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PREDICTORS OF HEMORRHAGIC COMPLICATION IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Резюме

ПРЕДИКТОРИ ГЕМОРАГІЧНИХ УСКЛАДНЕНЬ У ПАЦІЄНТІВ З ГОСТРИМ КОРОНАРНИМ СИНДРОМОМ
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Частота геморагічних ускладнень у хворих з гострим коронарним синдромом (ГКС) коливається в межах від 1% до 10%. Навіть у випадку відсутності геморагічних подій під час терапії ГКС за допомогою антикоагулянтів або тромболітиків, у 1,6% та 2,5% хворих зі стентуванням коронарних артерій на подвійній антитромбоцитарній терапії (ПАТТ) впродовж 12 і 18 місяців відповідно виникають кровотечі.

Мета. Визначити загальноклінічні та клініко-лабораторні предиктори виникнення геморагічних ускладнень у хворих, які підлягають терапії з приводу ГКС.

Матеріали та методи. Проаналізовано загальноклінічні показники, результати клініко-лабораторного дослідження 59 пацієнтів, які підлягали терапії ГКС в Державній науковій установі «Науково-практичний центр профілактичної та клінічної медицини» Державного управління справами (2014-2016 рр.).

Результати. У хворих на ГКС геморагічні ускладнення спостерігаються у 20,33 % випадків. В структурі геморагічних ускладнень BARC як перший, так і другий типи кровотеч представлені в 41,67 % епізодів, а третій А тип – 16,66 % випадків. Підтверджено, що частота кровотеч при ГКС вища серед жінок (38,09 %), ніж серед чоловіків (10,52 %), а жіноча стать збільшує ймовірність виникнення кровотеч в 2,41 раза. Також доведено, що частота розвитку геморагічних ускладнень у пацієнтів з анемією на момент встановлення їм діагнозу ГКС вища, ніж у хворих без неї, та дорівнює 43,75 %. Ризик виникнення кровотеч за умови наявності анемічного синдрому у хворих на ГКС зростає в 3,04 раза. Підтверджено, що анемія самостійно (F = 5,311), незалежно від рівню креатиніну, як показнику ниркової недостатності, є предиктором розвитку кровотеч у пацієнтів із ГКС.

Ключові слова: **гострий коронарний синдром, геморагічні події, подвійна антитромбоцитарна терапія.**

INTRODUCTION

The frequency of hemorrhagic events in patients with acute coronary syndrome (ACS) ranges from 1.0% to 10.0% [1]. The high likelihood of bleeding complications in ACS patients is caused by the appointment of anticoagulant and antiplatelet therapy and prolonged use of the latest [2]. Be noted that even in the case of hemorrhagic events absence during aggressive treatment of ACS with help of anticoagulants or thrombolytic, in 1.6% and 2.5% of coronary arteries stenting patients, who received dual antithrombotic therapy (DATT) during 12 and 18 months respectively, were observed bleedings [3].

The occurrence of acute or chronic hemorrhagic syndrome on therapy for ACS refers to the adverse prognostic factors [4,5]. The relative risk of mortality in the presence of hemorrhagic episodes on a background of the therapy for ACS is 1.64 (95% CI = 1.18-2.28) [5].

At this moment different systems for the prediction of bleeding during treatment for ACS exists. However,

there is not integral algorithm for the assessing of a risk of hemorrhagic events [6].

So, the aim of our study is to determine clinical and laboratory parameters of patients with ACS, which would be most powerful predictors of hemorrhagic events.

MATERIAL AND METHODS

Results of clinical and laboratory parameters of patients with acute and chronic coronary heart disease (CHD) were analyzed. For to the preventing a specific selection of clinical cases, all patients with coronary artery disease were included in the study by the hospital-oriented principle. Thus, we included into the study patients, who were treated or consulted in the State scientific institution "Scientific-practical center of preventive and clinical medicine" of the State administration, during the period from 2014 to 2016. Materials for the study were obtained by the prospective study of patients and with help of the searching of historical data.

In the study were included 59 patients with ACS, 28 (47.45%) and 31 (52.55%) of there had myocardial infarction (MI) with ST-segment elevation (MI with ST) and without ST-segment elevation (MI without ST) accordingly.

