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A MODEL FOR PREDICTING LATE COMPLICATIONS OF MYOCARDIAL INFARCTION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Introduction. Late complications of myocardial infarction (MI) are important causes of re-hospitalization and mortality in patients with type 2 diabetes mellitus (DM).

The objective of the study was to predict the development of late complications after MI in type 2 DM patients, to improve the quality of diagnostic tests for this group of patients.

Material and methods. A total of 109 patients with type 2 DM after MI was divided into two groups: the study group (n = 74) and the validation group (n = 35). The levels of adropin and C1q/tumour necrosis factor-related protein 3 (CTRP 3) were measured by enzyme-linked immunosorbent assay. The model for predicting late complications of MI was calculated using binary logistic regression.

Results. The median age of patients was 61.0 (54.5 – 67.0) years and 68.8% were male. Mathematical model components on the 14th day of follow-up were qualitative adropin, qualitative CTRP3, total cholesterol (TC), triglycerides (TG), ejection fraction (EF), low-density lipoprotein (LDL), left atrium (LA). The model attained the highest under the receiver operating characteristic

Résumé

Modèle de prédiction des complications tardives de l'infarctus du myocarde chez les patients avec diabète de type 2

Introduction. Les complications tardives de l'infarctus du myocarde (IDM) constituent l'une des principales causes de ré hospitalisation et de mortalité parmi les patients avec diabète de type 2.

L'objectif de l'étude était de prévoir le développement des complications tardives de l'IDM chez les patients avec diabète de type 2 ce qui a permis d'améliorer les méthodes diagnostiques chez cette cohorte de patients.

Matériel et méthodes. Le total de 109 patients qui ont développé un diabète de type 2 après avoir subi un IDM, a été divisé en deux groupes : un groupe expérimental (n = 74) et un groupe témoin (n = 35). La détermination de l'adropine et C1q/Protéine 3 induite par le facteur de nécrose tumorale (CTRP3) a été réalisée au moyen de la méthode de dosage immuno-enzymatique. Le modèle de prédiction des complications tardives de l'IDM a été évalué en utilisant la régression logistique binaire.

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curve for predicting late MI complications in the study and control groups (0.949 and 0.966, respectively), with the highest diagnostic accuracy in both groups (94.6% and 97.1%, respectively).

Conclusions. This study has shown that the integral assessment of adropin, CTRP 3, TC, TG, EF, LDL, LA, measured on the 14th day after MI in type 2 DM patients who underwent percutaneous coronary intervention (PCI), could predict late complications of MI after PCI.

Keywords: complications, myocardial infarction, diabetes mellitus, model.

List of abbreviations:
AF – atrial fibrillation
AMI – acute myocardial infarction
AI – atherogenic index
AUC – area under the curve
AV block – atrioventricular block
CAD – coronary artery disease
CTRP3 – C1q/tumour necrosis factor – related protein 3
CVD – cardiovascular disease
DM – diabetes mellitus
EF – ejection fraction
HDL – high-density lipoprotein
HF – heart failure
LA – left atrium
LDL – low-density lipoprotein
LV – left ventricular
LVA – left ventricular aneurysm
MI – myocardial infarction
PCI – percutaneous coronary intervention
ROC – receiver operating characteristic
STEMI – ST-elevation myocardial infarction
TC – total cholesterol
TG – triglyceride
VLDL – very low-density lipoprotein

Résultats. L'âge moyen était de 61.0 (54.5 – 67.0) ans et 68.8% des patients étaient des hommes. Les composantes du modèle mathématique au 14e jour de suivi ont été l'adropine qualitative, CTRP3 qualitative, cholestérol total (CT), triglycérides (TG), fraction d'éjection (FE), lipoprotéines de basse densité (LDL), oreillette gauche (OG). Le modèle a donné la zone la plus importante sous la courbe caractéristique de fonctionnement du récepteur pour prévoir des complications tardives de l'IDM dans les groupes expérimental et témoin (0.949 et 0.966, respectivement) et a montré la plus grande précision dans les deux groupes (94.6% et 97.1% respectivement).

Conclusions. Cette étude a montré que la détermination de la teneur en adropine, CTRP3, TG, FE, LDL, OG, effectuée le 14ème jour après l'IDM chez les patients avec diabète de type 2, qui ont subi une intervention coronarienne percutanée (l'ICP), peut permettre de prévoir des complications tardives de l'IDM après l'ICP.

Mots-clés: complications, infarctus du myocarde, diabète de type 2, modèle.

