

Bleeding risk factors in patients with acute coronary syndrome: data from observational studies ORACUL II

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Aim. To identify the risk factors for bleeding of BARC scale 2-5 types in patients after acute coronary syndrome (ACS).

Material and methods. The data of 1502 patients from the open multicenter study, ORACUL II, were used — 894 men (59,5%) and 608 women (40,5%), mean age — 65,7±12,9 years. Five hundred sixty (37,3%) patients had ACS with ST-segment elevation and 942 (62,7%) — ACS without ST-segment elevation. Bleeding was recorded in 164 patients (10,9%), including index admission — in 39 (2,6%) patients, of which severe (types 3-5) — 0,5%, significant — 1,7% (types 2-5).

Results. Within a year after discharge, bleeding was observed in 126 (8,4%) patients, large — 0,8%, significant — 2,4%. The development of bleeding type 2-5 was associated with the presence of gastric ulcer and duodenal ulcer, gastrointestinal bleeding in history, decreased creatinine, hemoglobin clearance, age of patients, the use of anticoagulants in the composition of triple or double antithrombotic therapy, conducting of percutaneous interventional procedures, the presence of heart failure 2-4 Killip class at admission. ROC analysis showed that the predictive value of the ORACLE bleeding risk scale is 0,762, sensitivity — 62%, specificity — 78%.

Conclusion. Thus, we based on routine clinical practice have created a simple scale for assessing the risk of bleeding in patients with ACS.

Key words: acute coronary syndrome, bleeding, BARC, mortality, ORACLE risk scale. Conflicts of Interest: nothing to declare.

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Received: 11.02.2019

Revision Received: 17.02.2019

Accepted: 25.02.2019



For citation: Brazhnik V.A., Minushkina L.O., Guliev R.R., Averkova A.O., Rogozhina A.A., Koroleva O.S., Zubova E.A., Karmanchikova E.A., Khasanov N.R., Chichkova M.A., Boeva O.I., Galyavich A.S., Zateyshchikov D.A. Bleeding risk factors in patients with acute coronary syndrome: data from observational studies ORACUL II. *Russian Journal of Cardiology*. 2019;(3):7-16. (In Russ.) doi:10.15829/1560-4071-2019-3-7-16

Large-scale implementation of interventional management for acute coronary syndrome (ACS) and the widespread use of modern antithrombotic therapy (ATT) have made safety an urgent problem. Every 10th patient after an ACS episode develops bleeding within 2 years; up to 4% suffers it during initial hospitalization [1-3]. According to some reports, over the past 10 years, the risk of in-hospital bleeding in such patients has increased 1,8 times. At the same time, those who suffered serious bleeding in a hospital have a higher risk of ischemic events, including fatal ones, at least during the next year [4]. The listed facts provided the basis for the concept of “avoiding” the bleeding risk. However, it has not been widely used in clinical practice. An essential part of this concept is the bleeding risk management, and therefore research in this area is still relevant.

The aim of this study was to identify risk factors associated with the development of bleeding in ACS patients in actual clinical practice.

Material and methods

The present analysis is based on data obtained in the open-label observational multicenter study ORACUL II. The selection of patients was carried out in the period from 2014 to 2017. The inclusion criteria are described in detail in previous publications [5]. The rationale for inclusion in the study was the indications for percutaneous coronary interventions (PCI) in ACS patient, regardless of whether PCI was performed or not.

The presented analysis included data on 1502 patients who had at least 1 follow-up visit after discharge from the hospital. The exclusion criteria were no patient consent to take part in research or inability to contact the patient after discharge. The clinical characteristics of patients are presented in Table 1.

All patients received standard therapy based on current guidelines.

At follow-up visits (when discharged from the hospital, on day 25, 90, 180 and 360 from the inclusion), all cases of bleeding were recorded with a description of their nature, source, severity, management and classification according to the Bleeding Academic Research Consortium (BARC) scale [6]. Adverse outcomes were also recorded (death and its cause, repeated episodes of ACS, re-vascularization after discharge from the hospital, strokes and cases of complicated atherosclerosis). Pharmacological class, name and dose of drugs were also recorded.

The study was approved by the local ethics committees of the organizations participating in the study. All participants completed the informed consent.

