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IMPACT OF TYPE 2 DIABETES MELLITUS ON LOW-GRADE INFLAMMATION IN PATIENTS WITH ST-ELEVATED MYOCARDIAL INFARCTION

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Abstract. Impact of type 2 diabetes mellitus on low-grade inflammation in patients with ST-elevated myocardial infarction. Bielinskyi M.V., Seredyuk N.M., Vytryhovskiy A.I., Koroliuk V.D. *Chronic low-grade inflammation has emerged as a hallmark of type 2 diabetes mellitus (T2DM), contributing significantly to the pathogenesis of various cardiovascular diseases, notably ST-elevated myocardial infarction (STEMI). The intricate interplay between inflammation and cardiovascular health in the context of T2DM has been a subject of intensive research in recent years. In particular, the development of various markers of inflammation has provided valuable tools for better understanding the complex relationship between low-grade inflammation and cardiovascular disease in T2DM. Elevated levels of these markers have been consistently associated with increased cardiovascular risk in patients with T2DM, indicating their potential as prognostic indicators. The aim of the study was to investigate the potential association between type 2 diabetes mellitus and low-grade inflammation markers in patients with ST-elevated myocardial infarction through a comparative analysis of systemic immune-inflammation indices, fibronectin, and soluble suppression of tumorogenesis-2 (sST2) levels in ST-elevated myocardial infarction patients with and without type 2 diabetes mellitus. We enrolled 158 patients diagnosed with STEMI who were admitted to the Ivano-Frankivsk Regional Clinical Cardiological Center. The study population was divided into three groups: 1 – consisting of 45 patients with both STEMI and T2DM, and the 2 – consisting of 34 patients with STEMI only, T2DM only group – 69 patients, Control group – 10 healthy patients. In summary, the findings from the study provide compelling evidence to support the notion that patients who suffer from both STEM and T2DM exhibit a more robust inflammatory response and higher platelet count, compared to those with STEMI alone. These results suggest that the presence of T2DM may exacerbate the pro-inflammatory and pro-thrombotic state that is typically associated with STEMI, thereby emphasizing the critical need for early intervention to prevent or mitigate inflammation and platelet activation in this particular patient population. Type 2 diabetes mellitus patients with ST-segment elevation myocardial infarction show higher levels of inflammation markers and fibronectin, indicating greater low-grade inflammation. Elevated levels of soluble suppression of tumorigenicity 2 suggest myocardial remodeling. Targeting low-grade inflammation could be a potential therapy for STEMI in T2DM patients.*

Реферат. Вплив цукрового діабету 2 типу на запалення низького ступеня в пацієнтів з інфарктом міокарда з елевацією сегмента ST. Бєлінський М.В., Середюк Н.М., Витриховський А.І., Королюк В.Д. *Хронічне запалення низького ступеня є характерною ознакою цукрового діабету 2 типу (ЦД2), що робить значний внесок у патогенез різних серцево-судинних захворювань, зокрема інфаркту міокарда з підйомом сегмента ST (ІМзпST). Складний взаємозв'язок між запаленням і серцево-судинним здоров'ям у контексті ЦД2 є предметом багатьох досліджень останніх років. Зокрема, розробка різних маркерів запалення надала цінні інструменти для кращого розуміння складного взаємозв'язку між запаленням низького ступеня та серцево-судинними захворюваннями при ЦД2. Підвищені рівні цих маркерів постійно асоціюються з підвищеним серцево-судинним ризиком у пацієнтів з ЦД2, що вказує на їх потенціал як прогностичних індикаторів. Метою дослідження було дослідити потенційний зв'язок між цукровим діабетом 2 типу та маркерами запалення низького ступеня в пацієнтів з інфарктом міокарда з підйомом сегмента ST шляхом порівняльного аналізу показників системного імунозапалення, рівня*

