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Comorbidity and Gender of Patients at Risk of Hospital Mortality After Emergency Percutaneous Coronary Intervention

Aim	To study gender aspects of comorbidity in evaluating the risk of in-hospital death for patients with acute coronary syndrome (ACS) after a percutaneous coronary intervention (PCI).
Material and methods	The presented results are based on data of two ACS registries, the city of Sochi and RECORD-3. 986 patients were included into this analysis by two additional criteria, age <70 years and PCI. 80% of the sample were men. Analysis of comorbidity severity was performed for all patients and included 9 indexes: type 2 diabetes mellitus, chronic kidney disease, atrial fibrillation, anemia, stroke, arterial hypertension, obesity, and peripheral atherosclerosis. Group 1 (minimum comorbidity) consisted of patients with not more than one disease (n=367); group 2 (moderate comorbidity) consisted of patients with 2 or 3 diseases (n=499), and group 3 (pronounced comorbidity) consisted of patients with 4 or more diseases (n=120). In-hospital mortality was 2.7% (n=27).
Results	Significant data on the effect of comorbidity on the in-hospital prognosis were obtained only for men of the compared groups: 0.6, 1.8, and 8.8%, respectively (χ^2=21.6; p<0.0001). At the same time, among 44 women with minimum comorbidity, there were no cases of in-hospital death, and the presence of moderate (n=110) and pronounced comorbidity (n=40) was associated with a similar death rate (7.3 and 7.5%, respectively). Noteworthy, in moderate comorbidity, the female gender was associated with a 4-fold increase in the risk of in-hospital death (odd ratio, OR 4.3 at 95% confidence interval, CI from 1.5 to 12.1; p=0.003). In addition, both in men and women with minimum comorbidity, even a high risk by the GRACE scale (score ≥140) was not associated with increased in-hospital mortality, which was minimal (0 for women and 1% for men). At the same time, in the patient subgroup with moderate and pronounced comorbidity, a GRACE score ≥140 resulted in a 6-fold increase in the risk of in-hospital death for men (OR 6.0 at 95% CI from 1.7 to 21.9; p=0.002) and a 16-fold increase for women (OR 16.2 at 95% CI from 2.0 to 130.4; p=0.0006).
Conclusion	This study identified gender-related features in predicting the risk of in-hospital death for ACS patients with comorbidities after PCI, which warrants reconsideration of existing approaches to risk stratification.

Keywords	Acute coronary syndrome; percutaneous coronary intervention; comorbidity; gender, in-hospital prognosis
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According to the Federal State Statistics Service, coronary artery disease (CAD) caused one in four deaths as of 2019, a reduction in CAD mortality by about 1% compared to 2018 [1]. Patients who have survived acute coronary syndrome (ACS) are significantly affected. ACS is a leading cause of death in most countries, making it of high medical and social significance [2].

High mortality in ACS results from the inability to use all modern treatment methods for such patients in clinical practice and the absence of an effective complication risk assessment model. The search for new risk stratification methods in patients presenting with ACS will optimize treatment and diagnostic interventions and improve the long-term prognosis. due to cost-efficient and rational use of resources [3].

Recent studies have shown that co-morbidity [4–8] and female sex [9–11] are associated with an unfavorable ACS hospital prognosis. At the same time, there is no comprehensive approach to studying these risk factors, an especially important issue in patients who have undergone percutaneous coronary intervention (PCI).

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Aim

The objective was to study the sex-specific aspects of co-morbidity in assessing the risk of in-hospital death in patients with ACS subjected to PCI.

Material and methods

The presented results are based on data from two ACS registers: the Sochi register and RECORD-3. The Sochi register included 2,305 patients from 2016 to 2017, and the national Russian RECORD – 3 register included 1,835 patients in the period of March – April 2015. The inclusion of patients in the Sochi register within 2 years was continuous. It took place on the day of discharge (death) only if the diagnosis of myocardial infarction (MI) or unstable angina was confirmed according to the criteria described in the relevant guidelines [2, 12]. The RECORD-3 register study design was described earlier [13]. All patients signed an informed consent approved by the hospital's ethics committee.

