

## PREDICTORS OF LOW FUNCTIONAL RESERVES IN REHABILITATION OF PATIENTS WITH MYOCARDIAL INFARCTION COMPLICATED BY COMORBID PATHOLOGY

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**Background.** Myocardial infarction (MI) is one of the leading causes of death in working age population; the risk of cardiovascular complications for survivors of acute MI complicated by comorbid pathology (CP) is very high.

**Objective.** The study is aimed to search for reliable prognostic markers for risk of reducing the functional reserves of the cardiovascular system in myocardial infarction with comorbid pathology.

**Methods.** The prospective study involved 371 patients with MI, who received non-invasive therapy and were observed for a 90-day period after admission to the hospital. All patients were examined and treated according to current protocols.

**Results.** It was found that 6-minute walk test (6MWT) is a specific and highly sensitive prognostic marker of functional reserves for patients with MI with CP (specificity – 100%, sensitivity – 63%, prognostic value of a positive result – 100%) with the Charlson comorbidity index (CCI)  $\geq 2$ . The correlation of 6MWT performed on the 10<sup>th</sup>, 30<sup>th</sup> and 90<sup>th</sup> day of rehabilitation was revealed with the age of patients, SpO<sub>2</sub>, respiratory rate, systolic blood pressure, heart rate, left ventricular ejection fraction, levels of troponin T, creatinine, the number of lymphocytes in the peripheral blood, CCI ( $p < 0.05$ ).

**Conclusions.** During the 90-day rehabilitation period of a patient with MI complicated by CP, the markers of reduced exercise tolerance to be monitored are: blood pressure levels, respiratory rate, troponin T, creatinine, cholesterol, low-density lipoprotein, SpO<sub>2</sub>, the number of lymphocytes in the peripheral blood. To improve control over the process of rehabilitation in patients with MI complicated by CP the 6MWT and CCI should be used.

**KEYWORDS:** myocardial infarction; comorbid pathology, Charlson comorbidity index, 6-minute walk test, predictors of functional reserves.

### Introduction

Myocardial infarction (MI) is the main cause of cardiovascular mortality in the human population [1, 2]. To date, there is no single strategy for the use of clinical, laboratory, imaging parameters to predict risks in the treatment and rehabilitation of patients with MI. The task of risk prevention in patients with MI with comorbid pathology (CP) is particularly difficult [3, 4]. The objectives of this study were to identify and evaluate the predictors of severe MI with CP in the stages of rehabilitation.

### Methods

The prospective study involved 371 patients with MI, who received non-invasive therapy and were observed for a 90-day period from ad-

mission to the hospital in 2014-2019. All patients were examined and treated according to the current protocols. Clinical, laboratory and instrumental examinations were performed on the 1<sup>st</sup>, 10<sup>th</sup>, 30<sup>th</sup> and 90<sup>th</sup> days. Cardiovascular functional reserves were determined by the degree of heart failure (Killip and NYHA), echocardiography and 6-minute walk test (6MWT) on the 10<sup>th</sup>, 30<sup>th</sup> and 90<sup>th</sup> days of MI. Risk assessment was performed according to the GRACE scale and the AACPR cardiovascular risk scale. The Charlson Comorbidity Index (CCI) was used to estimate the degree of comorbidity [5, 6, 7]. Statistical analysis was performed using software products MSEXCEL 2000, EVIEWS 5.1. and SPSS.