Introduction

Cardiovascular disease (CVD) and diabetes mellitus (DM) are nowadays among the most common diseases. According to the World Health Organization, CVD remains one of the top-ten leading causes of human death, and DM was first registered on this list in 2020[1]. Acute myocardial infarction (AMI) is a critical condition that continues to be a major global cause of mortality and morbidity. Percutaneous coronary intervention (PCI), anticoagulation and anti-platelet therapy have been beneficial in reducing late complications of myocardial infarction (MI) in recent years. However, serious cardiovascular events still occur, especially in the combination of AMI and type 2 DM[2]. The risk of future clinical adverse effects is closely related to myocardial salvage, irreversible myocardial damage and left ventricular (LV) dysfunction after MI[3]. The risk of late complications of MI is significantly higher in type 2 DM comorbidity, impairing daily living activities of patients. Smolina et al.[4] showed that type 2 DM is a risk factor for recurrent MI. Type 2 DM patients after MI are more likely to develop late complications such as heart failure (HF) and arrhythmic complications, resulting in re-hospitalizations and higher mortality rates[5,6]. It has been demonstrated that the risk of HF and/or all-cause mortality during a 6-year follow-up after PCI for

ST-elevation myocardial infarction (STEMI) was increased in the presence of type 2 DM and diminished myocardial perfusion[7]. As concluded by Hashmi et al.[8], there wasn't any significant effect of various stratified confounder variables such as age, sex, diabetes, hypertension, smoking, dyslipidemia and duration of presentation after MI on the incidence of complete atrioventricular (AV) block, as it remained the same in all these groups. Hur et al.[9] reported that diabetic patients after MI had a higher incidence of systolic HF with LV ejection fraction (EF) less than 35% during a 2-year follow-up compared to non-DM patients. Early reperfusion and drug therapy substantially reduced the incidence of late complications associated with MI. However, despite several recent treatment advances, late complications of MI continue to occur in type 2 DM patients. One of the means to prevent the development of late complications is to provide further insights into the pathophysiological mechanisms of changes in type 2 DM patients after MI. Today, the biological markers linked to the onset and progression of late MI complications in type 2 DM patients remain to be clarified. In-depth studies on late complications of MI are needed to understand the processes of ventricular functional and systemic hemodynamic recovery in type 2 DM patients.

Adropin is a recently identified protein encoded by the energy homeostasis-associated gene, it maintains insulin sensitivity and is closely related to atherogenesis initiation and progression[10]. The endothelium plays a key role in the regulation of vascular homeostasis, and endothelial dysfunction is an early process involved in the pathophysiology of cardiovascular diseases[11]. Low serum adropin levels are associated with endothelial dysfunction and this protein may exert protective effects on endothelium[12].

C1q/tumor necrosis factor – related protein 3 (CTRP3) is an anti-inflammatory adipokine with regulatory effects on carbohydrate and lipid metabolism, secretion of other adipokines, as well as presenting cardioprotective properties[13]. Serum CTRP3 levels are associated with CVD and type 2 DM[14]. Kratochvilova et al.[15] report that CTRP3 may be a diagnostic and prognostic marker of CVD in patients with long-lasting type 2 DM. However, the issues of late complications after MI considering adropin and CTRP3 in type 2 DM patients need to be addressed.

The objective of the study was to predict the development of late complications after MI in type 2 DM patients using binary logistic regression to improve the quality of diagnostic tests for this group of patients.

Material and methods

The purpose of each examination was explained in detail, and all participants signed a written informed consent. The study protocol was approved by the Bioethical Committee of Kharkiv National Medical University (Protocol No. 2 dated April 2, 2018), and patient data were processed according to the 6th version (2008) of the 1975 Helsinki Declaration.

Patients' selection

A total of 109 participants with STEMI and type 2 DM were included in the study: 75 men (68.8%) and 34 women (31.2%); the median age was 61.0 (54.5 – 67.0) years. All the patients received treatment in the Government Institution "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine" and the Kharkiv Railway Clinical Hospital No. 1 of the branch "Centre of Healthcare" of Public Joint Stock Company "Ukrainian Railway", from 01 September 2018 to 31 December 2020. All the patients were diagnosed with AMI, late complications were examined, and a treatment was prescribed according to the European Society of Cardiology guidelines[16].