Statistical data processing was performed using SPSS 23.0 and MedCalc 18.5 software. An analysis of the distribution and its normality was carried out. Mean values and standard deviation values ($M \pm SD$) were calculated. If the distribution was considered normal, Student's t-test was used to analyze the

Table 1
Clinical characteristics of patients

Parameter	All patients (n=1502)
Men/Women (n, %)	894 (59,5%)/608 (40,5%)
Age, years	65,7 $\pm$ 12,9
BMI, kg/m ²	28,3 $\pm$ 4,99
STE-ACS/ NSTEMI-ACS, (n, %)	560 (37,3%)/942 (62,7%)
History of CAD, (n, %)	1132 (74,7%)
History of MI, (n, %)	466 (31,5%)
History of HTN, (n, %)	1320 (87,9%)
History of stroke, (n, %)	164 (12,6%)
HF before current hospitalization, (n, %)	769 (51,2%)
Class 2-4 by Killip, n (%)	297
Peripheral artery disease, (n, %)	401 (26,8%)
Diabetes, (n, %)	354 (23,6%)
COPD, (n, %)	66 (4,3%)
Asthma, (n, %)	36 (2,3%)
Sleep Apnea, (n, %)	30 (2,0%)
Gastroduodenal ulcer, (n, %)	216 (14,3%)
History of GIB, (n, %)	26 (1,7%)
Hepatic disorders, (n, %)	95 (6,3%)
Thyroid disorders, (n, %)	178 (11,8%)
History of anemia, (n, %)	131 (8,7%)
History of kidney disease, (n, %)	584 (38,8%)
History of cancer, (n, %)	131 (8,7%)
Alcohol consumption, (n, %)	672 (44,7%)
Smoking, (n, %)	405 (26,9%)
History of CVD, (n, %)	553 (36,8%)

Abbreviations: BMI — body mass index, STE-ACS — ST segment elevation ACS, NSTEMI-ACS — non-ST segment elevation ACS, CAD — coronary artery disease, MI — myocardial infarction, HTN — hypertension, HF — heart failure, COPD — chronic obstructive pulmonary disease, GIB — gastrointestinal bleeding, CVD — cardiovascular disease.

Table 2

The source and severity of bleeding recorded at different follow-up visits

	Discharge	Day 25	Day 90	Day 180	Day 360
Number of patients with bleeding	39	39	31	41	45
Source					
GIB	8	7	4	4	8
Hemorrhoids	1	4	1	1	2
Paracentesis-induced bleeding	19	1 (CABG)			
Spontaneous subcutaneous hematomas	2	1	1	1	2
Hematuria	3	1	3	5	2
Nosebleeds	1	20	15	20	22
Uterine bleeding		1	1	1	1
Bleeding gums		2	1	7	6
Hemopericardium	1				
Aortic dissection	1				
Intracranial bleeding			1		
Postoperative bleeding			1 (CABG)	1	
Hemoptysis				1	
Unspecified source	3	2	1		2
Severity by BARC classification					
Type 1	12	30	19	34	36
Type 2	18	5	8	6	5
Type 3	8	3	1	1	2
Type 4		1	1		
Type 5	1		2		2

Abbreviations: GIB — gastrointestinal bleeding, BARC — Bleeding Academic Research Consortium.

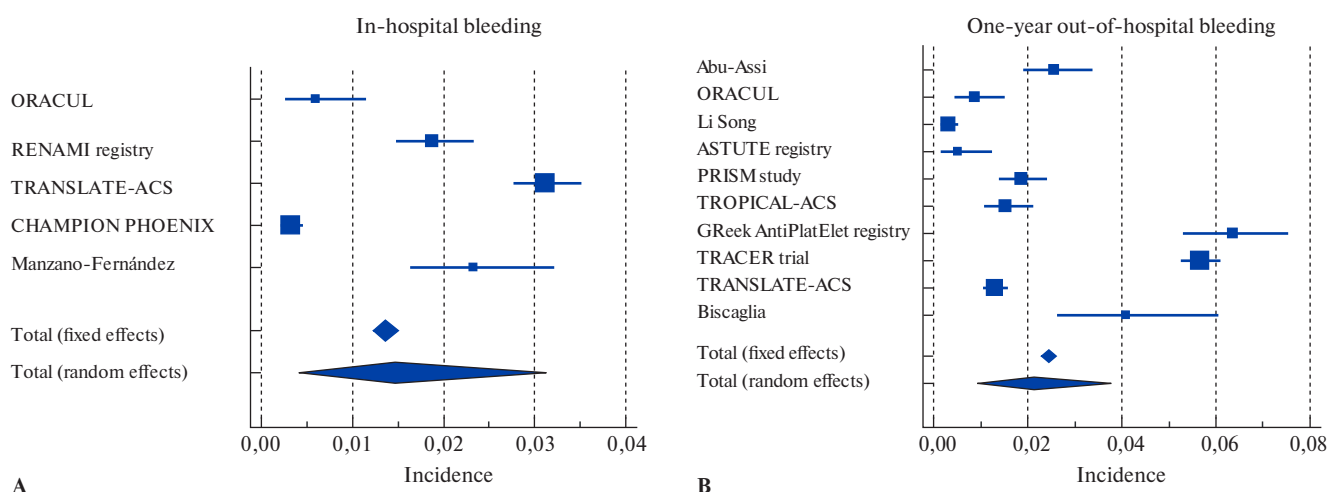


Fig. 1 (A, B). A meta-analysis of the incidence of in- (A) and out-of-hospital (B) bleeding in patients after ACS.