This analysis included 986 patients (513 from the Sochi register and 473 from RECORD-3) who met two additional criteria: age under 70 years and a history of PCI during the hospital stay. Male patients made up 80% of the sample. The incidence of ACS with ST-segment elevation and MI was 67.2% and 81.2%, respectively. Despite the exclusion of patients older than 70 years from the sample, the mean age of male versus female patients was almost 5 years less: 57.1 (95% confidence interval [CI] 56.5–57.6) versus 61.8 (95% CI 60.9–62.7); p=0.055. All patients were analyzed for co-morbidity severity for the nine most common diseases: type 2 diabetes mellitus (DM), chronic kidney disease (CKD), atrial fibrillation (AF), anemia, history of stroke, hypertension, obesity, peripheral atherosclerosis, and thrombocytopenia. The nosology data allows taking into account both cardiovascular and non-cardiovascular aspects of co-morbidity. All of the above are included in the patented K9 co-morbidity model (receipt acknowledged). The choice of co-morbidity components is not accidental but is based on high prevalence and reproducibility in many register studies. Group 1 (minimal co-morbidity) included patients with not more than one disease (n=367); Group 2 (moderate co-morbidity) those two or three diseases (n=499); and Group 3 (severe co-morbidity) patients with four or more diseases (n=120). In-hospital mortality was 2.7% (n=27). The GRACE ASC Risk Model score was applied for each patient to assess the in-hospital mortality.

Statistical processing of the research data was performed using SPSS Statistics version 22.0.0.0 (IBM Corp., USA). Quantitative data are presented as the mean value and 95% confidence interval. Categorical data are expressed as the absolute and relative (percentage) rates. To identify relationships between quantitative indicators, we performed both univariate analysis with the calculation of Spearman's rank correlation coefficient (r) and multivariate analysis using the Cox regression and subsequent construction of ROC curves. The rate differences in the different groups were analyzed using Pearson's χ^2 test. The odds ratio (OR) and 95% CI were calculated to quantify the probability of a fatal outcome in the presence of a risk factor in comparison with its absence. The differences between the comparison groups were statistically significant at $p<0.05$.

Results

The mean risk of in-hospital death (GRACE score) is slightly higher in female patients than in male patients: 135.4 (95% CI 131.2 to 139.6) versus 130.5 (95% CI 128.3 to 132.6); p=0.055. Mortality in male and female patients was 2.0% and 5.7%, respectively (χ^2=7.8, p=0.005). Table 1 shows the rates of the main co-morbidity components calculated using the proprietary 9-point scale in 792 male and 194 female patients with ACS who underwent PCI. Female subjects were significantly more likely to have co-morbidity components such as DM, hypertension, obesity, anemia, and CKD than males. However, there is a tendency to more frequent detection of thrombocytopenia in males.

Female sex was associated with a two-fold increase in the severe co-morbidity risk (20.6% vs 10.1%, p=0.001); male sex with minimal comorbidity (40.8% vs. 22.7%, p=0.0001). Most female and male patients had moderate co-morbidity: 56.7% and 49.1%, respectively. The mean age of female

Table 1. Main components of comorbidity according to the nine-point score in male and female patients with ACS subjected to CCV

Component	Male, n=792	Female, n=194	χ^2 p
Diabetes mellitus	114 (14.4)	54 (27.8)	19.9; 0.00001
Atrial fibrillation	49 (6.2)	13 (6.7)	0.07; 0.79
History of stroke	32 (4.0)	7 (3.6)	0.08; 0.78
Hypertension	598 (75.5)	170 (87.6)	13.3; 0.0003
Obesity	206 (26.0)	79 (40.7)	16.4; 0.00005
Peripheral atherosclerosis	87 (11.0)	29 (15.0)	2.4; |0.12
Anemia	105 (13.3)	47 (24.2)	14.4; 0.0002
Thrombocytopenia	158 (20.0)	27 (13.9)	3.7; 0.054
CKD	181 (22.9)	71 (36.6)	15.5; 0.00008

Data are presented as the absolute number of patients (%).
CCV, coefficient of component variance; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CKD, chronic kidney disease with glomerular filtration rate (CKD-EPI) <60 mL/min/1.73 m^2.

