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GENDER DIFFERENCES IN THE INFLUENCE OF COMORBID CONDITIONS ON THE LONG-TERM OUTCOMES OF PATIENTS WITH ACUTE CORONARY SYNDROME

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Background. *Gender differences in the baseline characteristics of patients with the acute coronary syndrome (ACS) have been widely acknowledged. Women are known to be generally older with a higher prevalence of comorbidities.*

Objectives. *Gender differences in the baseline characteristics of patients with the acute coronary syndrome (ACS) have been widely acknowledged. Women are known to be generally older with a higher prevalence of comorbidities. At the same time, it is now yet clear which comorbid conditions have the most significant impact on the long-term outcomes of patients with ACS and if there are any gender differences in this respect.*

Methods. *We performed a retrospective cohort study of 167 patients (109 men and 58 women) admitted to the acute coronary unit of Ternopil Municipal Hospital with ACS in 2016-2017. All relevant clinical information has been recorded in the pre-designed data charts. The incidence of repeated major adverse cardiovascular events (MACEs) has been assessed over 36 months after the hospital discharge via an e-Health electronic system.*

Results. *In this cohort, female patients with ACS had a higher prevalence of comorbid conditions: 15.5% of women vs. 11% of men with ACS had ≥5 comorbidities, 65.5% of women and 60% of men had 2-4 comorbid conditions, and 19% of women vs. 29% ≤1 concomitant disease. The comorbidity structure also differed between genders. Women more often had concomitant cerebrovascular diseases (17.2% vs. 7.3%, p=0.05), dementia (15.5% vs. 5.5 %, p=0.03), connective tissue disorders (17.25 vs. 6.42%, p=0.03) and thyroid disease (12.1% vs. 2.8%, p=0.02). Men more often suffered from peptic ulcer (13.7% vs. 3.4%, p=0.05). The incidence of MACEs during the follow-up period rose sharply with age and was higher in females (55% vs. 33%, p=0.003). In the multivariable model, PAD (OR 9.5, 95% CI: 1.7-52.3, p=0.01) and thyroid disease (OR 7.2, 95% CI: 1.19-43.2, p=0.03) demonstrated the most significant impact on the long-term event-free survival of females in the cohort. In turn, a solid metastatic tumor was the most significant predictor of poor prognosis in men (OR 6.3, 95% CI: 2.13-18.9, p=0.001).*

Conclusions. *We observed significant gender differences in the prevalence of comorbid conditions and their influence on the three-year event-free survival of patients with ACS. The predictive value of comorbidities should be further investigated, preferably, with the involvement of larger cohorts.*

KEYWORDS: acute coronary syndrome; gender; outcomes.

Introduction

Cardiovascular disease (CVD) remains the number one cause of death of males and females all around the world with coronary heart disease (CHD) representing the major proportion [1]. The common misconception about CHD being predominantly "male" disease has been confronted few decades ago, and gender differences in clinical presentation and treatment strategies have been widely acknowledged. Significant body of evidence suggests that females presenting with acute coronary syndrome (ACS) are usually older and more often have concomitant arterial hypertension (AH) and diabetes mellitus (DM) [7]. It is also known that female patients with ACS have generally worse short-term and long-term outcomes as compared with males [3-6]. Studies indicate that such disparities may be attributed to older age and higher prevalence of comorbidities in female patients [5, 6]. Nevertheless, it is still not well-established which comorbid conditions have the most significant impact on the long-term outcomes of men and women with ACS.

In this study, we analyzed existing gender differences in the prevalence of comorbid conditions in patients with ACS. We also aimed at identifying which comorbidities had the most significant impact on the long-term prognosis of men and women with ACS.