### Results

There were 67.4% of men and 32.6% of women aged (66.2 $\pm$ 10.4) years involved in the study. Comorbid pathology was detected in

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93.8 % of the patients: arterial hypertension – in 84.9%; diabetes mellitus – in 25.1%; vascular pathology – in 35.6%. Analysis of exercise tolerance and rehabilitation potential in the study cohort showed that inpatients had predominantly high heart failure and reduced cardiac reserves. Thus, the six-minute walk test performed in patients on the 10<sup>th</sup> day after admission was (76.1±35.2) m; on the 30<sup>th</sup> and 90<sup>th</sup> days – (133.8±49.6) m and (207.6±74.1) m, respectively. Their NYHA functional class was high (2.9±0.7), and the risk on the GRACE scale and the AACPR risk scale was high and very high (2.9±0.3) and (2.7±0.6), respectively. Rehabilitation and hemodynamic potentials, reflected by the functional class according to the rehabilitation classification and parameters of left ventricular systolic function, also indicated a significant depletion of functional reserves of the cardiovascular system. Thus, the functional class according to echocardiography was (2.9±0.8) points, and the class according to the rehabilitation classification was (3.3±0.7).

The possible correlations between the degrees of cardiovascular risk according to the GRACE, AACPR scales, functional classes according to the rehabilitation classification, functional classes of heart failure (Killip, NYHA) and the presence and severity of comorbid pathology were assessed. High reliability ( $p < 0.0001$ ) relationships were found between the presence of CP and the categorical indicators of functional class of heart failure according to Killip, NYHA and the degree of risk according to AACPR (Table 1).

The proportion of patients at maximum risk for GRACE was significantly higher in patients with MI with CP than in those without CP (Z-test = -4.399;  $p < 0.0001$ ). Risk levels for GRACE in patients with MI with CP directly correlated with age ( $r = 0.267$ ;  $p < 0.0001$ ), respiratory rate ( $r = 0.248$ ;  $p = 0.001$ ), glucose levels ( $r = 0.2$ ;  $p = 0.007$ ) and CCI ( $r = 0.275$ ;  $p < 0.0001$ ). High

specificity (92.5%) and sensitivity (87.1%) of the GRACE calculator and the AACPR risk scale (94.2% and 71.0%, respectively) with a high prognostic value of a positive result (97% for both risk scales) and CCI  $\geq 2$  was determined. The obtained data allow using the GRACE calculator and the AACPR risk scale to predict early risks and possible negative consequences of the standard rehabilitation program at the hospital stage, as well as stratification of comorbid patients into individualized rehabilitation programs in the acute phase of rehabilitation.

The correlation of high reliability of CCI with risk levels according to GRACE ( $r = 0.542$  according to the association coefficient), functional class according to NYHA and 6MWT on the 10<sup>th</sup>, 30<sup>th</sup> and 90<sup>th</sup> days of rehabilitation was revealed; ( $r_{6MWT10} = -0.318$ ;  $r_{6MWT30} = -0.397$ ;  $r_{6MWT90} = -0.425$ ) ( $p < 0.0001$ ).

It was established that the six-minute walk test is a specific and highly sensitive prognostic marker of functional reserves for patients with MI and CP (specificity – 100%, sensitivity – 63 %, prognostic value of a positive result – 100%), CCI  $\geq 2$ . The correlation of 6MWT performed on the 10<sup>th</sup>, 30<sup>th</sup> and 90<sup>th</sup> days of rehabilitation (6MWT<sub>10</sub>, 6MWT<sub>30</sub> and 6MWT<sub>90</sub>) was revealed regarding the age of patients ( $r_{6MWT10} = -0.199$ ;  $r_{6MWT30} = -0.287$ ;  $r_{6MWT90} = -0.410$  respectively;  $p < 0.05$ ), SpO<sub>2</sub> ( $r_{6MWT10} = 0.399$ ;  $r_{6MWT30} = 0.265$ ;  $r_{6MWT90} = 0.248$ ;  $p < 0.05$ ), respiratory rate ( $r_{6MWT10} = -0.318$ ;  $r_{6MWT30} = -0.357$ ;  $r_{6MWT90} = -0.298$ ;  $p < 0.0001$ ), systolic blood pressure ( $r_{6MWT10} = 0.179$ ;  $r_{6MWT90} = 0.205$ ;  $p < 0.05$ ), heart rate ( $r_{6MWT30} = -0.259$ ;  $r_{6MWT90} = -0.179$ ;  $p < 0.05$ ), left ventricular ejection fraction ( $r_{6MWT10} = 0.706$ ;  $r_{6MWT30} = 0.706$ ;  $r_{6MWT90} = 0.670$ ;  $r_{6MWT90} = 0.583$ ;  $p < 0.0001$ ), levels of troponin T ( $r_{6MWT10} = -0.210$ ;  $r_{6MWT30} = -0.312$ ;  $p < 0.05$ ), creatinine ( $r_{6MWT10} = -0.148$ ;  $p < 0.05$ ), lymphocyte count in peripheral blood ( $r_{6MWT10} = -0.303$ ;  $r_{6MWT30} = -0.278$ ;  $r_{6MWT90} = -0.294$ ;  $p < 0.0001$ ), CCI ( $r_{6MWT10} = -0.323$ ;  $r_{6MWT30} = -0.398$ ;  $r_{6MWT90} = -0.427$ ;  $p < 0.0001$ ).