Table 2. Mean age and mean risk (GRACE) in different comorbidity subgroups in male and female patients

Parameter	Male, n=792			Female, n=194		
Groups	Group 1 (n=323)	Group 2 (n=389)	Group 3 (n=80)	Group 1 (n=44)	Group 2 (n=110)	Group 3 (n=40)
Age, years	55.4 (54.4–57.9)*	57.9 (57.1–58.6)**	59.9 (58.4–61.5)#	60.1 (57.9–62.4)*	61.5 (60.2–62.8)**	64.6 (63.5–65.7)#
GRACE risk, score	127.7 (124.5–130.9)	131.0 (128.0–134.0)	139.1 (130.8–147.5)	129.2 (120.3–138.0)	134.9 (129.1–140.7)	143.7 (135.4–151.9)

The data are expressed as the mean and 95% CI. #, p=0.0002; *, p=0.0006; **, p=0.000001. CI, confidence interval.

patients was 5 years greater than that of males (p<0.001) in each co-morbidity subgroup. The GRACE score did not show significant inter-sex differences in CV risk (Table 2).

As shown in Table 3, in most subgroups (formed depending on the presence or absence of each of the nine diseases mentioned above), female sex was associated with increased hospital mortality. Particular attention should be paid to the fact that the low risk (GRACE score) was equally rarely associated with death in either male and female subjects. However, the risk of death for female patients increased three-fold compared to that of males (OR 3.4, 95% CI 1.4–8.2; p=0.009) with a higher (≥140 points) GRACE score. It is also noteworthy that among 87 male patients with peripheral atherosclerosis, a relatively high mortality rate was recorded (5.8%), three times higher than in males without peripheral atherosclerosis (OR 3.8, 95% CI 1.3–11.2; p=0.009). There were no deaths among the 30 female patients with peripheral atherosclerosis.

With an increase in co-morbidity severity (minimal to severe), in-hospital mortality significantly increases: 0.5 (54.8%) and 41 (8.3%), respectively (χ^2=20.9; p=0.0001). However, reliable data on the effect of co-morbidity on the prognosis were obtained only for males: 0.6%, 1.8%, and 8.8%, respectively (χ^2 =21.6; p<0.0001), whereas there were no cases of in-hospital mortality in 44 female subjects with minimal co-morbidity. Moderate (n=110) and severe co-morbidity (n=40) was associated with a high mortality rate, 7.3% and 7.5%, respectively (Figure 1). It should be noted that the risk of in-hospital death in female patients with moderate co-morbidity is four times higher than that in males with moderate co-morbidity (OR 4.3, 95% CI 1.5–12.1; p=0.003).

We found that even non-cardiovascular co-morbidity negatively affected hospital prognosis. For example, two or more diseases (DM, thrombocytopenia, anemia, obesity, CKD) increased in-hospital mortality from 1.7% to 5.2% (OR 3.1, 95% CI 1.5–6.7; p=0.002). This relationship was equal for both male and female patients.

It was found (Figure 2) that, in both male (n=323) and female patients (n=44) with minimal co-morbidity, even a high risk (GRACE ≥140) was not associated with increased in-hospital mortality, which remained minimal (0% in female, 1% in male subjects). In the subgroup of patients with moderate and severe co-morbidity, a GRACE score of ≥140 led to a six-fold increase in the risk of in-hospital death in male patients (OR 6.0, 95% CI 1.7–21.9; p=0.002) – a 16-fold increase in female patients (OR 16.2, 95% CI 2.0–130.4; p=0.0006). It should also be noted that among 40 female patients with severe co-morbidity, 22 (55%) had a low GRACE score (<140 points), which was associated with no mortality. In contrast, the 80 male patients in this category showed high mortality rates (4.3%). Sex differences in the GRACE score's predictive value were significant in moderate co-morbidity (Figure 2).

Cox's regression survival analysis was performed as the final stage of this study (Table 4).