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Methods

We performed a retrospective cohort study of 167 patients admitted to the acute coronary unit of Ternopil Municipal Hospital with ACS in 2016-2017. Study sample was divided into two gender groups (109 males and 58 females). Relevant clinical data has been extracted from medical records and indicated in pre-designed data charts. Comorbidity structure in the following cohort has been assessed drawing on Charlson Comorbidity Index. The 3-year follow-up of the patients has been conducted through e-Health system and in rare cases patients have been contacted by phone. The incidence of repeated major adverse cardiovascular events (MACEs) throughout 36 months after hospitalization has been assessed which included all-cause death, acute myocardial infarction and unstable angina.

ACS included ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). Comorbid conditions of patients were mentioned in their medical records or diagnosed during their hospital stay according to the guideline-based diagnostic criteria. Such comorbidities from Charlson Comorbidity Index were analyzed in the study: prior acute myocardial infarction (prior AMI), congestive heart failure (HF), AH, peripheral artery disease (PAD), chronic kidney disease (CKD), liver disease, chronic obstructive pulmonary disease (COPD), leukemia, hemiplegia, metastatic solid tumor, AIDS, lymphoma, connective tissue disorders, cerebrovascular disease, dementia, DM, peptic ulcer. Additionally, we analyzed the prevalence of thyroid disease and anemia in selected patients.

All statistical information has been processed using IBM SPSS Statistics 22.0 software. Continuous variables were expressed as mean± standard deviation (SD). Numbers and percentages were used for categorical data. Differences between groups were analyzed using Student's *t*-test for continuous data and Pearson's Chi-square test for categorical variables. A p-value of <0.1 was considered significant. The evaluation of prognostic impact of particular comorbidities was performed in multivariable analysis adjusting to various confounders, such as age, cardiogenic shock, elevated cardiac troponin levels. The predictors of MACE were presented as adjusted odds ratios (OR). The analysis was performed separately for two gender groups.

Results

Women in the following cohort were in general 10 years older than men (69.5±21.5 vs. 59.5±28.5, p<0.001). Female patients with ACS more often experienced nausea, vomiting, palpitations and fatigue instead of typical chest pain. They were also more likely to be hospitalized more than 12 hours after the symptom onset (64% vs. 41%, p=0.006). Men were more often smokers while women were more often obese. Female patients with ACS more often than male had preserved ejection fraction (55.0% vs. 38.0%, p=0.04), but at the same time, they more often developed cardiogenic shock (12.0% vs. 3.7%, p=0.04). STEMI was more often diagnosed in male patients (55% vs. 36%, p=0.02), while NSTEMI and UA more often occurred in females (64% vs. 45%, p=0.02).

We observed significant gender differences in clinical profiles of patients in the following cohort. In general, female patients with ACS had higher prevalence of comorbid conditions: 15.5% of women vs. 11% of men with ACS had ≥5 comorbidities, 65.5% of women and 60% of men had 2-4 comorbid conditions and 19% of women vs. 29% ≤1 concomitant disease (Table 1).

In the following cohort of patients with ACS, women more often had concomitant cerebrovascular diseases (17.2% vs. 7.3%, p=0.05), dementia (15.5% vs. 5.5 %, p=0.03) and connective tissue disorders (17.25 vs. 6.42%, p=0.03). Thyroid disease was also more often diagnosed in female patients (12.1% vs. 2.8%, p=0.02). Men more often suffered from peptic ulcer (13.7% vs. 3.4%, p=0.05). We did not observe statistically significant gender differences in the prevalence of arterial hypertension (AH), peripheral artery disease (PAD), prior myocardial infarction (prior AMI), chronic kidney disease (CKD), liver disease and COPD in the selected cohort. Diabetes mellitus was more often found in female pa-

Table 1. Gender differences in the prevalence of comorbid conditions

Number of comorbidities	1 group (men)	2 group (women)
≤1	32 (29%)	11 (19%)
2-4	66 (60%)	38 (65.5%)
≥5	12 (11%)	9 (15.5%)

tients (34.5% vs. 25%), but the difference was not considered significant (p=0.1). Gender differences in the comorbidity structure are demonstrated in the table 2.