significance of differences; non-parametric methods were used in cases of non-normal distribution. Discrete values were compared by Pearson's chi-squared test.

To assess the bleeding incidence in comparison with literature data, a meta-analysis of research data published in 2015–2018 was carried out. A literature search was conducted using PubMed with the key-

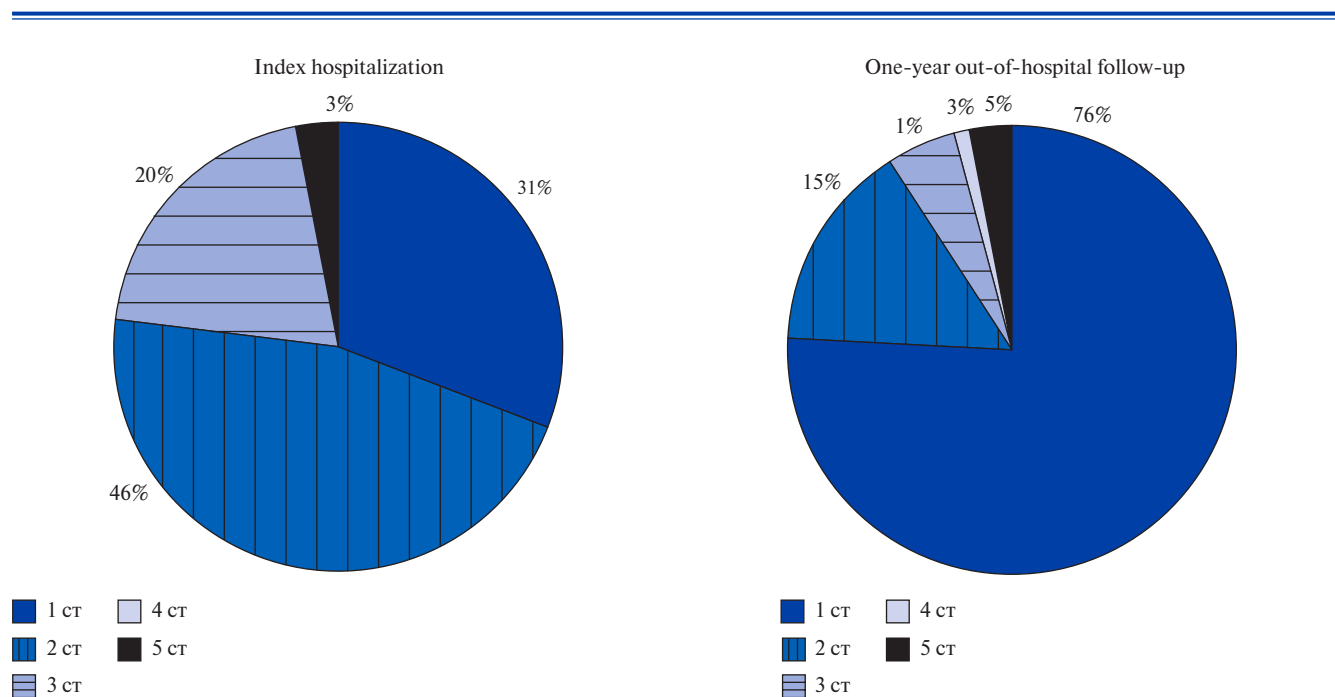


Fig. 2. The severity of bleeding during the index hospitalization and one-year out-of-hospital follow-up.