Table 3. In-hospital mortality (n (%)) in male and female patients according to the groups formed depending of the presence or absence of diseases included in the comorbidity assessment

Component		Male, n=792	Female, n=194	p
Diabetes mellitus	No	10 (1.5)	7 (5.0)	0.008
	Yes	6 (5.3)	4 (7.4)	0.58
Atrial fibrillation	No	11 (1.5)	8 (4.4)	0.01
	Yes	5 (10.2)	3 (23.1)	0.22
History of stroke	No	12 (1.6)	10 (5.4)	0.002
	Yes	4 (12.5)	1 (14.3)	0.89
Hypertension	No	1 (0.5)	0	0.72
	Yes	15 (2.5)	11 (6.5)	0.01
Obesity	No	13 (2.2)	9 (7.8)	0.002
	Yes	3 (1.5)	2 (2.5)	0.54
Peripheral atherosclerosis	No	11 (1.6)	11 (6.7)	0.0002
	Yes	5 (5.8)	0	0.19
Anemia	No	11 (1.6)	5 (3.4)	0.15
	Yes	5 (4.8)	6 (12.8)	0.08
Thrombocytopenia	No	12 (1.9)	11 (6.6)	0.001
	Yes	4 (2.5)	0	0.40
CKD with GFR (CKD-EPI) <60 mL/min/1.73 m^2	No	11 (1.8)	3 (2.4)	0.63
	Yes	5 (2.8)	8 (11.3)	0.006
Risk of in-hospital death (GRACE ≥140)	No	4 (0.8)	1 (0.8)	0.94
	Yes	12 (4.3)	10 (13.2)	0.009

Data are presented as the absolute number of patients (%). CKD, chronic kidney disease.

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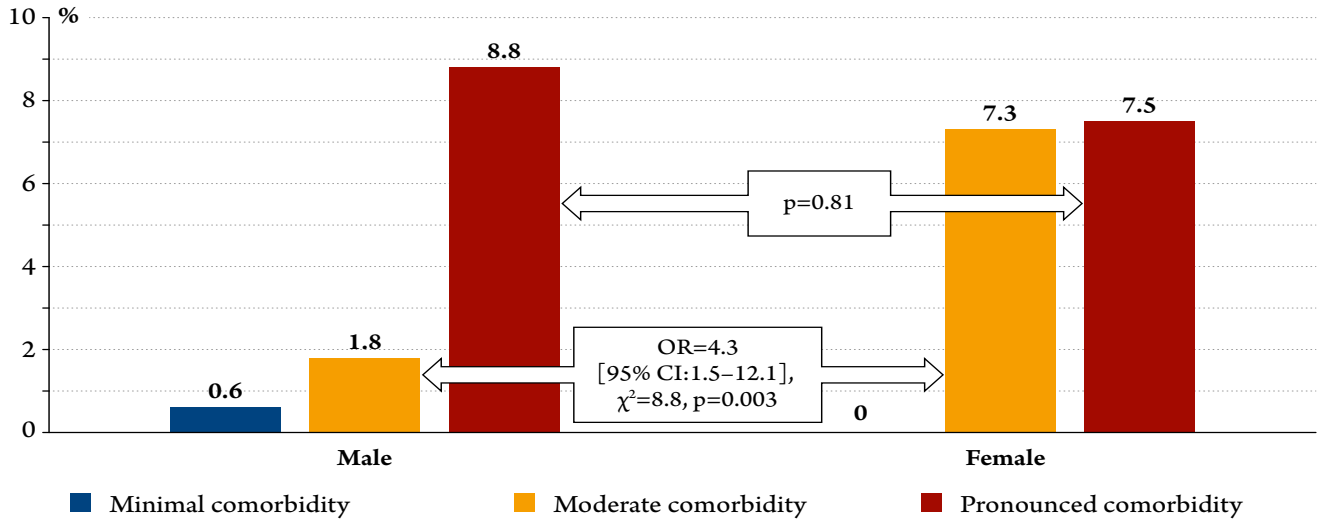
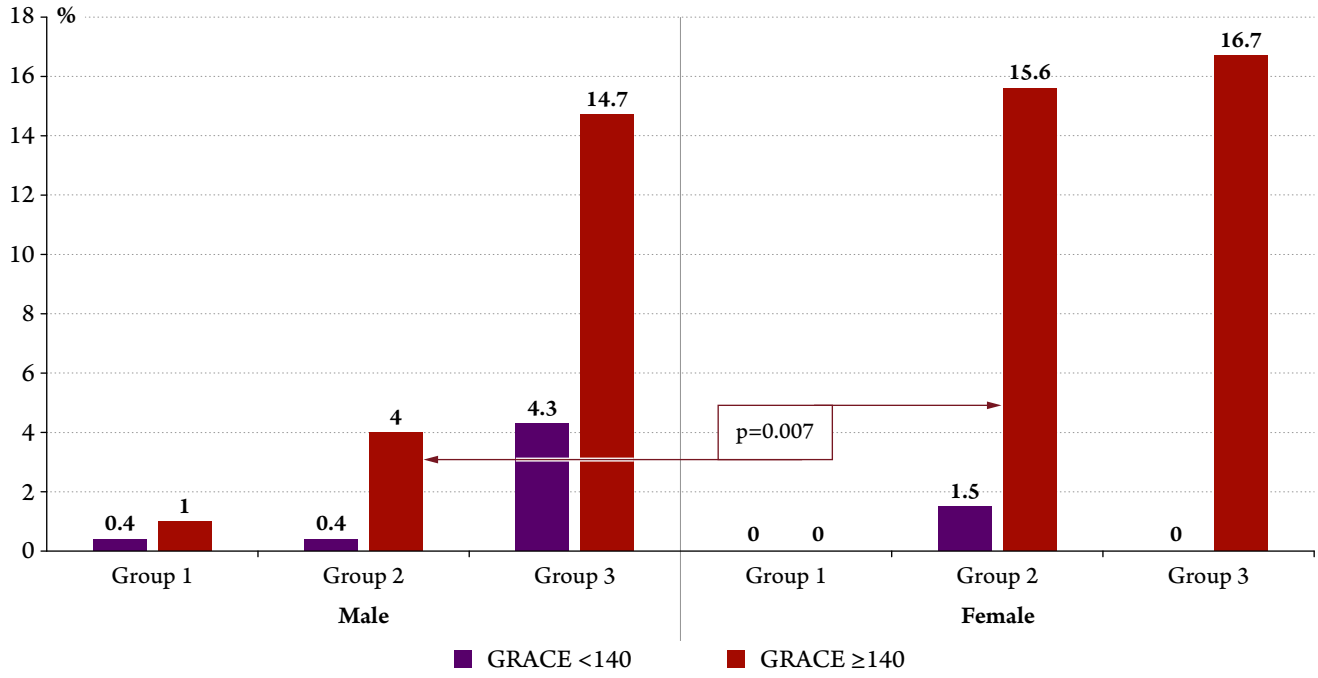
Figure 1. In-hospital mortality (%) in male and female patients with ACS who have undergone PCI according to severity of the underlying co-morbidity