The incidence of MACEs during the follow-up period was significantly higher in females than in males (55% vs. 33%, p=0.003). The probability of adverse outcomes rose sharply with age. Among female patients with ACS aged 65 and older, the cumulative MACEs rate was significantly higher than in younger women (66% vs. 30%). Similarly, 27% of men younger than 65 years old experienced recurrent MACEs within the following 3 years after hospital discharge and 44% of men, aged 65 and older. Kaplan-Meier analysis identified significant gender differences in the 3-year event-free survival of patients older than 65 years old and no sex differences in the prognosis of younger patients (Figure 1, 2).

Table 2. Gender differences in the comorbidity structure

Comorbid condition	1 group (men) n=109	2 group (women) n=58	p-value
Prior Acute Myocardial Infarction	n=32 (29%)	n=18 (31%)	p=0.8
Congestive heart failure	n=16 (15%)	n=10 (17%)	p=0.5
Peripheral artery disease	n=11 (10%)	n=5 (9%)	p=0.9
Dementia	n=6 (5.5%)	n=9 (15.5%)	p=0.03
Diabetes Mellitus	n=27 (25%)	n=20 (34.5%)	p=0.1
Cerebrovascular disease	n=8 (7%)	n=10 (17%)	p=0.05
COPD	n=6 (5.5%)	n=3 (5%)	p=0.9
Connective tissue disorders	n=7 (6%)	n=10 (17%)	p=0.03
Peptic ulcer	n=15 (14%)	n=2 (3%)	p=0.05
Chronic kidney disease	n=17 (16%)	n=8 (14%)	p=0.7
Hemiplegia	n=0 (0%)	n=0 (0%)	–
Leukemia	n=1 (1%)	n=0 (0%)	–
Lymphoma	n=0 (0%)	n=0 (0%)	–
Metastatic solid tumor	6 (5.5%)	n=1 (2%)	p=0.2
Liver disease	n=26 (24%)	n=14 (24%)	p=0.9
AIDS	n=0 (0%)	n=0 (0%)	–
Arterial hypertension	n=89 (82%)	n=53 (91%)	p=0.1
Other comorbidities			
Thyroid disease	n=3 (3%)	n=7 (12%)	p=0.02
Anemia	n=13 (12%)	n=7 (12%)	p=0.2

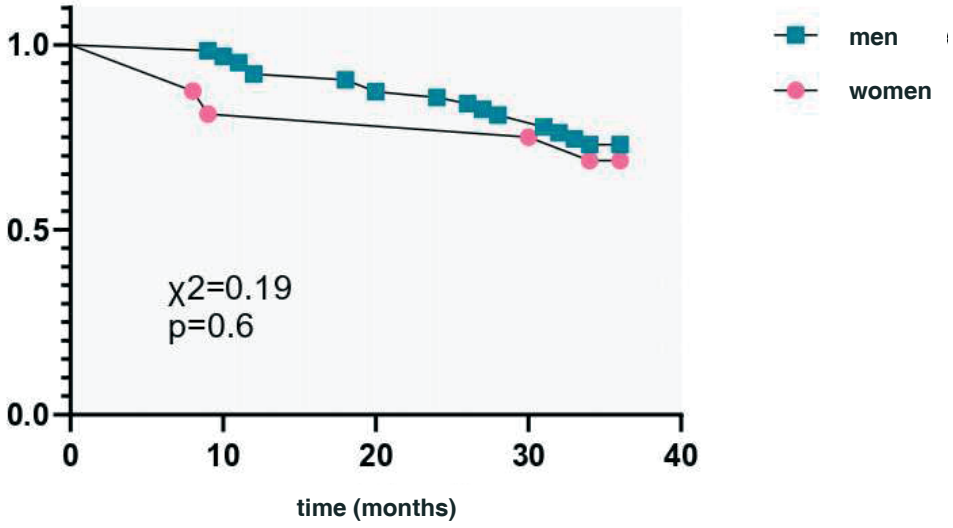

Fig. 1. Event-free survival (36 months) of patients older than 65 years.