The gender analysis determined, that in a cohort of patients with ACS (64.41%) men met more often, than women (35.59%) (38 from 59 vs 21 from 59; $p = 0.003$).

Average age in the overall cohort of ACS patients was 68.94 ± 12.42 years. The age of MI with ST patients and MI without ST patients was equal to 67.53 ± 11.03 years and 70.20 ± 13.61 years, respectively ($p = 0.411$).

STATISTICS ANALYZE

Parametric indicates with Poisson distribution were described by the arithmetic mean (M) with an accuracy arithmetic mean value (m). Average values in the tables and text were presented as $M \pm m$. Differences between samples with normally distribution were assessed by parametric the Student's test (t) in bidirectional version. Non-parametric indicators were compared using the Fisher exact test in bidirectional version (F). The degree of association between categorical (nonparametric indicators) was expressed as the relative risk (RR) with 95% confidence interval (CI). For the estimation of the influence of factors on the indices change and for the calculating of the contribution of different factors into variability we used single-factor (ANOVA) analysis of the dispersion. We applied discriminant analysis for the determining of the optimal level of age for predicting hemorrhagic events which is conducted by constructing ROC - curve. The area under the ROC-curve, which is equal to 0.5-0.6, corresponds to unsatisfactory, 0.6-0.7 - average, 0.7-0.8 - good, 0.8-0.9 - very good and 0.9-1.0 - excellent predictive models. Also, we analyzed the operating characteristics of the age factor for prediction of hemorrhagic complications (sensitivity, specificity and predictive value of a positive result (PVPR), predictive value of a negative result (PVNR)).

Digital data were analyzed using the software package Statistica 10,0 (StatSoft, USA), MedCalc 12.5.0.0 (MedCalc Software bvba, Belgium) and using "Excel" from the package "Microsoft office 2010".

RESULTS

Patients with MI with elevation of ST-segment and with MI without ST were represented 47.45% (28 of 59 people) and 52.54% (31 of 59 people) of total ACS cases respectively. Recurrent cardiovascular events in the cohort of individuals with ACS met in 16.94% (10 of 59 people) patients. Cases of the stent thrombosis were not observed.

Hemorrhagic complications were represented 20.33% (12 of 59 people) of cases in the group of ACS patients. According to the BARC stratification system, the structure of bleeding events in ACS patients was presented as follows: 41.67% (5 of 12 episodes) belonged to the first type of bleeding, 41.67% (5 of 12 episodes) and 16 66% (2 of 12 episode) - the second type and the third type accordingly (Fig. 1.1).

There was not the significant prevalence ($p = 0.370$) of the first or second type hemorrhagic events over the third A type in patients with ACS.

Given the fact that currently there are many stratification systems to assess of the likelihood of bleeding during treatment of ACS with the inclusion of different theirs predictors [7], in this study we take into

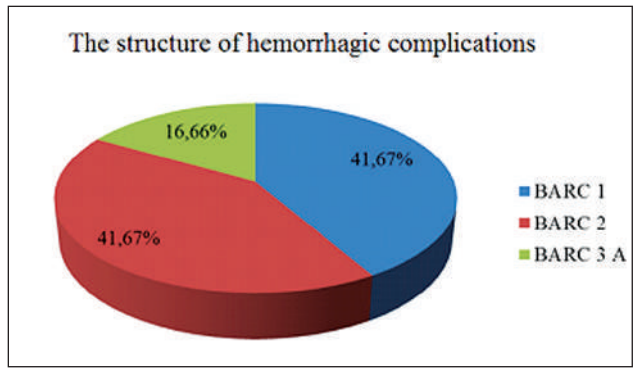

Fig.1.1 – The structure of bleeding events according to the BARC stratification system in patients with ACS.

Table 1.1

The operating characteristics of the reliability and efficiency of age as factor for predicting of hemorrhagic complications in patients with ACS

Index	Value
The discrimination level	> 61 years
Area under ROC-curve	0.60 (0.46 – 0.72)
p	0.230
Sensitivity	91.6 (61.5 – 99.8)
Specificity	29.7 (17.3 – 44.9)
PVPR	25.0 (13.1 – 40.3)
PVNR	93.3 (66.8 – 99.9)

account the most potentially powerful triggers of the bleeding.