OR, odds ratio; CI, confidence interval.

Figure 2. In-hospital mortality (%) based on sex, GRACE risk, and underlying comorbidity in patients with ACS who have undergone PCI



Group 1, patients with minimal co-morbidity (not more than one disease);
Group 2, patients with moderate co-morbidity (2–3 diseases); Group 3, patients with severe co-morbidity (4 or more diseases).

Figure 3 shows ROC curves obtained by Cox regression survival analysis, GRACE score, and the risk model adjusted for co-morbidity and sex (GRACE+K9+sex). The modified GRACE model had a larger area under the ROC curve, with 95% CI: 0.82 (0.73–0.91), versus 0.77 (0.67–0.77).

These study findings provide reliable evidence of the significance of the sex-based approach in assessing co-morbidity in patients with ACS subjected to PCI.

Discussion

In this study, female subjects with ACS were older and more likely to have a co-morbidity, which corresponded to other studies [11, 14, 15]. However, most data indicate no sex differences in co-morbidity prevalence in patients with stable CAD [16]. Comparing the prevalence of particular diseases found that female patients were significantly more likely to have DM, hypertension,

Table 4. The results of Cox's regression survival analysis

Parameter	B	SE	Wald	p	Risk ratio with 95% confidence interval
GRACE risk, score	0.033	0.004	61.886	0.0001	1.03 (1.03–1.04)
Comorbidity	0.362	0.122	8.807	0.003	1.44 (1.13–1.82)
Sex (0 – male, 1 – female)	0.888	0.405	4.807	0.028	2.43 (1.1–5.38)