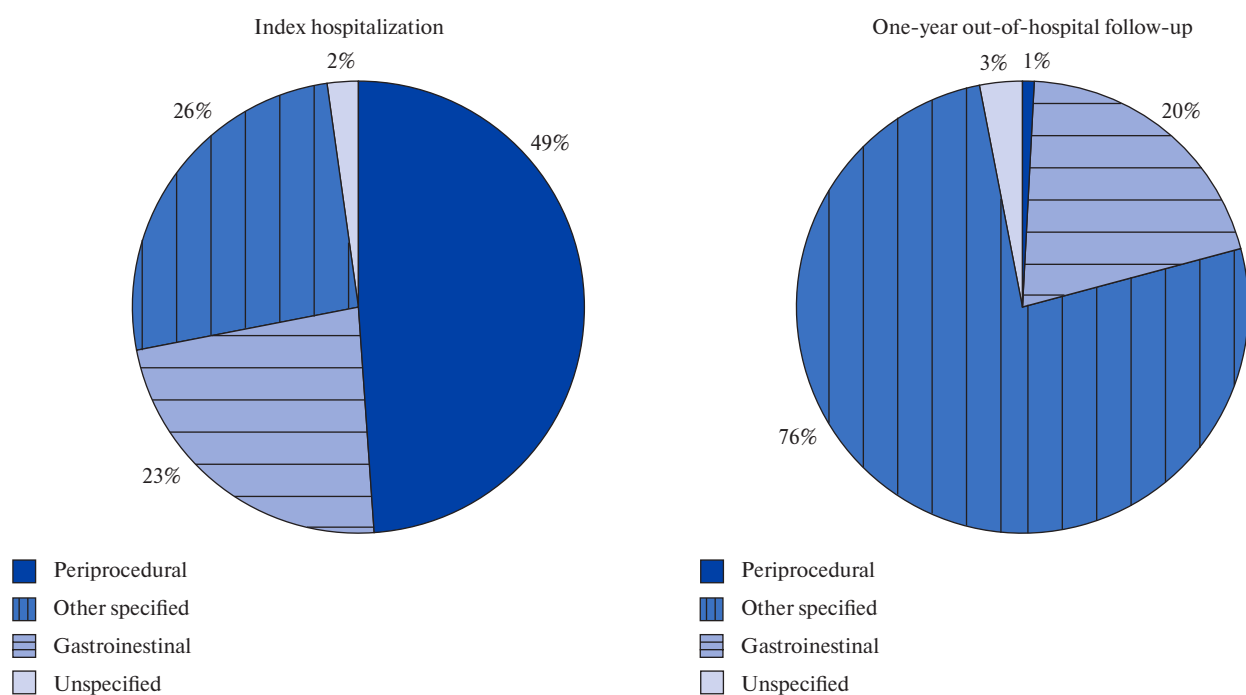


Fig. 3. Sources of bleeding during the index hospitalization and one-year out-of-hospital follow-up.

words “acute coronary syndrome”, “bleeding”, “BARC”. The meta-analysis included studies with follow-up periods comparable to the ORACUL study. The meta-analysis of proportions was carried out using the MedCalc statistical software with the Freeman-Tukey’s transformation. The heterogeneity of the model was evaluated by the Q and I² tests.

Logistic regression was used to assess the independence of the effects of clinical factors on the bleeding risk. Parameters that demonstrated statistical significance in a univariate model were included in a multivariate analysis. The coefficients for forecast formula were calculated by linear regression analysis. Internal validation was performed using

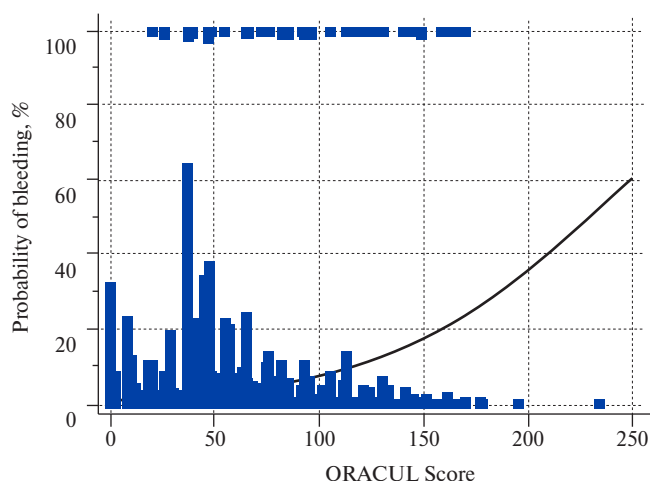


Fig. 4. Distribution of ORACUL whole-numbered risk score and the probability of clinically significant bleeding (type 2-5 by BARC classification) within 1 year after ACS.

the bootstrap method. Classification and assessment of the goodness of fit was carried out by Hosmer-Lemeshow test. Classification was considered adequate when $p > 0,20$.

Analysis of the diagnostic accuracy of the test scale was conducted by constructing receiver operator characteristic curves (ROC-curves) for each diagnostic criterion and finding the area under the curves. Also, for each tested diagnostic criterion, sensitivity and specificity were calculated. Comparison of diagnostic values in different clinical groups was carried out by comparing the areas under the ROC-curves by the Hanley and McNeil test.