фібронектину та розчинної форми рецептор-стимулювального чинника зростання, що експресується геном 2 (sST2) у хворих на інфаркт міокарда з підйомом сегмента ST з цукровим діабетом 2 типу та без нього. Обстежено 158 пацієнтів з діагнозом ІМзеST, які перебували на стаціонарному лікуванні в Івано-Франківському обласному клінічному кардіологічному центрі. Досліджувані пацієнти були розподілені на три групи: 1 – 45 пацієнтів з ІМзеST та ЦД2, 2 – 34 пацієнти тільки з ІМзеST, група пацієнтів тільки з ЦД2 – 69, контрольна група – 10 здорових пацієнтів. Результати дослідження надають переконливі докази на користь того, що в пацієнтів, які страждають як на ІМзеST, так і на ЦД2, спостерігалася більш виражена запальна реакція і вища кількість тромбоцитів, ніж у пацієнтів з одним лише ІМзеST. Ці результати свідчать про те, що наявність ЦД2 може посилювати прозапальний і протромботичний стани, які зазвичай асоціюються з ІМзеST, тим самим підкреслюючи критичну необхідність раннього втручання для запобігання або пом'якшення запалення й активації тромбоцитів у цій конкретній популяції пацієнтів. Пацієнти з цукровим діабетом 2 типу, які перенесли інфаркт міокарда з підйомом сегмента ST, мали вищі рівні маркерів запалення та фібронектину, що свідчить про більш виражене запалення низького ступеня. Підвищений рівень розчинної форми рецептор-стимулювального чинника зростання, що експресується геном 2, свідчить про виражене ремоделювання міокарда. Вплив на запалення низького ступеня може бути потенційною ціллю лікування ІМзеST у пацієнтів з ЦД2.

ST-elevated myocardial infarction (STEMI), a severe form of heart attack, is a significant global health concern that leads to substantial morbidity and mortality. Timely detection and management of STEMI are vital for minimizing myocardial damage and improving patient outcomes [1].

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder that has been linked to the development of numerous cardiovascular diseases, including STEMI [2]. Patients with T2DM are at a higher risk of developing STEMI due to multiple factors, including insulin resistance, oxidative stress, and chronic low-grade inflammation. Chronic low-grade inflammation is now recognized as a hallmark of T2DM and is implicated in the pathogenesis of various chronic diseases, particularly cardiovascular disease [3].

Chronic low-grade inflammation is characterized by persistent, low-level immune system activation, leading to increased levels of cytokines and other inflammatory mediators [4]. The mechanisms connecting chronic low-grade inflammation and these diseases are complex and multifaceted, involving various pathways such as endothelial dysfunction, oxidative stress, and insulin resistance. However, the presence of low-grade inflammation is thought to contribute significantly to the development and progression of these conditions [5].

Low-grade inflammation has been recognized as a key factor in the pathogenesis of a variety of chronic diseases, including cardiovascular disease. Therefore, various markers of inflammation have been developed to better understand the role of low-grade inflammation in these conditions. These markers have been used to predict disease development and poor outcomes in various populations. Among the commonly used markers of low-grade inflammation are systemic immune-inflammation index (SII), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI), fibronectin, and soluble suppression of tumorigenicity 2 protein (sST2) [6].

Each of these markers provides a unique perspective on the state of the immune system, with some being more relevant in specific populations or for certain diseases. For instance, NLR and PLR reflect the balance between pro-inflammatory and anti-inflammatory cells in the bloodstream, while SII and SIRI provide a more comprehensive assessment of the systemic inflammatory state. Moreover, fibronectin and sST2 have shown to be useful markers of inflammation in the context of cardiovascular disease, specifically in identifying patients at high risk for adverse outcomes. As such, these markers may be valuable tools in identifying patients who require closer monitoring or more aggressive interventions to manage their disease [7].

The objective was to investigate the potential association between type 2 diabetes mellitus and low-grade inflammation markers in patients with ST-elevated myocardial infarction through a comparative analysis of systemic immune-inflammation indices, fibronectin, and soluble suppression of tumorogenesis-2 levels in ST-elevated myocardial infarction patients with and without type 2 diabetes mellitus.

MATERIALS AND METHODS OF RESEARCH

Study Design: This was a cross-sectional study conducted at Municipal Non-Profit Enterprise Ivano-Frankivsk Regional Clinical Cardiology Center of Ivano-Frankivsk Regional Council between January 2019 and December 2022.

Participants: A total of 158 participants were enrolled in the study, including 69 patients who had only T2DM (Group 1), 34 patients with STEMI but without T2DM (Group 2), 45 patients with STEMI and T2DM (Group 3), and 10 control subjects without STEMI or T2DM (Control Group). The research was approved by the Biomedical Ethics Committee of the Ivano-Frankivsk National Medical University (Protocol No. 111/19 dated 19.11.2019)

and was conducted in accordance with the written consent of the participants and in accordance with the principles of bioethics set forth in the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects and the Universal Declaration of Bioethics and Human Rights (UNESCO).