Late complications associated with MI included the occurrence of AV block, persistent atrial fibrillation (AF), progression of HF, formation of left ventricular aneurysm (LVA) at the apex and interventricular septum, reduced LVEF <40%. All patients underwent PCI. Diagnosis and treatment of type 2 DM were based on the recommendations of the American Diabetes Association and the European Association for the Study of Diabetes[17,18]. Inclusion criteria were adopted for acute STEMI and type 2 DM: age ≥ 45 years, the absence of contraindications to PCI. All 109 patients fulfilled these criteria. The patients with severe comorbidities (type 1 DM, autoimmune diseases, MI secondary to functional class IV chronic HF, chronic obstructive pulmonary disease, bronchial asthma, heart valve disease, symptomatic hypertension, severe liver and kidney dysfunction, severe anemia, bleeding, severe coronavirus disease 2019, malignancy), inability to give written informed consent were excluded from the present study.

The study group (n = 74) was assigned to study variables related to the probability of late MI complications in type 2 DM patients. The reproducibility of the model was checked with the validation group (n = 35). The study group included 65 patients with late MI complications and 9 patients without. The validation group included 26 patients with late MI complications and 9 patients without. All the patients underwent PCI.

Instrumental methods of diagnosis

Conventional Doppler echocardiography was performed with an ultrasound scanner Radmir ULTIMA Pro30 (Ukraine). Standard 12-lead electrocardiography was recorded using a three-channel electrocardiograph "Fukuda" FX–326U (Japan).

Laboratory tests

Diagnostic testing was performed in the Biochemical Department of the Central Research Laboratory of Kharkiv National Medical University. Serum samples were collected from patients on days 1-2 and 14 and stored at –80 °C. Serum total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol were analysed by peroxidase enzymatic method using assay kits "Human Cholesterol Liquicolor" (Germany) and HDL Cholesterol liquicolor (Germany), respectively. Triglyceride (TG) levels were measured by enzymatic colorimetric method using an assay kit "Triglycerides GPO" produced by "Human" company (Germany). The atherogenic index (AI) was calculated by the standard A.M. Klimov formula. The levels of very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) were estimated by the Friedewald formula. Serum adropin and CTRP3 levels were measured by enzyme-linked immunosorbent assay using an analyzer "Labline-90" (Austria) using a commercial test system "Human Adropin" (Elabscience, USA) and "Human CTRP3" (Aviscera Bioscience Inc., USA), respectively, following the manufacturers' instructions. The principle of method used to quantify the adropin and CTRP3 levels is based on the sandwich technique characterized by an antibody pair of the capture antibody and biotin-labeled detection antibody binding to captured analyte. We determined the mean and reference range for CTRP 3 as 315.85 (287.06 – 371.02) ng/mL and adropin as 23.58 (20.86 – 26.3) pg/mL.

Statistical analysis

The obtained data were statistically processed with IBM SPPS software version 27.0, (IBM Inc., USA, license No. L-CZAA-BKKMKE, 2020). The Kolmogorov-Smirnov criterion was used to assess the normality of studied parameters distribution. Statistical analysis involved quantitative and qualitative variables. Qualitative data were presented as percentages; quantitative as median and interquartile range (25 and 75 percentiles). Quantitative indicators were compared via the nonparametric Mann-Whitney ranking criterion. The frequency of signs in the groups was compared using the Pearson $\chi 2$ test. The critical level of significance for testing statistical hypotheses in this study was 0.05. A prognostic model for detecting late MI complications in type 2 DM patients was developed using the data obtained from the training set, and then tested on the validation set data. The patients were randomized to the training set and validation set with ratio 68% to 32%. Binary logistic regression was used to construct the model for predicting late MI complications in type 2 DM patients. Regression coefficients were calculated for each factor. To evaluate the synthesized mathematical model performance, receiver operating characteristic (ROC) analysis was performed.

Results

The model was constructed based on the data obtained from the study group and verified with the validation group. There was no difference in baseline characteristics between the study and validation groups. Characteristics of patients, including demographic, and laboratory parameters are shown in Table 1. In the study group, reduced LVEF was detected in 23% of patients, AV block in 4% of cases, persistent AF in 8%, LVA of the apex and interventricular septum in 3%, progressive HF in 66%. In the validation group, reduced LVEF was seen in 23% of patients, AV block in 6%, persistent AF in 11%, LVA of the apex and interventricular septum in 3%, progressive HF in 49%. The levels of adropin and CTRP3 were decreased by 40.12% and 30.88% on day 1-2 according to adropin and CTRP 3 reference values ($p<0.05$), and the dynamic follow-up showed a subsequent increase in these levels by 41.43% and 20.01%, respectively, compared to those on day 1-2 ($p<0.05$). The concentration of adropin and CTRP3 on day 14 remained low (Table 1).