This independent, open-label, observational, multicenter study was organized by the Department of Therapy, Cardiology and Functional Diagnostics of the Central State Medical Academy (Moscow,

Table 3

Clinical characteristics of patients with ACS depending on the presence of clinically significant bleeding

Parameter	Patients without bleeding or with type 1 bleeding 1 (by BARC classification) (n = 1443)	Patients with type 2-5 bleeding (by BARC) (n = 59)	p
Men/Women (n, %)	863 (59,7%)/580 (40,1%)	32 (54,2%)/27 (45,8%)	0,648
Age, years	65,6±12,91	70,8±12,70	0,002
BMI, kg/m ²	28,3±5,01	28,0±4,49	0,477
STE-ACS/ NSTE-ACS, (n, %)	541 (37,4%)/902 (62,6%)	19 (32,0%)/40 (68,0%)	0,233
History of CAD, (n, %)	1075 (74,4%)	47 (76,7%)	0,789
History of MI, (n, %)	441 (31,0%)	25 (42,4%)	0,066
History of HTN, (n, %)	1270 (88,0%)	50 (84,7%)	0,239
History of AF, (n, %)	267 (18,5%)	16 (37,1%)	0,102
History of stroke, (n, %)	160 (10,2%)	4 (6,9%)	0,145
HF before current hospitalization, (n, %)	737 (51,1%)	32 (54,2%)	0,666
Class 2-4 by Killip, n (%)	280 (19,1%)	17 (28,1%)	0,050
Peripheral artery disease, (n, %)	388 (27,0%)	13(22,0)	0,671
COPD, (n, %)	63 (4,4%)	3 (5,1%)	0,781
Asthma, (n, %)	32 (2,2%)	4 (6,8%)	0,052
Sleep apnea, (n, %)	29 (2,0%)	1 (1,7%)	0,844
Gastroduodenal ulcer, (n, %)	202 (14,1%)	14 (23,7%)	0,038
History of GIB, (n, %)	21 (1,5%)	5 (8,9%)	0,003
Hepatic disorders, (n, %)	91 (6,3%)	4 (6,8%)	0,792
Thyroid disorders, (n, %)	168 (11,7)	10 (16,9%)	0,482
History of anemia, (n, %)	119 (8,6%)	12 (20,7%)	0,010
History of kidney disease, (n, %)	556 (38,7%)	28 (44,1%)	0,759
History of cancer, (n, %)	124 (8,6%)	7 (12,1%)	0,673

Alcohol consumption, (n, %)	651 (45,6%)	21 (35,6%)	0,434
Smoking, (n, %)	390 (27,0%)	15 (25,4%)	0,758
History of CVD, (n, %)	528 (38,9%)	25 (43,1%)	0,713
Antithrombotic therapy upon discharge from the hospital			
No therapy, (n, %)	6 (0,5%)	2 (3,7%)	0,052
ASA or clopidogrel (monotherapy), (n, %)	87 (6,6%)	2 (3,7%)	0,056
ASA+ticagrelor, (n, %)	563 (43,0%)	21 (38,9%)	0,156
ASA+clopidogrel, (n, %)	543 (41,5%)	20 (37,0%)	0,169
Triple ATT, (n, %)	58 (4,4%)	5 (9,3%)	0,008
Antiplatelet agent+anticoagulant, (n, %)	45 (3,4%)	4 (7,4%)	0,003
Anticoagulant, (n, %)	5 (0,4%)	0	0,237
PCI in index hospitalization, (n, %)	748 (56,3%)	42 (75,0%)	0,006
Laboratory parameters upon admission to the hospital			
HB, *10 ⁹ /L	135,9±19,15	125,6±6,82	0,001
Hematocrit, %	40,6±6,36	38,2±0,68	0,011
Leukocytes, *10 ¹² /L	11,0±22,30	9,9±3,85	0,626
Platelets, 10 ³ /μL	236,5±75,79	227,5±82,65	0,522
Glucose, mmol/L	8,32±4,74	8,42±3,11	0,532
Total cholesterol, mmol/L	5,63±2,641	5,49±1,671	0,791
LDL, mmol/L	3,24±1,122	3,21±1,466	0,184
HDL, mmol/L	1,11±0,394	1,18±0,431	0,669
Triglycerides, mmol/L	1,74±1,231	1,51±1,009	0,249
Uric acid, mmol/L	396,7±279,98	489,77±214,547	0,083
Creatinine, μmol/L	98,87±36,435	100,11±25,443	0,578
CrCl by Cockcroft-Gault equation, ml/min	78,8±32,76	66,4±25,17	0,01
GFR by MDRD equation, ml/min/1,73 m ²	42,07±13,361	44,87±11,274	0,297