Table 1. Dependence of functional categorical indicators in patients with myocardial infarction on the presence of comorbid pathology

Index	FC according to Killip	FC according to NYHA	Risk degree according to AACPR	FC according to rehabilitation classification
Pearson's coefficient of mutual conjugation	0.258	0.237	0.370	0.286
Chuprov coefficient of mutual conjugation	0.189	0.206	0.334	0.251
Cramer's coefficient of mutual conjugation	0.267	0.244	0.398	0.299
$\chi^2$ (p-value)	<0.0001	<0.0001	<0.0001	<0.0001

According to the results obtained, most of these dependence factors are repeated at all three stages of rehabilitation; therefore, their significant impact on exercise tolerance during the 90-day period of the cardiorehabilitation program is obvious. In general, the patients with MI with CP and high age indices, RR, heart rate, creatinine, troponin T and Charlsson comorbidity index, as well as low SBP in the acute period of MI, SpO<sub>2</sub> and LVEF have significantly lower tolerance to physical activity at all stages of rehabilitation. Therefore, the above parameters can be considered to be the main functional clinical, hemodynamic and laboratory markers of reduced tolerance to exercise; they should be used to monitor the response to increased physical activity and predict the tolerability of rehabilitation measures in patients with MI associated with comorbid pathology.

### Discussion

Profound disturbances of functional reserves in this category of patients were associated with late treatment (20.34±15.11 hours), and, accordingly, the lack of timely revascularization of the infarct-related artery. The age category of patients (mean age (66.16±10.41) years) and the presence of comorbid pathology in most patients (93.8%) were also significant. This profile of infarct patients, which is characterized by late treatment, and, consequently, the loss of timely revascularization of infarct-related artery, the presence of comorbid pathology and old age of patients, is still common in Ukraine and requires special approaches unprescribed in the current protocols of rehabilitation. Most studies [8-13] confirm the significant negative impact of comorbid pathology on the functional state and reserve capacity of the cardiovascular system in patients with MI with a high efficiency of adequate rehabilitation programs.

The study confirms the possibility of using the Charlsson index to quantify the degree of comorbidity in patients with MI and various comorbid pathologies and predict their reaction to exercise tolerance in the rehabilitation stages. So, the interdependence of the degree

of Charlsson comorbidity and the six-minute walk test in the stages of rehabilitation was analyzed [14, 15]. It was established that 6MWT<sub>10</sub>, 6MWT<sub>30</sub> and 6MWT<sub>90</sub>, which reflect exercise tolerance, in the acute (inpatient) and subacute (early and late outpatient) phases of rehabilitation process in the patients with a higher degree of comorbidity were significantly lower ( $p < 0.0001$ ),  $r_{6MWT10} = -0.318$ ;  $r_{6MWT30} = -0.397$ ;  $r_{6MWT90} = -0.425$ , respectively.