Therefore, we analyzed the contribution into the increasing of the frequency and the risk of bleeding such indicator, as age, female sex, anemia, increased levels createnine and the presence of comorbidities (diabetes, cardiovascular disease, stroke history).

In addition we investigated the effect on the likelihood of bleeding the factors, which based on the type of the management of ACS patients. Namely, we took into account the fact of presence of the stent or coronary artery bypass graft, the use of the triple antithrombotic therapy on the background of atrial fibrillation and some of P2Y12 receptor inhibitors in DATT. Also, some authors consider, that the availability of the ST-segment elevation in ACS patients is the one of the factors of the higher likelihood of bleeding [7, 8].

In our study we did not found the relationship between the frequency of bleeding and the ST-segment elevation in patients with ACS. The frequency of bleeding complications in patients with MI with ST was 17.85%, and in patients with IM without ST – 19.35%. The difference between the incidence of bleeding in patients with and without the ST-segment elevation did not define (5 from 28 vs 6 from 31; p = 1.000).

Also, between patients, who underwent the coronary artery stenting or coronary artery bypass graft (29.92%) and patients, whom it was not conducted (15 15%), the frequency of bleeding complications did not differ (7 from 26 vs 5 from 33 persons; p = 0.335)

Next, there was analyzed the role of the age factor for the predicting of bleeding in ACS patients.

In the cohort of ACS patients the average age amounted to 68.94 ± 12.42 years. The average age of ACS patients with hemorrhagic syndrome did not differ from that, which was observed in ACS patients without bleeding (72.16 ± 7.95 years against 67.93 ± 13.35 years; p = 0.299).

Also, there was not found the statistically significant discrimination age level for the prediction of bleeding (tab. 1.1).

However, in the study was defined the relationship between the occurrence of bleeding and gender of ACS patients.

It was confirmed, that the incidence of bleeding during ACS treatment was higher among women (38.09%), than among men (10.52%) (8 from 21 vs 4 from 38; p = 0.018). Also, it was calculated, that the belonging of ACS patients to the female sex increases the likelihood of bleeding in 2.41 times (95% CI = 1.3-4.4).

The overall frequency of vascular diseases in a cohort of individuals with ACS represented 35.59% (21 of 59 people) of episodes.

We did not find any association between the occurrence of bleeding in ACS patients and the vascular pathology presence, including metabolic angiopathy, varicose veins of the lower extremities, atherosclerotic vascular lesions of the lower extremities, transient ischemic attack and hemorrhagic or ischemic stroke.

Hemorrhagic complications in ACS patients with the vascular pathology and without it met in 28.57% and 15.78% respectively, but the difference between the frequency did not reach the level of statistical significance (6 from 21 vs 6 from 38 persons; p = 0,315).

The percent of patients with diabetes was 18.64% (12 of 59 people) of cases in the study cohort. During the comparison the incidence of bleeding complications in a cohort of ACS patients with diabetes and without it, the difference was not find (1 from 11 vs 11 from 48 persons; p = 0.438).

Table 1.2

Multivariate dispersion analysis

Factor	MS	F	p
The common input of the combination	1,35	8,88	0,004
the increase of serum creatinine	0,09	0,63	0,428
Anemia	0,80	5,31	0,024
The interaction of factors	0,002	0,01	0,902

However, on the limits of the statistical evidence (3 of 5 vs 9 of 54 people; p = 0,052), there was determined the prevalence of bleeding complications in ACS patients with atrial fibrillation on triple therapy (60.00%), in comparison with patients on DATT (16.66%).

In the study was analyzed the incidence of bleeding in ACS patients, whom were getting different inhibitors of P2Y12 receptor (DATT) during 12 months. Note, that only 15.38% (4 of 26 people) of patients with stents received ticagrelor and aspirin. The other 84.62% (22 of 26 people) of patients used a combination of aspirin with clopidogrel.

In case of PATT with ticagrelor the frequency of bleeding events equaled to 75.00% of cases and was higher, than in case of PATT with clopidogrel (40.99%). However, between patients, who took ticagrelor, and subjects, who got clopidogrel, the difference of the bleeding frequency did not reach of statistical significance (3 from 4 vs 9 from 22 people; p = 0.306).