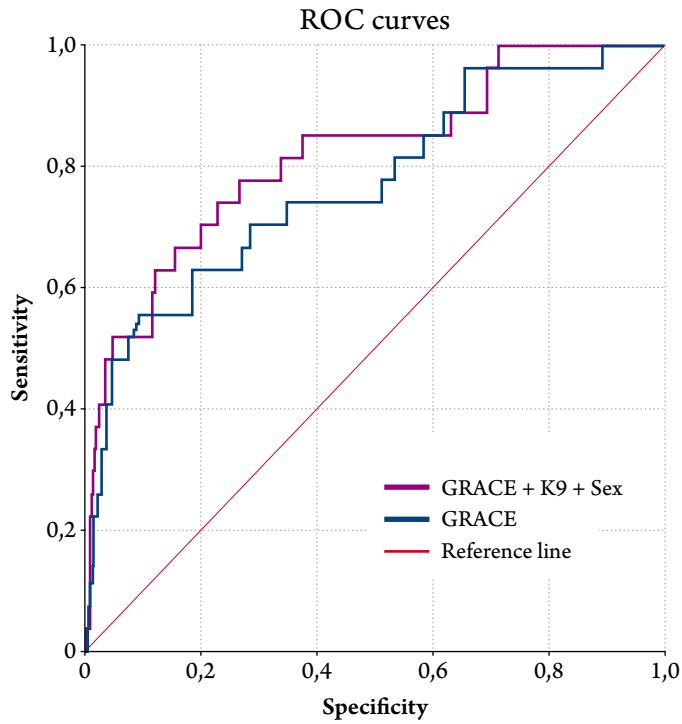
B, Cox's regression coefficients; SE, standard error for Cox's regression coefficient;
Wald coefficient tests a zero hypothesis that the relative risk of death associated with this variable is equal to 1.

obesity, anemia, and CKD than were males. In the VIRGO study, female subjects with ACS more often had dyslipidemia, hypertension, DM, chronic obstructive pulmonary disease (COPD), CKD, thyroid disease, history of stroke/transient ischemic attack. By contrast, male subjects more often had a history of MI, PCI, or coronary artery bypass grafting [17]. Similar results were obtained in another major study [11]. According to Worrall-Carter et al. (2016), females with ACS were more likely to have hypertension, arrhythmia, and congestive heart failure (CHF), and males more often had peripheral atherosclerosis [18]. In the Russian population, female patients with ST-segment elevation MI (STEMI) were more likely to have hypertension, a history of angina, CHF, DM, hypercholesterolemia, and AF. Male patients more often had a history of myocardial revascularization and smoking [15].

It can be concluded, then, that female patients have a wider range of co-morbidities that can often initiate and lead to a faster progression and an unfavorable course of atherosclerosis. Males are more likely to have atherosclerosis sequelae, such as a history of cardiovascular disease or myocardial revascularization. The differences between the data of the above studies and our findings were most likely due to the sampling peculiarities of evaluating co-morbidity components and are not fundamental.

Our study also revealed a direct relationship between co-morbidity severity and in-hospital mortality. Many studies have shown an adverse effect of co-morbidity on the hospital prognosis in patients with ACS [4, 5, 7]. For patients who have undergone PCI, the contribution of individual co-morbidity components (DM, renal dysfunction, systolic myocardial dysfunction) is proven [13, 19, 20]. A comprehensive assessment of co-morbidity and its prognostic role in patients subjected to emergency PCI has been studied much less frequently. Singh et al. (2008) assessed co-morbidity using the Mayo Clinic Risk Score (MCRS – age, emergency/urgent PCI, New York Heart Association [NYHA [functional class III–IV CHF, multivessel coronary disease, thrombosis in any segment, moderate/severe renal dysfunction, shock before PCI, ≥70% stenosis of the left coronary artery [LCA]) and the

Figure 3. ROC curves obtained using Cox's survival regression analysis, GRACE score, and the risk model adjusted for co-morbidity and sex (GRACE+K9+sex)



coronary artery disease – specific index (CAD index) – smoking, hypertension, history of stroke/transient ischemic attack, DM, DM with complications, COPD, peripheral atherosclerosis, tumor/lymphoma/leukemia, metastatic disease, moderate/severe renal dysfunction. [21] The in-hospital C-statistic of the MCRS score for cardiovascular complications was 0.78. Adding the CAD score parameters to the MCRS score did not increase the potency of the latter [21]. Thus, the authors of this study showed the in-hospital prognostic significance only of cardiovascular diseases and the course of the index event. In our study, non-cardiovascular co-morbidity was also taken into account. In J. Potts et al. (2018) the data of 6601526 CHQ [22] were analyzed. The Charlson index was used to assess co-morbidity. After equalizing the groups for several parameters, an increase in co-morbidity was independently associated with in-hospital mortality, other complications, and the duration and cost

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of the hospital stay. The risk of death in patients with a Charlson score of 1 increased 1.19 times, 2–1.5 times, 3 – ≥2 times or more [22].