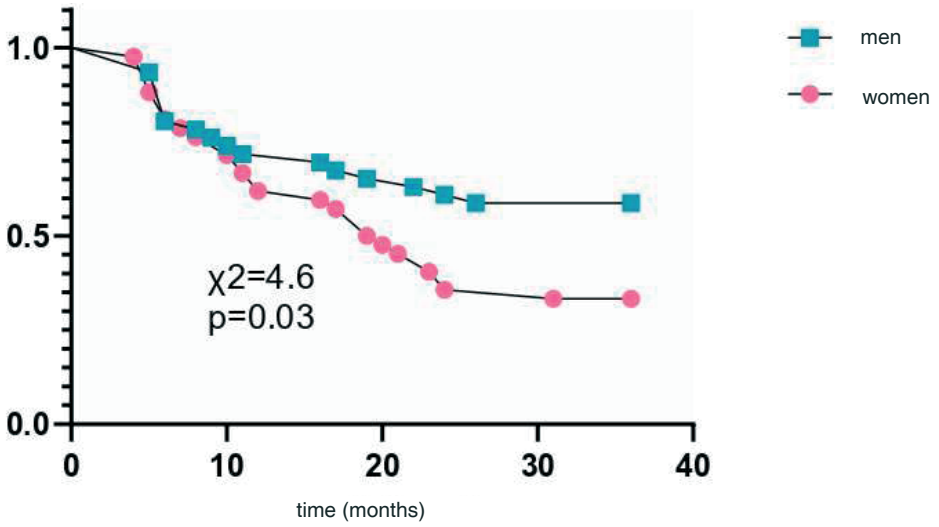

Fig. 2. Event-free survival (36 months) of patients younger than 65 years.

Multivariable analysis identified 7 comorbid conditions that most significantly influenced the prognosis in men (Table 3). According to obtained results, the greatest negative impact on the event-free survival of male patients in this cohort had metastatic solid tumor (OR 6.3, 95% CI: 2.13-18.9, p=0.001). Cerebrovascular disease, peptic ulcer, dementia and CKD were associated with more than twice higher chances of MACEs in the future while PAD and prior MI- with 1.5 times higher probability of MACEs.

In the multivariable model, PAD (OR 9.5, 95% CI: 1.7-52.3, p=0.01) and thyroid disease (OR 7.2, 95% CI: 1.19-43.2, p=0.03) demonstrated the most significant impact on the long-term event-free survival of females in this cohort. Congestive HF (OR 2.92, 95% CI: 0.6-14.2, p=0.06), prior MI (OR 1.86, 95% CI: 0.6-5.7, p=0.075) and AH (OR 2.3, 95% CI: 0.4-12.0, p=0.06) also negatively affected the prognosis of women with ACS. Higher incidence of recurrent MACEs was found in females with ACS and gynecological diseases, such as endometriosis, polycystic ovary syndrome, dyshormonal states of the reproductive system, uterine extirpation, etc. (OR 5.4, 95% CI: 0.9-10.3, p=0.04), (Table 4).

Discussion

This article provides an additional insight into gender-related differences in the prevalence of comorbidity in patients with ACS as well as the prognostic impact of comorbid conditions

Table 3. Multivariable analysis of the prognostic impact of comorbid conditions in men with ACS

Variables				95% CI	
	SE	p-value	OR	Lower	Upper
Age	0.017	0.510	1.011	0.979	1.045
Elevated cardiac troponin levels*	0.380	0.849	1.075	0.511	2.264
Ectopic rhythm	0.493	0.563	0.752	0.286	1.975
Cardiogenic shock	0.045	0.501	1.054	0.453	1.843
Prior MI	0.424	0.090	1.403	0.612	3.219
Congestive HF	0.577	0.740	0.826	0.267	2.558
PAD	0.580	0.084	1.901	0.610	5.925
Dementia	0.948	0.096	2.591	0.404	16.606
DM	0.550	0.077	0.781	0.129	1.110
Cerebrovascular disease	0.951	0.098	2.555	0.396	16.475
Peptic ulcer	0.496	0.065	2.493	0.943	6.585
CKD	0.533	0.083	2.088	0.734	5.935
Metastatic tumor	0.556	0.001	6.343	2.132	18.868