Abbreviations: BMI — body mass index, STE-ACS — ST segment elevation ACS, NSTEMI-ACS — non-ST segment elevation ACS, CAD — coronary artery disease, MI — myocardial infarction, HTN — hypertension, HF — heart failure, COPD — chronic obstructive pulmonary disease, GIB — gastrointestinal bleeding, CVD — cardiovascular disease, ASA — acetylsalicylic acid, ATT — antithrombotic therapy, PCI — percutaneous coronary intervention, Hb — hemoglobin, LDL — low density lipoproteins, HDL — high density lipoproteins, CrCl — creatinine clearance, GFR — glomerular filtration rate.

Russia). The authors do not declare conflicts of interest.

Results

During the follow-up period, bleeding was noted in only 164 out of 1502 patients (10,9%), during the index hospitalization — in 39 (2,6%), within year after the index hospitalization — in 126 (8,4%); repeated bleedings on several visits was recorded in 19 (1,2%) patients. The incidence of major bleeding (types 3-5 by BARC) during hospitalization was 0,5%, significant bleeding — 1,7% (types 2-5 by

BARC). For bleeding that developed after discharge from the hospital, the incidence was 0,8%, for significant — 2,4%. The severity and sources of bleeding are described in Table 2.

Fig. 1 shows the results of meta-analysis of bleeding incidence in ACS patients according to studies published in 2015-2018 [7-18]. Meta-analysis contains only those studies where the bleeding severity was assessed according to BARC criteria. The incidence of bleeding in hospitalization and within 1 year after an ACS episode was analyzed. It should be noted that the data are very heteroge-

Table 4

Independent predictors of type 2-5 bleeding by BARC classification

Factors	Type 2-5 bleeding by BARC classification			
	Univariate analysis		Multivariate analysis	
	OR (CI 95%)	p	OR (CI 95%)	p
Age, quartiles	2,58 [1,59-4,18]	0,001	2,66 [1,19-2,31]	0,003
Class 2-4 by Killip upon admission	2,16 [1,51-3,11]	0,017	2,01 [1,17-2,96]	0,033
Gastroduodenal ulcer	1,91 [1,03-3,55]	0,04	5,00 [1,154-1,71]	0,031
History of GIB	6,23 [2,26-17,19]	0,001	0,95 [0,68-1,32]	0,799
History of anemia	2,55 [1,32-4,93]	0,005	1,13 [0,63-1,68]	0,754
Anticoagulants as part of a triple or dual ATT	2,24 [1,07-4,72]	0,032	1,74 [1,01-2,47]	0,047
PCI in index hospitalization	2,31 [1,25-4,28]	0,007	3,03 [1,44-6,37]	0,003
Hb, quartiles	2,29 [1,59-3,33]	0,0001	1,97 [1,06-2,87]	0,045
Hematocrit, quartiles	1,94 [1,08-2,76]	0,03	0,99 [0,67-1,38]	0,899
CrCL by Cockcroft-Gault equation, ml/min, quartiles	1,60 [1,13-2,28]	0,008	2,12 [1,43-2,86]	0,02

Abbreviations: GIB — gastrointestinal bleeding, ATT — antithrombotic therapy, PCI — percutaneous coronary intervention, Hb — hemoglobin, CrCl — creatinine clearance.

neous both for the in- and out-of-hospital bleeding (Q-test 319,62 and 820,53, respectively). Funnel analysis for in-hospital bleeding incidence shows symmetrical distribution, and for out-of-hospital bleeding, asymmetrical distribution, which indicates a greater variety of influencing factors. In both cases, the ORACUL study data were within the 95% confidence interval.

During the index hospitalization, bleeding associated with coronary angiography (CAG) and revascularization were the most frequent — 49%; gastrointestinal bleeding (GIB) were in the second place — 23%. One of the bleeding was fatal (aortic dissection) (Fig. 2). After discharge from the hospital, nasal, gingival, urological and some other hemorrhages were most common (76%); GIB were in the second place (20%). Periprocedural (1%) and unspecified (3%) bleeding were rare (Fig. 3). During the index hospitalization, the severity of bleeding corresponded to type 2 (40%) and type 3 (22%) by BARC classification; there was 1 case of fatal bleeding (3%) (type 5). After discharge from the hospital, nuisance bleeding was more often observed (type 1) (76%). Two cases of bleeding associated with coronary artery bypass grafting (CABG) (type 4) and 3 cases of fatal bleeding (type 5) were noted. In general, type 2-5 bleeding (minor, major, CABG-related and fatal) was noted in 64 patients (37,6%).