Inclusion criteria: Patients with verified STEMI (new ST segment elevation at the J point in at least two contiguous leads of ≥2 mm (0.2 mV) in men or 1.5 mm (0.15 mV) in women in leads V2-V3 and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads and troponin level >1 ng/ml), age – 18-80 years, glomerular filtration rate >30 ml/min/1.73 m^2.

Exclusion criteria: unstable angina pectoris, myocarditis, cardiomyopathy, progressive liver diseases, malignant neoplasms, alcoholism, pregnancy.

Sample Collection and Laboratory Analysis: Blood samples were collected from all participants and immediately transferred to EDTA-containing tubes. Plasma was separated by centrifugation at 3000 rpm for 10 minutes at 4°C and stored at -80°C until analysis.

The diagnoses of STEMI and T2DM were established based on the 2020 European Society of Cardiology Guidelines for the diagnosis and management of STEMI, and the consensus report by the American Diabetes Association and the European Association for the Study of Diabetes respectively [8, 9].

The full blood count was performed using the Medonic M-series M 32B (Boule Medical AB, Sweden). Biochemical tests were performed on the SAT 450 (AMS Srl, Italy). ELISA tests were perfomed using the LabLine-020 (WestMedica, Austria)

We calculated inflammation indices by the following formulas [10]:

Systemic immune-inflammation index (SII) = = (Neutrophils x Platelets) / Lymphocytes;

Neutrophil-to-lymphocyte ratio (NLR) = = Neutrophils / Lymphocytes;

Platelet-to-lymphocyte ratio (PLR) = = Platelets / Lymphocytes;

Systemic immune-inflammation index (SIRI) = = (Neutrophils x Monocytes) / Lymphocytes;

Aggregate index of systemic inflammation (AISI) = = (Neutrophils x Platelets x Monocytes) / Lymphocytes

Fibronectin Measurements: Fibronectin levels were measured in plasma samples using a sandwich Human Fibronectin ELISA Kit (ab219046, Abcam, Italy), following the manufacturer's instructions. Briefly, microplate wells were coated with monoclonal antibodies against human fibronectin. The plasma samples were then added to the wells and incubated for 2 hours. After washing the wells, biotinylated monoclonal antibodies against fibronectin were added to each well, followed by the addition of streptavidin-conjugated horseradish peroxidase. The plates were incubated for an additional hour, and then the substrate solution was added to each well. The reaction was stopped, and the absorbance was measured at 450 nm using a microplate reader. The concentration of fibronectin in the samples was determined by comparing the optical density of the samples to the standard curve generated using known concentrations of fibronectin.

sST2 Measurements: sST2 levels were measured in plasma samples using a sandwich Human sST2 ELISA Kit (IL1RL1) (ab254505, Abcam, Italy), following the manufacturer's instructions. Briefly, microplate wells were coated with monoclonal antibodies against human sST2. The plasma samples were then added to the wells and incubated for 2 hours. After washing the wells, biotinylated monoclonal antibodies against sST2 were added to each well, followed by the addition of streptavidin-conjugated horseradish peroxidase. The plates were incubated for an additional hour, and then the substrate solution was added to each well. The reaction was stopped, and the absorbance was measured at 450 nm using a microplate reader. The concentration of sST2 in the samples was determined by comparing the optical density of the samples to the standard curve generated using known concentrations of sST2.

Quality Control: Internal and external quality control measures were taken to ensure the accuracy and precision of the laboratory tests. Internal quality control was performed using control samples with known concentrations of fibronectin and sST2, and the results were monitored over time to ensure consistent performance of the assays. External quality control was performed by participating in the External Quality Assurance Scheme for sST2 and fibronectin testing.