Table 4. Multivariable analysis of the prognostic impact of comorbid conditions in women with ACS

Factors				95% CI	
	SE	p-value	OR	Lower	Upper
Age	0.034	0.001	1.22	1.050	1.198
Prior MI	0.574	0.075	1.860	0.604	5.724
Congestive HF	0.805	0.060	2.925	0.604	14.166
PAD	0.870	0.010	9.498	1.725	52.303
Liver disease	0.634	0.880	0.909	0.262	3.149
AH	0.843	0.063	2.301	0.441	12.010
Thyroid disease	0.916	0.031	7.188	1.194	43.253
Gynecological diseases	0.675	0.044	5.412	0.895	10.342

in male and female patients. According to the results obtained, female patients with ACS more often experienced nausea, vomiting, palpitations and fatigue instead of typical chest pain. They were also more likely than men to be hospitalized >12 hours after the symptom onset. In the following cohort, STEMI was more often diagnosed in men and NSTEMI or UA more often occurred in women.

A substantial body of evidence suggests that female patients with ACS are usually older and have more comorbid conditions, such as diabetes mellitus (DM) and arterial hypertension (AH) [2, 7-10]. At the same time, limited number of scientific articles analyzes the prevalence of other comorbidities. In accordance with previous studies, women in the following cohort were also older and had generally worse risk profiles. Nevertheless, we did not observe significant gender differences in the prevalence of DM and AH in our study. Instead, women more often than men had concomitant cerebrovascular diseases, dementia, connective tissue disorders and thyroid disease. In turn, men more often suffered from peptic ulcer (13.7% vs. 3.4%, P=.05).

Female patients with ACS showed significantly higher 3-year cumulative MACEs rates, as compared with their male counterparts. Nevertheless, such gender difference was mainly attributed to the higher incidence of recurrent events in older patients (>65 years old). Kaplan–Meier analysis did not identify any significant gender differences in the prognosis of younger patients (< 65 years old). The above mentioned results reflect the general trend in the outcomes of women with ACS. It is widely acknowledged that premenopausal women are generally protected with the anti-atherogenic and vasoprotective effects of estrogen [11, 12]. The situation changes dramatically when females reach the menopause. In such women, we observe not only a sharp increase in the incidence of de novo CVD cases, but also a worse overall prognosis after acute ischemic events [13].

According to the results of numerous studies, female patients with ACS have generally worse unadjusted short-term and long-term mortality rates after ACS. Nevertheless, after adjustment for various factors, the gender difference was attenuated [3-6, 14]. Scientists suggest that the mortality is most likely attributed to the older age and higher prevalence of comorbidity in female patients [5, 6]. In this study, we analyzed the prognostic impact of comorbid conditions, which were included to Charlson Comorbidity Index. We also investigated the prognosis of patients with concomitant thyroid disease and the prognosis of females with gynecological diseases.

The greatest impact on the 3-year event-free survival of male patients with ACS in this cohort demonstrated solid metastatic tumor. This comorbid condition was associated with six-fold risk of MACEs during the follow-up period. Men with ACS and concomitant cerebrovascular disease, peptic ulcer, dementia and CKD had more than twice higher chances of MACEs as compared with men with no such conditions. Finally, PAD and prior MI increased the probability of recurrent MACEs in 1.5 times in male patients with ACS. The influence of other comorbidities on the long-term prognosis of men in this cohort was less significant.

PAD and thyroid disease demonstrated the most significant impact on the long-term event-free survival of women with ACS in this cohort. Females with gynecological diseases also had significantly higher incidence of recurrent MACEs within 3 years after ACS as compared with females with no history of gynecological issues. Congestive HF, prior MI and AH also negatively affected the prognosis of female

patients with ACS in this cohort. The prognostic impact of other comorbid conditions was not considered statistically significant.