Additionally, we analyzed the contribution in to the increase of the frequency and the risk of bleeding such factor as anemia and increasing of creatinine level.

The increasing of creatinine concentration was determined in 32.23% (19 of 59) of patients with ACS. There was no find of the prevalence of bleeding events in ACS patients with the increasing levels of creatinine (31.57%), compared with patients with normal concentrations of it (15.00%) (6 from 19 vs 6 from 40 persons; p = 0.173).

However, in the study was demonstrated, that the increasing of the creatinine concentration was found in 50.00% of ACS patients with hemorrhagic syndrome and it was higher, than in the group of patients without bleeding (12.76%) (6 from 12 vs 6 from 47 persons; p = 0.010). It was calculated, that the hemorrhagic episodes will increase the serum creatinine level in 3.91 (95% CI = 1.53-10.00) in ACS patients.

We also prove that anemia at the time of diagnosis ACS was found in 27.11% (16 of 59 people) of patients, but its number was rising to 42.37% (25 of 59 people) during the period of hospitalization.

It was noted that, the incidence of bleeding in patients with anemia (7 from 16 vs 5 from 43; p = 0.011) was higher, than in patients without anemia (43.75% compared to 11.62% cases) at the time of ACS diagnosis. The availability of anemic syndrome increased the risk of bleeding at 3.04 times (95% CI = 1.42-6.49) in ACS patients.

Anemic syndrome may be caused by chronic renal failure. Considering the last thesis and according to the fact, that anemia and the increasing of creatinine could be separate predictor of hemorrhagic events, we conducted the multivariate analysis of the variance with the definition of contribution to the development of the hemorrhagic events the combination of the factors and theirs separately impact (Table. 1.2 and Fig. 1.2).

There was demonstrated that anemia independently from creatinine as an indicator of renal failure is predictive of bleeding in patients with ACS.

Summing up all the above, in 20.33% of ACS patients occur hemorrhagic complications, the predictor

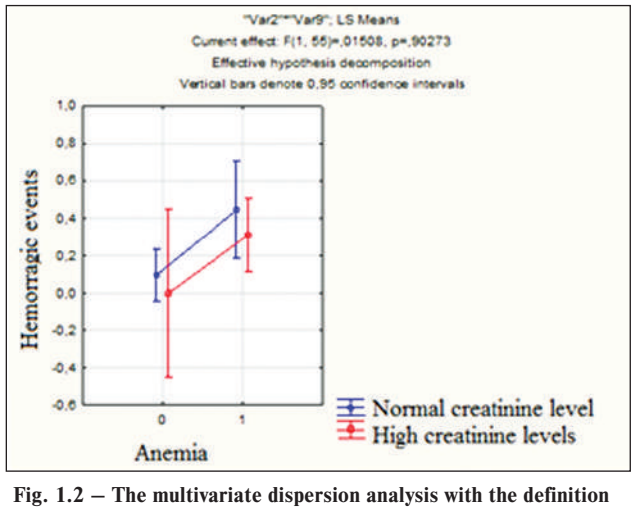

Fig. 1.2 – The multivariate dispersion analysis with the definition of the interaction between the criterions of "Anemia" and "High creatinine levels", which aimed to the changing the status of hemorrhagic patients with ACS.

of which is female gender and the presence of anemia. It was also demonstrated, that in ACS patients with hemorrhagic episodes experienced higher levels of creatinine.