The data analysis for this study was carried out using IBM SPSS Statistics version 26.0 software (License QA2WSWS3QTR5TG6Y7TG6RF59JUY7H, Product Key: AQ2WS89K09IK98J7H4S3WSF5G6). The study variables were categorized into two groups – categorical variables and continuous variables. Categorical variables, such as gender and the presence of comorbidities, were presented as frequencies and percentages, and were compared between the groups using the $\chi 2$ test and Fisher's exact test, where appropriate. Continuous variables, such as age and laboratory results, were expressed as median with 25th to 75th interquartile range (IQR 25-75%). To assess the normal distribution of the variables, the Kolmogorov-Smirnov and Shapiro-Wilk tests were

used. The Mann-Whitney test was used. To determine the diagnostic accuracy of the markers of interest, receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was calculated. Logistic regression analysis was performed to evaluate the independent impact of each study variable on the study outcome with 95% confidence interval (CI 95%). All statistical analyses used a two-tailed significance test, with a p-value of less than 0.05 considered statistically significant and were based on Antomonov M.Y. et al [11].

RESULTS AND DISCUSSION

The Table 1 displays the results of a study comparing several biomarkers in three groups of patients.

The age of the participants was significantly different between the groups, with the STEMI group being the oldest (65.50 [58.75;72.00] years) followed by the STEMI+T2DM group (mean age: 61.00 [54.00;68.50]), T2DM only group – 59.00 [49.00;67.00], and the Control group being the youngest (mean age: 55.50 [51.00;59.00]). The Chi-square test was conducted, which aimed to test the independence of two variables. The test resulted in a Pearson Chi-Square value of 2.86 with 3 degrees of freedom, and a corresponding asymptotic significance (2-sided) of 0.414. There were no significant differences in the sex distribution among the groups.

When comparing the two patient groups, the results showed some notable differences. First, the platelet count was significantly higher in the STEMI+T2DM group compared to the STEMI group, as well as the T2DM only and Control groups. This suggests that T2DM may be associated with an increased platelet response to inflammation, which could contribute to a higher risk of thrombosis and adverse outcomes in these patients.

In addition, the SII and NLR were significantly higher in the STEMI+T2DM group compared to the STEMI, T2DM only and Control groups, indicating a stronger inflammatory response in patients with both conditions. This could be due to the presence of T2DM, which is known to cause chronic inflammation and endothelial dysfunction, leading to increased cardiovascular risk. Also, patients without STEMI, but with T2DM had higher levels of these indices compared to Control group.

On the other hand, there were no significant differences in lymphocyte count between the STEMI and STEMI+T2DM groups. This may suggest that T2DM does not have a significant impact on the lymphocyte response to inflammation in the setting of STEMI.

Furthermore, while the SIRI and AISI were significantly higher in both patient groups compared to the T2DM only and Control groups, there were no significant differences between the STEMI and STEMI+T2DM groups. This suggests that the systemic immune response to STEMI may be similar in patients with and without T2DM.

Lastly, fibronectin and sST2, markers of cardiac fibrosis and inflammation, respectively, were significantly higher in both patient groups compared to the Control group, with no significant differences between the STEMI and STEMI+T2DM groups. This indicates that the inflammatory and fibrotic response to STEMI may be similar in patients with and without T2DM. Also, patients with T2DM only had higher values of these markers, what suggests, that T2DM alone leads to the myocardial damage without STEMI.

In summary, the study provides evidence that patients with STEMI+T2DM have a stronger inflammatory response and higher platelet count compared to patients with STEMI alone. This suggests that T2DM may exacerbate the pro-inflammatory and prothrombotic state associated with STEMI, highlighting the need for early intervention to prevent or reduce inflammation and platelet activation in these patients.

The results of the univariable regression analysis comparing the two patient groups (Table 2), STEMI and STEMI + T2DM, showed some interesting findings. First, age was not a significant predictor of group membership, indicating that the age difference observed between the two groups in the descriptive statistics was not a confounding variable. Second, male sex was not a significant predictor of group membership, suggesting that the sex distribution was similar between the two groups.

Interestingly, SII was a significant predictor of group membership, with the STEMI + T2DM group having a higher SII value than the STEMI group. This finding suggests that the systemic inflammatory response is stronger in patients with both STEMI and T2DM compared to those with STEMI alone. NLR, on the other hand, was not a significant predictor of group membership, indicating that the neutrophil-to-lymphocyte ratio did not differ significantly between the two groups.