A novel model for the assessment of late complications of MI in type 2 DM patients

Mathematical model components on the 14th day of follow-up were qualitative adropin, qualitative CTRP3, TC, TG, LVEF, LDL, left atrium (LA). Using binary logistic regression, the model was constructed to determine the probability of late complications after MI (P) in type 2 DM patients: $P = [1+ \exp(-4.046 \times \text{qualitative Adropin} - 2.714 \times \text{qualitative CTRP3} + 6.270 \times \text{TC} - 2.988 \times \text{TG} - 0.288 \times \text{LVEF} - 7.407 \times \text{LDL} - 1.398 \times \text{LA} + 19.259)]^{-1}$. The p-value ranged between 0 to 1 (the closer it was to 1, the higher the probability of late complications).

Table 2 presents several correct and incorrect predictions. It can be concluded that out of the total number of patients assigned to the group with complications, consisting of 65 patients, the test correctly identified 63 individuals, and two were erroneously assigned to the group without complications. The accuracy of the test was 96.9%. Accordingly, in the

Table 1. Baseline characteristics of the groups

Variables		*Study group (n=74)*	*Validation group (n=35)*
Males	No.	51	24
	%	68.9	68.6
Females	No.	23	11
	%	31.1	31.4
Age, years		60.0 (52.0 – 66.25)	62.0 (58.0 – 67.0)
BMI, kg/m^2		28.1 (26.0 – 31.1)	28.4 (26.0 – 32.0)
Height, cm		170.0 (165.0 – 178.0)	168.0 (163.0 – 175.0)
Body weight, kg		85.0 (75.75 – 92.0)	80.0 (75.0 – 90.0)
LVEF on the 1st day, %		50.0 (45.0 – 55.25)	53.0 (48.0 – 56.0)
LVEF on the 14th day, %		49.0 (43.75 – 56.0)	48.0 (44.0 – 50.0)
LA on the 1st day, cm		3.8 (3.4 – 4.2)	3.8 (3.4 – 4.1)
LA on the 14th day, cm		3.8 (3.4 – 4.3)	3.88 (3.6 – 4.1)
TC on the 1st day, mmol/L		4.98 (4.17 – 6.08)	5.14 (4.79 – 5.53)
TC on the 14th day, mmol/L		4.56 (4.01 – 5.59)	4.94 (4.77 – 5.52)
TG on the 1st day, mmol/L		1.94 (1.38 – 2.65)#	2.0 (1.83 – 2.15)
TG on the 14th day, mmol/L		1.45 (1.12 – 2.01)	1.63 (1.11 – 1.87)
LDL on the 1st day, mmol/L		2.93 (2.25 – 3.83)	2.82 (2.35 – 3.18)
LDL on the 14th day, mmol/L		2.74 (2.05 – 3.47)	2.78 (2.34 – 3.17)
VLDL on the 1st day, mmol/L		0.92 (0.66 – 1.21)#	0.90 (0.77 – 0.99)
VLDL on the 14th day, mmol/L		0.39 (0.23 – 0.45)	0.42 (0.36 – 0.50)
HDL on the 1st day, mmol/L		1.08 (0.95 – 1.26)	1.10 (1.0 –1.28)
HDL on the 14th day, mmol/l		1.15 (1.0 – 1.33)	1.17 (1.02 – 1.28)
AI on the 1st day		3.62 (2.6 – 4.7)#	3.42 (2.67 – 4.42)
AI on the 14th day		2.96 (2.25 – 3.75)	3.22 (2.65 – 4.31)
Adropin on the 1st day, pg/mL		14.12 (9.44 – 16.94)#	14.14 (11.29 – 15.93)
Adropin on the 14th day, pg/mL		19.97 (16.35 – 21.0)	19.83 (18.01 – 20.88)
CTRP 3 on the 1st day, ng/mL		218.32 (191.95 – 268.68)#	230.76 (196.61 – 268.57)
CTRP 3 on the 14th day, ng/mL		262.01 (225.32 – 288.84)	274.46 (226.39 – 286.06)

Data are presented as median and interquartile range unless noted otherwise.
Note: # – p<0.05 in comparison between the findings on day 1-2 and day 14 in the study group.
Abbreviations: AI, atherogenic index; BMI, body mass index; CTRP3, C1q/tumor necrosis factor – related protein 3; HDL, high-density lipoprotein; LA, left atrium; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; TC, total cholesterol; TG, triglyceride; VLDL, very low-density lipoprotein.