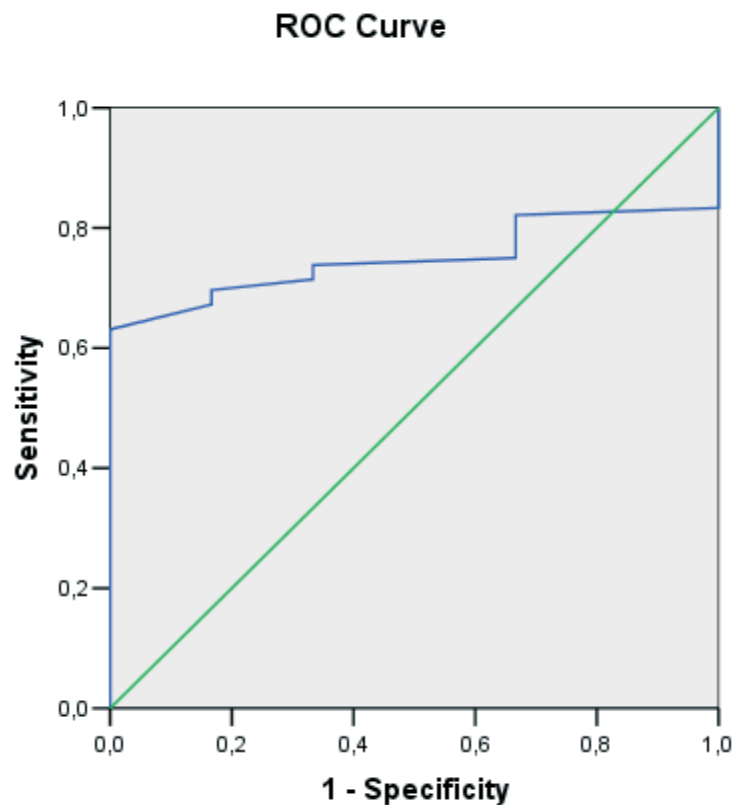
Analysis of the specificity and sensitivity of the six-minute walk test on the 10<sup>th</sup> day of rehabilitation of postinfarction patients with the parameters of the Charlsson comorbidity index  $\geq 2$  showed high specificity and prognostic value of a positive result of this marker for comorbid patients (Table 2, Fig. 1). According to the results of the ROC analysis, it was established that the best quality of the model for 6MWT<sub>10</sub> (AUC=0.75, 95% CI (0.672-0.828) provides a threshold value (distribution point)  $< 83.5$  m with the specificity of 100%, sensitivity – 63%, and the prognostic value of a positive result – 100%.

The corresponding values for 6MWT performed on the 30<sup>th</sup> and 90<sup>th</sup> days after the beginning of MI were also with the maximum specificity (100%) and prognostic value of a positive result (100%) for 6MWT<sub>30</sub> values in the range from 147 to 166.5 m (95% CI (0.766-0.904),  $p = 0.005$ ; area under the ROC curve 0.835) and 6MWT<sub>90</sub> in the range of 199.5-227.5 m (95% CI (0.741-0.933),  $p = 0.005$ ; area under ROC curve 0.837). Thus, the analysis of the specificity and sensitivity of the six-minute walk test on the 10<sup>th</sup>, 30<sup>th</sup> and 90<sup>th</sup> days of rehabilitation of postinfarction patients with CCI values  $\geq 2$  showed maximum specificity (100%) and prognostic value of a positive result (100%) of this marker in comorbid patients. Accordingly, the 6MWT targets by the end of the first decade of the rehabilitation period in patients with MI with the Charlsson comorbidity index  $\geq 2$  were in the range of 83.5-98 m, by the end of the first month of rehabilitation – 147.0-166.5 m and by the end of the first trimester after the index date – 199.5-227.5 m. The results suggest that the Charlsson comorbidity index and the six-

Table 2. Matrix for sensitivity and specificity of 6MWT<sub>10</sub> at CCI values  $\geq 2$

6MWT <sub>10</sub> value	Sensitivity	Specificity	Prognostic value of a positive result
83.5	0.63	1	1
98.0	0.80	0.33	0.97
100.5	0.81	0.33	0.97

Note. 95% CI (0.672-0.828),  $p = 0.038$ .