CONCLUSIONS

1. Hemorrhagic complications in ACS patients were observed in 20.33% of cases. According to BARC stratification system, the structure of bleeding events in ACS patients was presented as follows: 41.67% belonged to the first type of bleeding, 41.67% and 16 66% - the second type and the third type accordingly.
2. There was confirmed that the frequency of bleeding higher among women (38.09%) than among men (10.52%). The belonging of ACS patients to female sex increases the likelihood of bleeding in 2.41 times (95% CI = 1.3-4.44).
3. On the limits of the statistical evidence (p = 0,052), there was determined the prevalence of the rate of bleeding complications in ACS patients with atrial fibrillation and triple therapy (60.00%) compared with patients on DATT (16.66%).
4. In the study was demonstrated that the increasing of the creatinine concentration was found in 50.00% of ACS patients with hemorrhagic syndrome and it was higher, than in the group of patients without bleeding (12.76%). It was calculated, that the hemorrhagic episodes will increase the serum creatinine level in 3.91 (95% CI = 1.53-10.00) in ACS patients.
5. The incidence of bleeding complications in patients with anemia (p = 0.011) was higher, than in patients without anemia (43.75% vs 11.62%) at the time of the ACS diagnosis. The availability of anemic syndrome increased the risk of bleeding at 3.04 times (95% CI = 1.42-6.49) in ACS patients.
6. It was proved that anemia (F = 5.31) itself, regardless of the level of creatinine as an indicator of renal failure, is predictive of bleeding in patients with ACS.

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Резюме

ПРЕДИКТОРЫ ГЕМОРРАГИЧЕСКИХ ОСЛОЖНЕНИЙ У ПАЦИЕНТОВ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ

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Частота геморрагических осложнений у больных с острым коронарным синдромом (ОКС) колеблется в пределах от 1% до 10%. Даже в случае отсутствия геморрагических событий в период терапии ОКС антикоагулянтами или тромболитиками, у 1,6% и 2,5% больных со стентированием коронарных артерий на фоне двойной антитромбоцитарной терапии (ДАТТ) в течение 12 и 18 месяцев соответственно возникают кровотечения.

Цель. Определить общеклинические и клинико-лабораторные предикторы возникновения геморрагических осложнений у больных, подлежащих терапии по причине ОКС.

Материали и методы. Проанализированы общеклинические показатели, результаты клинико-лабораторных исследований 59 пациентов, подлежащих терапии ОКС в Государственном научном учреждении «Научно-практический центр профилактической и клинической медицины» Государственного управления делами (2014–2016 гг).

Результаты. У больных с ОКС геморрагические осложнения наблюдаются в 20,33 % случаев. В структуре геморрагических осложнений BARC как первый, так и второй типы кровотечений представлены в 41,67 % эпизодов, а третий А тип – 16,66 % случаев. Подтверждено, что частота кровотечений при ОКС выше среди женщин (38,09 %), чем среди мужчин (10,52 %), а женский пол увеличивает вероятность возникновения кровотечений в 2,41 раза. Также доказано, что частота развития геморрагических осложнений у пациентов с анемией на момент установления им диагноза ОКС выше, чем у больных без неё, и составляет 43,75 % случаев. Риск возникновения кровотечений при условии наличия анемического синдрома у больных с ОКС возрастает в 3,04 раза. Подтверждено, что анемия самостоятельно (F = 5,311), независимо от уровня креатинина, как показателя почечной недостаточности, является предиктором развития кровотечений у пациентов с ОКС.

Ключевые слова: **острый коронарный синдром, геморрагические события, двойная антитромбоцитарная терапия.**

Summary

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Aim. The aim of our study is to determine clinical and laboratory parameters of patients with ACS, which would be most powerful predictors of hemorrhagic events.

Material and methods. Results of clinical and laboratory parameters of 59 patients with ACS, who were treated or consulted in the State scientific institution "Scientific-practical center of preventive and clinical medicine" of the State administration (2014-2016 y.), were analyzed.

Results. Hemorrhagic complications in ACS patients were observed in 20.33% of cases. In the BARC structure of hemorrhagic events, the first and second types of bleeding were presented 41.67% of cases,

and the second type - 16 66% of cases. There was confirmed that the frequency of bleeding higher among women (38.09%) than among men (10.52%). The belonging of ACS patients to female sex increases the likelihood of bleeding in 2.41 times. The incidence of bleeding complications in patients with anemia at the time of the ACS diagnosis was higher, than in patients without anemia and equal to 43.75%. The availability of anemic syndrome increased the risk of bleeding at 3.04 times in ACS patients. It was proved that anemia (F = 5.31) itself, regardless of the level of creatinine as an indicator of renal failure, is predictive of bleeding in patients with ACS.

Keywords: **acute coronary syndrome, hemorrhagic events, dual antiplatelet therapy.**

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