Conclusions

We observed significant gender differences in the clinical profiles and the prevalence of comorbidity in patients with ACS. The cumulative incidence of 3-year MACEs was higher in women than in men. At the same time, statistically significant gender difference in the long-term outcomes has been observed exceptionally in the cohort of older patients. The influence of comorbid conditions on the event-free survival of patients with ACS differed between genders. The predictive value of comorbidities should be further investigated, preferably, with an involvement of larger cohorts.

Limitations

First of all, this is a retrospective study and the cohort of patients involved is relatively small. That is why we deem it reasonable to conduct further research on this subject with an involvement of larger patient samples. Second, the selected patients never (or very rarely) developed leukemia, AIDS, hemiplegia and lymphoma; hence, it was impossible to investigate the influence of these conditions on the long-term prognosis in the following cohort. Third, we did not have a chance to observe the 3-year event-free survival in female patients with diagnosed metastatic tumor due to a small number of cases.

Conflict of Interests

Authors declare no conflict of interest.

Author's Contributions

Tetiana Lunova – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Ivan Klishch* – data curation, writing – reviewing and editing.

ГЕНДЕРНІ ВІДМІННОСТІ ВПЛИВУ КОМОРБІДНИХ СТАНІВ НА ВІДДАЛЕНІ НАСЛІДКИ У ПАЦІЄНТІВ З ГОСТРИМ КОРОНАРНИМ СИНДРОМОМ

***Т. В. Луньова, І. М. Кліщ**

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *Вплив статі на клінічний перебіг гострого коронарного синдрому (ГКС) у пацієнтів є широко відомим. Жінки з таким діагнозом зазвичай старші та мають більше супутніх захворювань.*

Мета. *У даній роботі ми мали на меті дослідити, які фактори впливають на довготривалий прогноз та відділені наслідки у пацієнтів з ГКС.*

Методи. *Ретроспективне когортне дослідження включало 167 пацієнтів (58 жінок та 109 чоловіків), які проходили лікування на базі Тернопільської міської комунальної лікарні № 2 у 2016-2017 рр. з діагнозом ГКС. Уся інформація була записана у спеціально створені карти пацієнтів. Частоту повторних серцево-судинних подій оцінювали протягом 36-ти місяців після виписки зі стаціонару.*

Результати. *Жінки у цій когорті були старшими та мали вищу частоту супутніх захворювань: 15,5% жінок та 11% чоловіків з ГКС мали ≥5 коморбідностей, 65,5% жінок і 60% чоловіків мали 2-4 коморбідності, і 19% жінок та 29% чоловіків ≤1 коморбідне захворювання. Жінки частіше мали супутні цереброваскулярні захворювання (17,2% проти 7,3%, p=0,05), деменцію (15,5% проти 5,5 %, p=0,03), хвороби сполучної тканини (17,25% проти 6,42%, p=0,03) і захворювання щитоподібної залози (12,1% проти 2,8%, p=0,02). Чоловіки частіше мали виразкову хворобу (13,7% проти 3,4%, p=0,05). Частота повторних серцево-судинних подій була вищою у жінок (55% проти 33%, p=0,003). Хвороба периферичних артерій (OR 9,5, 95% CI: 1,7-52,3, p=0,01) хвороби щитоподібної залози (OR 7,2, 95% CI: 1,19-43,2, p=0,03) продемонстрували найбільший вплив на прогноз у жінок. Онкологічні захворювання мали найбільших вплив на виживання у чоловіків (OR 6,3, 95% CI: 2,13-18,9, p=0,001).*

Висновки. *Ми спостерігали суттєві гендерні відмінності у структурі коморбідності та вільному від подій виживанні пацієнтів з ГКС. Доцільно провести подальші дослідження із залученням більших когорт пацієнтів.*

КЛЮЧОВІ СЛОВА: гострий коронарний синдром; стать; прогноз.

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