Diagonal segments are produced by ties.

**Fig. 1.** ROC-curve of sensitivity and specificity of 6MWT<sub>10</sub> at values of CI >2 (area under the curve 0.75, standard error 0.040;  $p=0.038$ ).

minute walk test are highly specific and sensitive prognostic markers of exercise tolerance in patients with MI with comorbid pathology at all stages of rehabilitation.

#### Conclusions

During the 90-day rehabilitation period of a patient with myocardial infarction and CP, the markers of reduced exercise tolerance to be monitored are blood pressure levels, heart rate, respiratory rate, SpO<sub>2</sub>, troponin T, creatinine, the number of lymphocytes in the peripheral blood. The basic test for monitoring functional reserves in patients with MI and CP during the 90-day period is 6MWT. To improve control over

the process of rehabilitation in patients with MI and CP, the Charlson comorbidity Index should be used in addition to GRACE and AACPR cardiovascular risk scales.

#### Conflict of Interests

Authors declare no conflict of interest.

#### Author's Contributions

*Larysa V. Levytska* – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Viktoriia V. Yurkiv* – data curation, writing – reviewing and editing; *Mykhaylo M. Korda* – investigation, formal analysis, writing – reviewing and editing.

# ПРЕДИКТОРИ НИЗЬКИХ ФУНКЦІОНАЛЬНИХ РЕЗЕРВІВ У ХВОРИХ НА ІНФАРКТ МІОКАРДА, УСКЛАДНЕНИЙ КОМОРБІДНОЮ ПАТОЛОГІЄЮ

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ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ,  
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**Вступ.** Інфаркт міокарда (ІМ) є однією з головних причин смертності у працездатному віці, а ризик серцево-судинних ускладнень для тих, хто виживає в гострий період ІМ з коморбідною патологією (КП), є дуже високим.

**Мета.** Пошук надійних прогностичних маркерів ризику зниження функціональних резервів серцево-судинної системи при інфаркті міокарда з коморбідною патологією.

**Методи.** У проспективне дослідження було включено 371 хворого на інфаркт міокарда, які отримували неінвазивне лікування та спостерігалися протягом 90 днів з моменту надходження до стаціонару. Усі пацієнти були обстежені та проліковані згідно з діючими протоколами.

**Результати.** Встановлено, що тест шестихвилинної ходьби (ТШХ) є специфічним і високочутливим прогностичним маркером функціональних резервів у хворих на ІМ з КП (специфічність – 100%, чутливість – 63%, прогностичне значення позитивного результату – 100%) з ІКЧ  $\geq 2$ . Виявлено кореляцію ТШХ, проведеного на 10, 30 і 90 день реабілітації, з віком пацієнтів, частотою дихання (ЧД),  $SpO_2$ , систолічним артеріальним тиском, частотою серцевих скорочень (ЧСС), фракцією викиду лівого шлуночка (ФВ), рівнями тропоніну Т, креатиніну, кількістю лімфоцитів в периферичній крові та індексом коморбідності Чарльсон ІКЧ ( $p < 0,05$ ).

**Висновки.** Протягом 90-денного періоду реабілітації хворих на інфаркт міокарда з коморбідною патологією маркерами зниженої толерантності до фізичних навантажень, які потребують моніторингу, є рівні артеріального тиску, ЧСС, ЧД,  $SpO_2$ , тропоніну Т, креатиніну, кількість лімфоцитів в периферичній крові. Для покращення контролю за процесом реабілітації у хворих на ІМ з КП доцільно використовувати ТШХ та ІКЧ.

**КЛЮЧОВІ СЛОВА:** інфаркт міокарда; коморбідна патологія, індекс коморбідності Чарльсон, тест 6-хвилинної ходьби, предиктори функціональних резервів.

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