Our study demonstrated higher in-hospital mortality in female patients. There is currently conflicting evidence about the independent predictive significance of sex. Some researchers have attributed worse prognosis in female subjects with ACS to older age, co-morbidity, and treatment differences [14, 18, 23]. To the contrary, other researchers identified an independent predictive role for female sex [24], citing data indicating that female sex has an independent negative influence on the prognosis depending on age. For example, a study by Khera et al. (2015) that included 632,930 patients with STEMI younger than 60 years, showed that female patients had a worse hospital prognosis than male patients, regardless of myocardial revascularization [9]. Cenko et al. (2018) identified that female subjects with STEMI younger than 60 years old had a higher short-term (30-day) risk of death than did male subjects. No such data were obtained for other age categories [25]. There were also conflicting data on the independent prognostic role of sex in patients subjected to PCI. In a large study by Potts et al. (2018), female sex was an independent predictor of in-hospital death after PCI [11]. The same findings were produced in a large meta-analysis performed in 2018 [26]. However, some studies have not shown an independent association between female sex and in-hospital mortality after emergency PCI [27–29].

We have not found any studies focused on a comprehensive assessment of the role of sex-dependent co-morbidity in the development of early complications after PCI. This study's main objective was not to compare in-hospital mortality in male and female patients but to study the sex-related influence of the co-morbidity on the ACS course after PCI to assess the possibility of applying the data obtained in real-world practice. At the same time, we excluded patients over 70 years old to reduce the likelihood of age-related influence on the choice of management and extent of treatment during the hospital stay. Regardless of co-morbidity subgroup (minimal, moderate, or severe), female patients' mean age was higher than that of males by 5 years. At the same time, in-hospital mortality in the minimal co-morbidity subgroup was extremely low in 323 (0.6%) male patients, and in the female subgroup (n=44), there were no deaths. In the severe co-morbidity subgroup, mortality rates were equally high in male and female patients (8.8% and 7.5%, respectively). Thus, even though a nearly 5-year difference in mean age was recorded between male and female subjects in all co-morbidity subgroups (presence of two to three diseases), female sex was associated with a four-fold increase in the risk of death only in moderate comorbidity.

The final point of the study was an attempt to improve the predictive significance of the GRACE score by adding co-morbidity and sex components. This idea is based on the negative predictive role of female sex and co-morbidity and their mutually potentiating effect. Our findings showed that 44 female patients with minimal co-morbidity were at high risk according to the GRACE score (≥140 points) in 30% of cases, and there were no in-hospital deaths. By contrast, the presence of even moderate co-morbidity worsened multiple fold the hospital prognosis. Similar modifications of the GRACE score were not found in the literature. However, a study assessed the addition of a sex component to the GRACE score, which did not significantly increase the predictive potency of this model in patients with STEMI [30].

Another study concluded that the GRACE score did not require integration of the sex component since there was no significant interaction between the GRACE score components and sex [31]. These differences may be due to patient samples: the significance of this GRACE score modification was evaluated only in patients with STEMI in the above studies. Conflicting evidence was found for the joint assessment of the GRACE score and co-morbidity. For example, in one study, adding the Charlson co-morbidity index to the GRACE score resulted in a significant improvement in the latter's prognostic significance (observation after 6 months) [32]. According to another study, adding the Charlson co-morbidity index to the GRACE score did not significantly increase the long-term predictive significance of the latter [33]. This study showed the feasibility of modifying the GRACE score to assess in-hospital death risk in patients with ACS after PCI.

Conclusion

In this study, sex-specific differences were identified in predicting the risk of in-hospital death in co-morbid patients with acute coronary syndrome who underwent percutaneous coronary intervention, demonstrating a need to review existing risk stratification approaches.

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No conflict of interest is reported.

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