Given the absolute number of bleeding and the significance of types 2-5 bleeding, they were com-

bined to calculate the risk. It was revealed that the development of type 2-5 bleeding is associated with a gastric and duodenal ulcers, a history of GIB, kidney diseases and creatinine clearance decrease, a history of anemia and levels of hemoglobin and hematocrit upon admission. It was also associated with age, anticoagulants as part of a triple or dual ATT, PCI during index hospitalization and class 2-4 by Killip upon admission (Table 3).

According to the regression analysis, the following factors were independently associated with bleeding: age, hemoglobin and creatinine clearance decrease, PCI in index hospitalization, the use of oral anticoagulants, class 2-4 by Killip, and a history of peptic ulcer disease (Table 4). These factors were included in the ORACUL risk assessment model. For computational convenience, the coefficients obtained in the regression analysis were converted to whole numbers (points). For each continuous variable, cut-off points were created at which the ratio between the variable and the bleeding risk became flat and clinically significant (Table 5). The point total for each patient was compared with the risk of bleeding (Fig. 4). With the internal validation, the following classification intervals were obtained: with a total of up to 67 points, the bleeding risk is low (<1,5%), 68-107 points — moderate (2,8%), 108-133 points — high (5,1%), over 134 points — very high — 11,7% (Table 6). Moreover, in the lower classification

Table 5

ORACUL score

Parameters	
Age up to 55 years old	0 points
56-65 years old	8 points
66-75 years old	16 points
Over 75 years old	24 балла
Hemoglobin upon admission >125 g/L	0 points
100-125 g/L	48 points
<100 g/L	96 points
Killip class upon admission	
Class 1	0 points
Class 2-4	17 points
Creatinine clearance	
≥90 ml/min	0 points
60-89 ml/min	6 points
<60 ml/min	12 points
History of gastroduodenal ulcer	20 points
Anticoagulant+ antiplatelet agents after ACS (dual or triple therapy)	36 points
PCI in index hospitalization	38 points

Abbreviations: ACS — acute coronary syndrome, PCI — percutaneous coronary intervention.

Table 6

Internal validation of ORACUL score

Internal	% adverse outcome	The ratio of the probability to the expected	95% CI
0-67	1,5%	0,555	0,388-0,792
68-107	2,8%	1,269	0,783-2,054
108-133	5,1%	1,987	1,021-3,868
134-250	11,7%	6,831	3,562-13,099

interval, the risk of bleeding was lower than expected, and in the intervals of 68 points or more — higher than expected.

The risk classification by the ordered score was adequate — $p=0,576$ by the Hosmer-Lemeshev test, and the prognostic value was high (ROC-curve — 0,762) (Fig. 5). The sensitivity of the model was 62%, specificity — 78%.

Discussion

Bleeding events in patients with ACS can be one of the most important unfavorable prognostic factors. For the first time, the effect of bleeding on the prognosis of ACS patients was shown in meta-analysis with 24 thousand patients of 3 studies — GUSTO

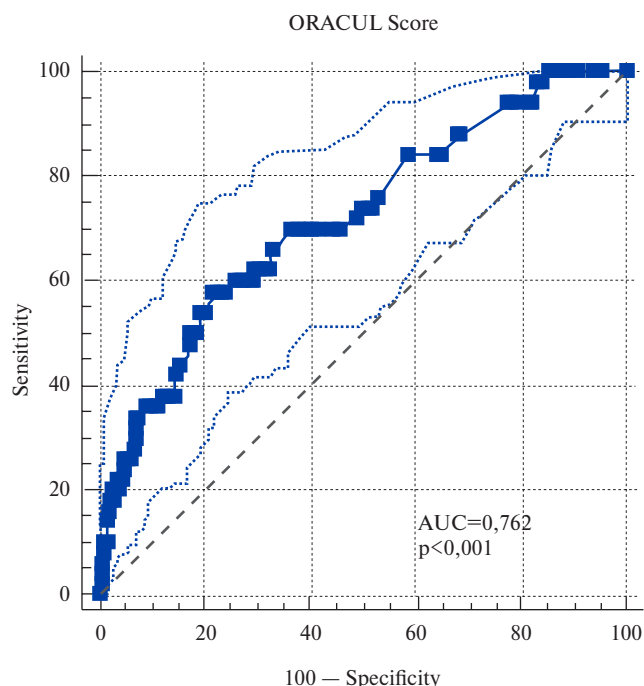


Fig. 5. ROC-curve for the ORACUL score.