Another significant predictor of group membership was fibronectin, a marker of cardiac fibrosis. The STEMI + T2DM group had a significantly higher fibronectin level than the STEMI group, indicating that these patients may have more severe cardiac fibrosis. Similarly, sST2, a marker of inflammation, was also a significant predictor of group membership, with the STEMI + T2DM group having a higher sST2 level than the STEMI group. This finding suggests that patients with both STEMI and T2DM have a higher level of inflammation compared to those with STEMI alone.

Table 1

General characteristics of study population

Variable	Control (n=10)	T2DM (Group 1) (n=69)	STEMI (Group 2) (n=34)	STEMI + T2DM (Group 3) (n=45)	p value (Kruskall-Wallis)
Age (years)	55.5 [51.00;59.00]	59.00 [49.00;67.00] p1-p2=0.330	65.50 [58.75;72.00] p1-p3=0.01	61.00 [54.00;68.50] p1-p4=0.028 p3-p4 =0.201	0.012
Male sex	6 (60.0%)	36 [50.9 %] p1-p2=0.518	14 (41.2%) p1-p3=0.245	16 (35.6%) p1-p4=0.143 p3-p4=0.391	0.414*
Leukocytes (10^9/L)	5.27 [4.82;5.68]	6.76 [6.46;6.99] p1-p2<0.001	8.90 [7.93;9.72] p1-p3<0.001	10.95 [10.27;11.99] p1-p4<0.001 p3-p4<0.001	<0.001
Neutrophils (10^9/L)	3.85 [3.63;4.13]	5.21 [4.94;5.53] p1-p2<0.001	7.36 [6.50;8.22] p1-p3<0.001	9.44 [8.78;10.35] p1-p4<0.001 p3-p4<0.001	<0.001
Lymphocytes (10^9/L)	1.20 [0.79;1.52]	1.25 [1.11;1.41] p1-p2=0.507	1.09 [0.87;1.27] p1-p3=0.464	1.19 [1.07;1.39] p1-p4=0.719 p3-p4=0.011	0.003
Monocytes (10^9/L)	0.18 [0.11;0.32]	0.23 [0.16;0.31] p1-p2=0.493	0.36 [0.21;0.45] p1-p3=0.012	0.29 [0.21;0.41] p1-p4=0.106 p3-p4=0.237	0.002
Platelets (10^9/L)	241.5 [212.25;272.00]	253.90 [245.20;268.50] p1-p2=0.216	230.00 [213.75;244.00] p1-p3=0.261	277.00 [248.50;302.00] p1-p4=0.007 p3-p4<0.001	<0.001
SII	779.45 [636.55;1063.13]	1132.46 [935.36;1261.38] p1-p2=0.008	1504.85 [1342.00;1943.38] p1-p3<0.001	2134.50 [1838.45;2453.25] p1-p4<0.001 p3-p4<0.001	<0.001
PLR	178.50 [166.88;291.03]	199.92 [180.34;241.80] p1-p2=0.507	213.25 [187.28;275.85] p1-p3=0.447	230.05 [189.05;262,65] p1-p4=0.230 p3-p4=0.614	0.069
NLR	3.25 [2.83;4.43]	4.27 [3.58;4.89] p1-p2=0.025	6.30 [5.80;8.60] p1-p3<0.001	7.80 [7.10;8.60] p1-p4<0.001 p3-p4=0.006	<0.001
SIRI	0.55 [0.38;1.48]	0.97 [0.73;1.31] p1-p2=0.180	2.25 [1.65;3.03] p1-p3<0.001	2.20 [1.40;3.40] p1-p4=0.001 p3-p4=0.953	<0.001
AISI	130.05 [85.58;380.28]	245.38 [187.09;339.08] p1-p2=0.125	471.9 [375.5;686.15] p1-p3<0.001	574.9 [362.55;953.2] p1-p4<0.001 p3-p4=0.239	<0.001
Fibronectin (ng/mL)	1.23 [1.20;1.24]	1.42 [1.36;1.51] p1-p2<0.001	2.34 [2.26;2.90] p1-p3<0.001	2.91 [2.85;2.98] p1-p4<0.001 p3-p4<0.001	<0.001
sST2 (ng/mL)	15.45 [13.68;17.88]	17.91 [17.11;18.68] p1-p2=0.011	21.01 [19.79;22.04] p1-p3<0.001	22.95 [22.52;23.67] p1-p4<0.001 p3-p4<0.001	<0.001

Notes: p1-p2 – statistical difference between control group and T2DM group; p1-p3 – statistical difference between control group and STEMI group; p1-p4 – statistical difference between control group and STEMI + T2DM group; p3-p4 – statistical difference between STEMI group and STEMI + T2DM group; * – chi-square test instead of Kruskall-Wallis test.

