurrence of death (Table 4). Unified cut-off point (40 mIU/L) resulted in the loss of specificity of PAPP-A concentration for events in single and combined (with GRACE) analysis. However, exceeding this cut-off was tied in with elevated TnT serum concentration tested on admission. In opposite to our findings, some studies have shown that serum concentration of TnT can be in the normal range when PAPP-A serum concentration is increased,[9] but still correlates with cardiovascular risk and with absolute TnT serum concentration.[13]

Global Registry of Acute Coronary Events risk score

The GRACE study involved 250 sites in 30 countries and more than 100,000 patients were recruited. Nine independent risk factors have been identified[14] as those that help to assess the risk of death during hospitalization and in 6 months after discharge.[15] Management and modification in the calculation algorithm reduced the number of statistically significant risk factors to 8, and helped to create a widely available online calculator. It makes risk calculation very accessible and easily assigns risk categories: low, intermediate and high. The risk factors are: age, heart rate, Killip class, initial serum creatinine concentration, elevated initial cardiac markers, cardiac arrest on admission, and ST segment deviation.[14] Risk factors that have the strongest influence in the risk stratification are cardiac arrest on admission and age. Apart from that, the calculator widens a time spectrum of a potential endpoint occurrence to 1 and 3 years from the episode of ACS. In addition, it lets to assess the risk of death and MI 1 year from the episode. Several studies and registries confirmed the utility of GRACE risk score in the last few years, as it showed its dominance over other risk scores and proved that it could be a valid tool in assessing the risk of death even 5 years after discharge from hospital.[16–18] The assessment of GRACE score can help doctors decide the kind and urgency of medical intervention, intensity of chronic treatment and further medical care. All patients with a score >140 (>3% risk of death) should be subjected to coronary angiography within 24 h.[19] In the current analysis, the GRACE risk score showed its efficacy as a negative predictor of death, MI and MACE when divided into categories: low, intermediate and high (Table 8). The PPV of GRACE score was significant for the occurrence of MACE (Table 8).

When we analyzed the combined strategy for variable cut-offs, it resulted in highly specific criteria which might improve the risk stratification in selected populations. The NPV for the occurrence of death was also high. The use of unified cut-off for PAPP-A resulted in the loss of specificity.

Limitations

A relatively small number of hard events (5 deaths, 14 MIs, 32 composite events) was recorded in our small-sized group of 70 patients, which affected the strength of our statistical analysis. Stronger conclusions require a larger size study.

Conclusions

Our analysis revealed that in patients with suspected ACS, GRACE scale has modest accuracy due to low PPV. The PAPP-A serum concentration represents a promising prognostic biomarker with a significantly improved PPV. The GRACE score is superior to stratification based on PAPP-A with regard to combined cut-off point for 1-year mortality, and combining PAPP-A concentration with GRACE score does not improve overall prognostic value.

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