IIb, PURSUIT and PARAGON B. Meta-analysis showed that patients who received a blood transfusion during hospitalization due to ACS have a significantly higher mortality rate and recurrent myocardial infarction (MI) during the first 30 days after ACS [19]. In the OASIS-5 study, fondaparinux was significantly safer than enoxaparin with similar efficacy during treatment. During follow-up after treatment, ischemic events were also significantly less common in the fondaparinux group, which suggests that every sixth death recorded in ACS patients in the first 30 days from the destabilization occurred in patients with bleeding during hospitalization [20]. A subanalysis of the PLATO study also showed that the increased risk of adverse outcome after early spontaneous ischemic events and after episodes of major bleeding is comparable. Moreover, bleeding often precede recurrent ischemic events [21]. A similar correlation of hemorrhagic and ischemic events was revealed in the Swiss cohort of patients with ACS, including 1901 patients. The risk assessment scale, which includes only 3 parameters (age, ejection fraction and creatinine level), made it possible to predict the risk of coronary events, death and strokes. At the same time, the severity of bleeding, evaluated by the TIMI and GUSTO scales, correlated with an increase in the number of points of the coronary risk [22]. ACS patients commonly (10-40% of cases) are diagnosed with anemia, which can also be a symptom of

severe concomitant diseases. In some patients, a hemoglobin decrease occurs during treatment in a hospital and is associated with active antithrombotic therapy and bleeding. As a rule, in-hospital bleeding and a hemoglobin decrease correlate with an unfavorable prognosis of coronary artery disease and an increased risk of thrombotic complications [23]. Such data emphasize the need for prediction and possible prevention of bleeding in ACS patients, as well as maintaining a balance of thrombotic and bleeding risks during therapy.

When using the BARC bleeding classification [6], it was shown that the increased risk of recurrent ischemic events in ACS patients is typical for type 2-5 bleeding; type 1 (nuisance) bleeding does not significantly affect the risk of adverse outcomes [24]. Prognostic value of class 3b hemorrhages was comparable with repeated MI. The mortality rate after recurrent MI was significantly lower than after class 3c bleeding [25].

In our paper, the incidence of significant bleeding was lower than in most previously published studies. Our meta-analysis showed a high heterogeneity of data on the bleeding incidence, which may be associated with ATT. At the same time, in-hospital bleeding during index hospitalization demonstrates a greater homogeneity of data. The large scatter of data requires additional analysis of methods for assessing the bleeding severity, and also indicates the need to improve forecast models.

In the BleMACS register, the incidence of major bleeding (3-5 types by BARC) in the first year after PCI was 3,2% per year (in our study — 2.3%). It is worth noting that these patients are close to those included in our study by their main clinical characteristics. Also, the factors used in BleMACS bleeding risk score was close to those from ORACUL study [26]. Both models include factors such as age, creatinine and hemoglobin levels. In our risk assessment model, a history of peptic ulcer was more significant factor than a bleeding history (as in BleMACS). The

history of cancer did not significantly affect the prognosis. It should be noted that factors such as age, hemoglobin level (or anemia history), decreased renal function are included in most risk assessment models for bleeding [27, 28]. A decrease in creatinine clearance below 60 ml/min is used as an independent factor in the PARIS score [29]. In our register, glomerular filtration rate (GFR) was not used. The American register of ACS patients, including 1699 patients from 3 centers, compared the prognostic value of GFR using the MDRD and CKD-EPI formulas and creatinine clearance using Cockcroft-Gault formula regarding the risk of hemorrhagic and thrombotic events. It showed that creatinine clearance had higher diagnostic value in assessing the risk of coronary events and overall mortality compared with MDRD GFR and risk of bleeding compared with CKD-EPI GFR [30].

In the PARIS score, one of the prognostic factors is the anticoagulant as a part of a triple ATT; in our risk score, any use of anticoagulants was a predictor of a high bleeding risk.

Heart failure upon admission to the hospital was another independent risk factor for bleeding in our study. Heart failure is also used in the ACTION and CRUSADE scores [31, 32]. In one study, a reduced ejection fraction was used as an independent risk factor for bleeding [33].

The management of patients was also significant in our study — patients after PCI had a 3 times higher risk of bleeding. This is consistent with the ACCOAST study, where PCI increased the risk of bleeding by 2,2 times [33].

Thus, the ORACUL score showed high prognostic value for assessing the risk of all significant bleeding within 1 year after ACS. The score is easy to use and predicts bleeding in actual clinical practice. These factors allow for the implementation of the score in practice.

Conflicts of Interest: nothing to declare.

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