On the other hand, PLR, SIRI, and AISI were not significant predictors of group membership, indicating that these variables did not differ significantly between the two groups. Overall, the results of the

univariable regression analysis suggest that patients with both STEMI and T2DM have a stronger systemic inflammatory response, more severe cardiac fibrosis, and higher levels of inflammation compared to those with STEMI alone. These findings may have important clinical implications, as they highlight the need for tailored treatment approaches for patients with STEMI and T2DM to reduce inflammation and prevent adverse outcomes. Further research is needed to confirm these findings and explore the underlying mechanisms of these differences between the two patient groups.

Table 2

Univariable regression analysis of study population

Variable	Odds ratio (CI 95%)	p value
Age (years)	**0.953 (0.909-0.998)**	**0.041**
Male sex	**1.186 (0.534-2.633)**	**0.675**
Multivessel disease	**2.289 (1.344-3.898)**	**0.002**
Body-mass index (kg/m^2)	**1.084 (1.021-1.152)**	**0.008**
Obesity	**3.202 (1.273-8.055)**	**0.013**
Leukocytes (10^9/L)	**5.110 (2.843-9.183)**	**<0.001**
Neutrophils (10^9/L)	**6.967 (3.512-13.822)**	**<0.001**
Lymphocytes (10^9/L)	**25.145 (3.269-193.390)**	**0.002**
Monocytes (10^9/L)	**0.457 (0.040-5.183)**	**0.527**
Platelets (10^9/L)	**1.057 (1.034-1.080)**	**<0.001**
SII	**1.004 (1.002-1.005)**	**<0.001**
PLR	**1.001 (0.993-1.008)**	**0.859**
NLR	**1.647 (1.138-2.382)**	**0.008**
SIRI	**1.138 (0.852-1.520)**	**0.382**
AISI	**1.001 (1.000-1.003)**	**0.037**
Fibronectin (ng/mL)	**4.524 (1.646-12.430)**	**0.003**
sST2 (ng/mL)	**3.594 (2.203-5.864)**	**<0.001**

Note. Regression of each studied variable as dependent variable and group membership (STEMI or STEMI + T2DM) as independent variable.

The results of the ROC analysis comparing STEMI + T2DM and STEMI alone (Table 3, Figure) showed that several markers had good diagnostic accuracy in distinguishing between the two groups. The AUC for SII was 0.830, indicating a high level of discrimination between the two groups. The AUC for fibronectin and sST2 were also relatively high, with values of 0.744 and 0.873, respectively. These results suggest that these markers may be useful in identifying patients with STEMI+T2DM compared to those with STEMI alone.

In contrast, the AUC values for PLR, NLR, SIRI, and AISI were relatively low, with values ranging from 0.496 to 0.681. These results suggest that these markers may not be as useful in distinguishing between STEMI + T2DM and STEMI alone.

The finding that SII had the highest AUC value suggests that it may be a particularly useful marker for identifying patients with STEMI + T2DM. SII is a measure of both platelet and leukocyte counts and has been shown to be a marker of systemic inflammation and a predictor of adverse cardiovascular outcomes. The high diagnostic accuracy of fibronectin and sST2 also suggests that these markers may be useful in identifying patients with STEMI + T2DM.

It is important to note that while these markers may have diagnostic utility in distinguishing between STEMI + T2DM and STEMI alone, they should not be used in isolation to diagnose or manage these conditions. The results of this study provide preliminary evidence regarding the diagnostic utility of these markers and further research is needed to confirm these findings in larger and more diverse patient populations.