Table 2. Classification results of the binary logistic regression model designed to predict late complications of MI in type 2 DM patients (study group)

The studied groups		*Predicted groups*		
		Late complications		*Correctly predicted (%)*
		no	*yes*	
Late complications	no	7	2	77.8
	yes	2	63	96.9
Total percentage				94.6

Table 3. The ROC analysis results of the study group

ROC curve			*Asymptotic 95% confidence interval*	
AUC	Standard error	Significance (p)	Lower bound	Upper bound
0.949	0.028	0.001	0.894	1.000

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

Table 4. Classification results of the model in the validation group

The studied groups		*Predicted groups*		
		Late complications		*Correctly predicted (%)*
		no	*yes*	
Late complications	no	9	0	100.0
	yes	1	25	96.2
Total percentage				97.1

Table 5. The ROC analysis results of the validation group

ROC curve			*Asymptotic 95% confidence interval*	
AUC	Standard error	Significance (p)	Lower bound	Upper bound
0.966	0.034	0.001	0.899	1.000

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

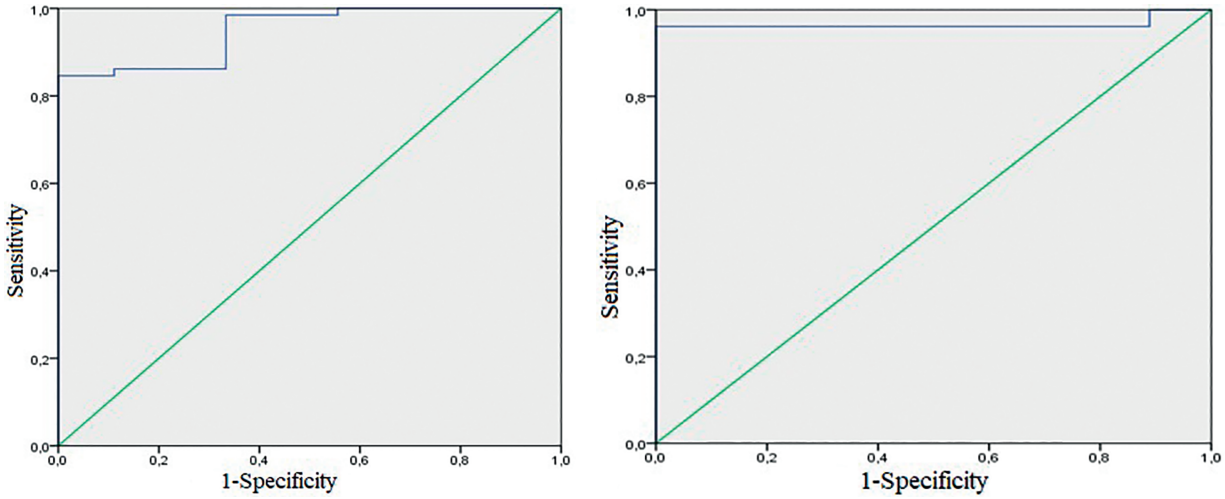

Figure 1: Receiver operating characteristic curves (ROCs) of the model for prediction of late complications after MI in the study (A) and validation (B) groups. **A.** The results of the ROC-curve showing AUC of the model 0.949, 95% CI 0.894 – 1.000, sensitivity 96.9%, specificity 77.8%, overall percentage of the model performance 94.6%. **B.** The results of the ROC-curve showing AUC of the model 0.966, 95% CI 0.899 – 1.000, sensitivity 96.2%, specificity 100%, overall percentage of the model performance 97.1%.

group of 9 patients without complications, the prediction correctness was confirmed by the test in 7 cases, and 2 were erroneously assigned to the group with complications. The accuracy of the test was 77.8%. Thus, 70 out of 74 cases were correctly identified, which corresponded to 94.6%.

To assess the diagnostic performance of the mathematical model, ROC analysis was performed with the ROC curve construction. ROC analysis of the developed model revealed characteristics indicating its excellent performance (Table 3).

The area under the curve (AUC)-ROC value, allowing the evaluation of the model diagnostic performance, was 0.949 [0.894; 1.000], indicating a very good quality of the model (Figure 1A). The usefulness of the mathematical model was tested practically with the validation group in predicting the development of late complications.

Out of the total number of patients with complications assigned to the corresponding group of 26 people, the test identified correctly 25, and one individual was erroneously assigned to the group without complications (Table 4). The accuracy of the test was 96.2%. Accordingly, in the group of 9 patients without complications, the test validated 9 cases. The test accuracy was 100.0%. Thus, 34 out of 35 cases were correctly identified, corresponding to 97.1%.