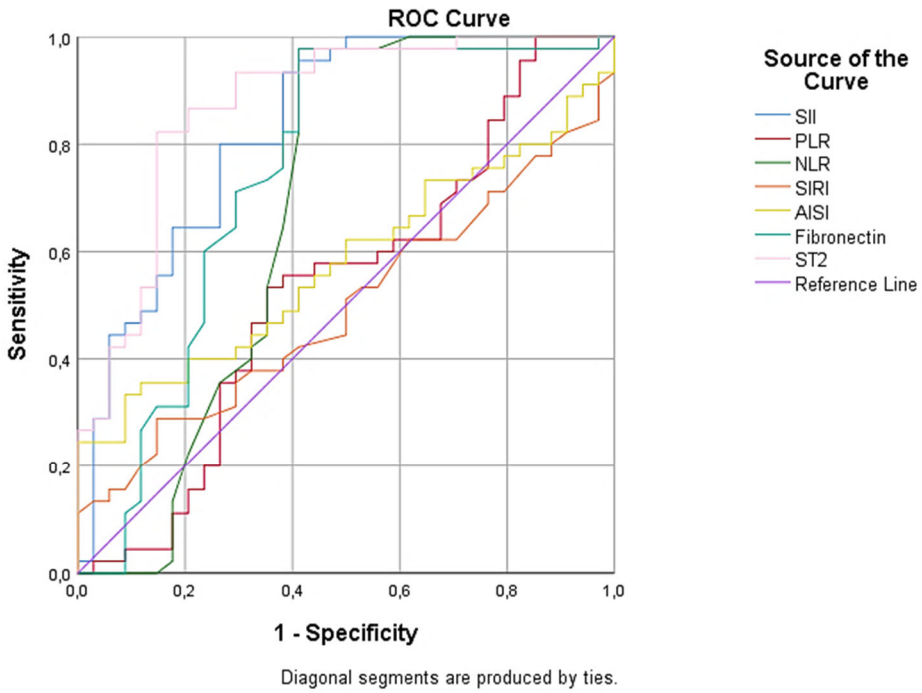
Table 3

ROC analysis for markers of inflammation

Variable	AUC (CI 95%)	p value
SII	**0.806 (0.710-0.903)**	**<0.001**
PLR	**0.515 (0.394-0.636)**	**0.801**
NLR	**0.675 (0.536-0.814)**	**0.002**
SIRI	**0.521 (0.417-0.624)**	**0.717**
AISI	**0.607 (0.509-0.705)**	**0.064**
Fibronectin	**0.638 (0.518-0.759)**	**0.017**
sST2	**0.862 (0.786-0.938)**	**<0.001**

Note. Each studied variable was test variable and group membership (STEMI or STEMI + T2DM) was state variable.

The findings of this study are consistent with previous research that has identified an association between T2DM and increased inflammation and oxidative stress in patients with cardiovascular disease. Specifically, our results show that patients with STEMI and T2DM have higher levels of sST2, fibronectin, and inflammation indices than those with STEMI alone. These findings are in line with previous studies that have demonstrated higher levels of high-sensitivity C-reactive protein in patients with T2DM and acute coronary syndrome compared to those without T2DM [12].



ROC curve for inflammation indices, fibronectin and sST2

Moreover, our study adds to the growing body of evidence supporting the use of inflammation indices as predictors of cardiovascular events and outcomes. Our results suggest that the SII is a reliable method for evaluating STEMI + T2DM. This is consistent with the study by Ya-Ling Yang et al., which found that the SII was a stronger predictor of major cardiovascular events in patients with coronary artery disease than traditional risk factors [13].

The study by Z. Ji et al. also supports our findings, as they found that the NLR was an independent predictor of major adverse cardiac events in patients with STEMI, with higher hazard ratios for death in patients with T2DM compared to those without. Similarly, K. Han et al. found that the SIRI was associated with a higher risk of major adverse cardiovascular events in patients with T2DM [14].

Several studies have investigated the use of inflammation and oxidative stress markers as predictors of cardiovascular events and outcomes in patients with diabetes and acute coronary syndromes. In a study by V.K. Tashchuk SIRI and NLR were found to be suitable markers for identifying the risk of adverse cardiovascular events and determines measures to regulate the activity of the inflammatory process in STEMI. However, in our study, we found that these indices were less reliable in STEMI patients with concomitant T2DM [15].

Similarly, in a study by M. Celik et al., PLR, NLR, and SII were found to be significant independent predictors of the occurrence of no-reflow phenomenon in STEMI patients. The SII was found to have a better predictive capability for no-reflow compared to NLR and PLR in STEMI patients [16].

Moreover, a review by Y. Kayama et al. suggested that patients with T2DM and coronary artery disease had higher levels of oxidative stress markers compared to those without T2DM, indicating that T2DM may cause an increase in oxidative stress that contributes to the development of cardiovascular disease. Overall, these studies highlight the importance of monitoring inflammation and oxidative stress markers in patients with T2DM and acute coronary syndromes to predict and prevent cardiovascular events [17].

In a study conducted by I. Valiente-Alandi et al, they investigated the use of an inhibitor for fibronectin polymerization as a potential therapeutic strategy for treating cardiac fibrosis and heart failure. The study found that administering a fibronectin polymerization inhibitor (pUR4) in vitro reduced the deposition of fibronectin and collagen in cardiac myofibroblasts, leading to decreased cell proliferation, migration, and extracellular matrix deposition. Furthermore, in vivo administration of pUR4 for 7 days after an ischemia / reperfusion injury resulted in improved myocardial function, reduced cardiac remodeling, and fibrosis. These findings suggest that inhibiting fibronectin polymerization may be a promising approach for treating heart failure [18].

Another study highlighted the role of calprotectin, an inflammatory marker, in patients with acute myocardial infarction and T2DM. They found that high concentrations of calprotectin were associated with disturbances in carbohydrate homeostasis and insulin resistance, which aligns with our findings of altered inflammation indices in STEMI patients with T2DM [19].

A third study focused on the biomarker sST2 in patients with acute myocardial infarction. They found that higher levels of sST2 were associated with worse cardiac remodeling, particularly in women and patients with reduced glomerular filtration rate. This supports our observation of higher sST2 levels in patients with STEMI and T2DM [20].

Lastly, a review emphasized the importance of biomarkers, including sST2, in diagnosing and managing heart failure, arterial hypertension, and T2DM. This underscores the potential clinical relevance of our findings regarding sST2 and inflammation indices in patients with STEMI and T2DM [21].

The results of our study are in agreement with the previous findings that T2DM is associated with increased levels of inflammation and oxidative stress, which may lead to the worse prognosis of cardiovascular diseases. This suggests that inhibiting the production of reactive oxygen species and inflammation could be a potential therapeutic strategy for reducing the risk of cardiovascular disease in individuals with T2DM.

As we look towards the future of research in managing inflammation in patients STEMI and T2DM, the potential therapeutic avenues are broadening. The addition of adenosine and quercetin to the standard treatment protocol is one such promising direction. These two agents, already known for their anti-inflammatory properties, could improve the way we handle inflammation in these patient cohorts. Adenosine, a purine nucleoside that has demonstrated cardioprotective and anti-inflammatory properties in several studies, could potentially be used to dampen inflammation post-STEMI, which can mitigate further damage to the myocardium. Quercetin, a plant flavonoid, has also shown potential in decreasing inflammation and insulin resistance, crucial in T2DM patients. However, more comprehensive and high-quality research is needed to establish the optimal doses, administration methods, and timing of these agents, as well as to explore their long-term effects and potential side effects. As we enter this era of precision medicine, the exploration of multi-drug

strategies, including adenosine and quercetin, could lead us to more effective, personalized treatment plans for patients with STEMI and T2DM.

CONCLUSIONS

1. Individuals with both ST-segment elevation myocardial infarction and type 2 diabetes had significantly higher levels of systemic immune-inflammation indices and fibronectin compared to those with ST-segment elevation myocardial infarction alone. This suggests that there is a higher degree of low-grade inflammation in this population, which may contribute to the development of ST-segment elevation myocardial infarction in individuals with type 2 diabetes.
2. The levels of soluble suppression of tumorigenicity 2, a marker of myocardial stress, were also found to be significantly elevated in ST-segment elevation myocardial infarction patients with type 2 diabetes, indicating more severe pathological changes in the myocardium compared to those without diabetes.
3. These findings provide concrete evidence that low-grade inflammation plays a significant role in the development of ST-segment elevation myocardial infarction in individuals with type 2 diabetes, and support the need for developing strategies to reduce low-grade inflammation as a potential therapeutic target for this population to improve their cardiovascular health and prognosis.

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Belinsky M.V. – conceptualization, methodology, formal analysis, research, writing – original draft;

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Vitrykhovskyi A.I. – conceptualization, methodology, writing – review and editing;

Koroliuk V.D. – methodology, research.

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