ROC analysis of the obtained model revealed characteristics pointing to its excellent quality (Table 5). The AUC-ROC was 0.966 [0.899; 1.000], demonstrating the high prediction accuracy (Figure 1B).

Discussion

Late complications of MI are a serious life-threatening problem and need to be studied in detail to

prevent rehospitalizations and deaths[19,20]. Afanasiev et al.[21] found that the long-lasting type 2 DM significantly worsened the prognosis in the post MI period. Various biological markers involved in the activation of inflammatory signaling pathways govern AMI occurrence and the development of its complications are currently discussed. Luo et al.[22] reported that patients with persistent AF were at significantly higher risk of HF hospitalization and post MI AF patients were related to cardiovascular death. It was also found that patients with LVEF of 40-49% had significantly higher rates of rehospitalization due to HF compared to patients with LVEF >50%. The model adjusted for a mean heart rate and LVEF of 40–49% identified independent association between each of these parameters and rehospitalization rate due to HF among patients after STEMI[23]. According to Thomsen et al.[24], AV block after MI occurs in both PCI-patients and non-revascularized patients. The study of Gang et al.[25] revealed that the incidence of AV block complicating STEMI was reduced after the implementation of PCI, but the findings were limited to analyzing patient registers without a control group, so it could lead to underestimation of the AV block incidence. Despite the numerous studies listed above, the late complications of MI in type 2 DM patients remain insufficiently studied.

Adropin is a new peptide that regulates energy and lipid metabolism in patients with AMI. Yu et al.[26] found that decreased serum adropin levels were independently associated with the presence of AMI. That suggested that adropin might represent a potential serum biomarker for the early diagnosis of AMI. Wang et al.[27] reported a decreased serum adropin concentration in AF patients compared with that in healthy controls or paroxysmal AF group. Wu et al.[28] found that coronary artery disease (CAD) patients had lower serum adropin levels compared with non-CAD patients, and lower serum adropin was associated with greater angiographic severity of coronary atherosclerosis in both type 2 DM patients and non-diabetic individuals. CTRP3 is a new adipokine with various properties and exerts multiple effects on carbohydrate, lipid metabolism and myocardial function. Wu et al.[29] and Yi et al.[30] indicated that CTRP3 attenuates further adverse cardiac remodeling after MI through its anti-fibrotic, anti-apoptotic, and angiogenic activity. Moradi et al.[31] showed decreased serum CTRP3 levels in type 2 DM patients. Despite the interest of numerous scientists, there is currently a lack of relevant studies on changes in adropin and CTRP 3 serum levels among type 2 DM patients with AMI.

In the present study, the serum levels of adropin and CTRP3 were low in type 2 DM patients on day 14 after MI. The model was constructed to predict the probability of late complications in type 2 DM patients after MI based on the content of qualitative adropin, qualitative CTRP3, TC, TG, EF, LDL, LA. The AUC-ROC value was 0.949 [0.894; 1.000] enabling prediction of late complications associated with MI in type 2 DM patients. The overall percentage of the obtained model performance was 94.6%. This study tested the model with the validation group, that was the main strength. The model succeeded to correctly predict, as the percentage of correct predictions was 97.1% of the cases. The AUC-ROC was 0.966 [0.899; 1.000] demonstrating the high accuracy for predicting late complications of MI in type 2 DM patients. The developed model would be useful for detecting cardiovascular complications of MI in type 2 DM patients and improving related diagnostic measures. However, there were several limitations associated with this study. Firstly, given that only type 2 DM patients with STEMI were enrolled, late complications of MI should be further assessed with a focus on testing among patients with STEMI without type 2 DM. Secondly, it would be interesting to examine cohorts of non-STEMI patients with and without type 2 DM, therefore further studies are required.

Conclusions

The study has found decreased levels of adropin and CTRP3 in type 2 DM patients on days 1-2 and 14 after MI. We have shown that integral assessment of adropin, CTRP 3, TC, TG, EF, LDL, LA, measured on the 14th day after MI in type 2 DM patients who underwent PCI, could predict late complications of MI. These results have proposed a new approach to risk stratification for late complications of MI in type 2 DM patients following successful coronary revascularization.

Author Contributions:

Conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing – original draft preparation, writing – review and editing, supervision, M.Y.K. The author has read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The author declares no conflict of interest regarding this article"

"The author declares that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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