ASSOCIATION OF MARKERS OF LOW-GRADE INFLAMMATION IN PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION WITH TYPE 2 DIABETES MELLITUS: A COMPARATIVE ANALYSIS

M.V. Bielinskyi, N.M. Seredyuk

Key words: myocardial infarction, diabetes mellitus, inflammation, atherosclerosis, ST2, fibronectin.

Abstract. Introduction. ST-elevated myocardial infarction (STEMI) remains a significant global health issue and early recognition and management are crucial for reducing damage and improving patient outcomes. Type 2 diabetes mellitus (T2DM), a common metabolic disorder, is linked to STEMI due to factors like insulin resistance, oxidative stress, and low-grade inflammation.

Aim. To determine the relationship between T2DM and low-grade inflammation markers in patients with STEMI by comparing the levels of systemic immune-inflammation indices, fibronectin, and soluble sST2 in STEMI patients with and without T2DM.

Materials and methods. We enrolled 131 patients diagnosed with STEMI and T2DM who were admitted to the Ivano-Frankivsk Regional Clinical Cardiological Center. The study population was divided into two groups: 1st - consisting of 97 patients with both STEMI and T2DM, and the 2nd - consisting of 34 patients with STEMI only.

Results. The Systemic immune-inflammation index (SII) (2074.50 (1838.45;2331.05) vs 1504.85 (1342.00;1943.38)), Neutrophil-to-lymphocyte ratio (NLR) (7.80 (7.10;8.60) vs 6.30 (5.80;8.60), p=0.002), and Aggregate index of systemic inflammation (AISI) (699.45±433.53 vs 531.80±217.27, p=0.033) were significantly higher in patients with STEMI and T2DM compared to patients with STEMI alone. Also, the levels of fibronectin (2.76±0.33 vs 2.53±0.44 ng/mL, p=0.002) and sST2 (23.06±1.19 vs 20.93±1.63 ng/mL, p=0.000) were higher in patients with STEMI and T2DM compared to patients with STEMI alone. The Platelet-to-lymphocyte ratio (PLR) (226.01±48.58 vs 224.19±59.61) and Systemic immune-inflammation index (SIRI) (2.59±1.54 vs 2.34±0.98) were not significantly different between the two groups. SII showed a very significant association with the 1st group (OR = 1.004 (1.002-1.005), p<0.001), NLR showed a significant positive association with the 1st group (OR = 1.647, 95% CI = 1.138-2.382, p = 0.008). The other markers showed no significant associations. Fibronectin (OR = 4.524, 95% CI = 1.646-12.430, p = 0.003) and sST2 (OR = 3.594, 95% CI = 2.203-5.864, p < 0.001) were both positively associated with the 1st group.

Conclusions. Factors such as age, BMI, and markers of inflammation (SII, sST2, NLR) were significantly linked to T2DM in patients with STEMI. sST2 and SII were better predictors of T2DM compared to other markers of inflammation. These results emphasize the importance of considering multiple factors in evaluating T2DM risk in STEMI patients.
Introduction. ST-elevation myocardial infarction (STEMI) remains a significant contributor to global morbidity and mortality. Prompt recognition and management of STEMI are crucial in reducing the extent of myocardial damage and improving patient outcomes [1].

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder that has been implicated in the development of a range of cardiovascular diseases, including STEMI [2]. Patients with T2DM are known to have a higher risk of developing STEMI, and this risk is now recognized as a hallmark of T2DM and has been implicated in the development of a range of chronic conditions, including cardiovascular disease [3].

Low-grade inflammation is a state of chronic, low-grade activation of the immune system, which is associated with elevated levels of cytokines and other inflammatory mediators [4]. The underlying mechanisms linking low-grade inflammation and these diseases are complex and multifactorial, but the presence of low-grade inflammation has been implicated in the development and progression of these conditions [5].

In order to better understand the role of low-grade inflammation in these diseases, various markers of inflammation have been developed and studied. These markers reflect the systemic inflammatory state and have been used as predictors of disease and poor outcomes in various populations. Some commonly used markers of low-grade inflammation include 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 different perspective on the state of the immune system, and some may be more relevant in certain populations or for specific diseases. For example, 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. Similarly, fibronectin and soluble sST2 have been shown to be useful markers of inflammation in the context of cardiovascular disease [8].

Aim. To determine the relationship between T2DM and low-grade inflammation markers in patients with STEMI by comparing the levels of systemic immune-inflammatory indices, fibronectin, and soluble sST2 in STEMI patients with and without T2DM.

Materials and methods. In this study, we enrolled 131 patients diagnosed with STEMI and T2DM who were admitted to the Ivano-Frankivsk Regional Clinical Cardiological Center. The study population was divided into two groups: 1st - consisting of 97 patients with both STEMI and T2DM, and the 2nd - consisting of 34 patients with STEMI only. All patients underwent revascularization. Data was collected from medical records, including demographic information, clinical and anthropometric characteristics, laboratory results, and imaging findings. All patients provided informed consent in accordance with the principles of the Declaration of Helsinki.

The diagnoses of STEMI and T2DM were established based on the 2020 European Society of Cardiology (ESC)
Guidelines for the diagnosis and management of STEMI, and the consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) respectively [9,10].

Body Mass Index (BMI) was calculated by dividing a person's weight in kilograms by the square of their height in meters. The formula is:

\[ \text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2} \]

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).

Fibronectin was measured using the LabLine-020 (WestMedica, Austria) and the Human Fibronectin ELISA Kit (ab219046, Abcam, Italy). Soluble sST2 was measured using the Human sST2 ELISA Kit (IL1RL1) (ab254505, Abcam, Italy).

We calculated inflammation indices by the following formulas [7]:

- **Systemic immune-inflammation index (SII)** =
  \[ \text{Neutrophils} \times \text{Platelets} / \text{Lymphocytes} \]

- **Neutrophil-to-lymphocyte ratio (NLR)** = \[ \text{Neutrophils} / \text{Lymphocytes} \]

- **Platelet-to-lymphocyte ratio (PLR)** = \[ \text{Platelets} / \text{Lymphocytes} \]

- **Aggregate index of systemic inflammation (AISI)** = \[ \text{Neutrophils} \times \text{Platelets} \times \text{Monocytes} / \text{Lymphocytes} \]

The statistical analysis for this study was performed using the IBM SPSS Statistics version 26.0 software. The study variables were categorized into two groups - categorical variables and continuous variables. Categorical variables, such as gender and presence of comorbidities, were expressed as frequencies and percentages and were compared between the groups using the χ² test and Fisher's exact test where appropriate. Continuous variables, such as age and laboratory results, were expressed as mean ± standard deviation or median with 25th to 75th interquartile range (IQR 25-75%). To determine the normal distribution of these variables, the Kolmogorov-Smirnov and Shapiro-Wilk tests were applied. Normally distributed continuous variables were compared between the groups using the independent t-test, while non-normally distributed continuous variables were compared using the Mann-Whitney test. Receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was calculated to determine the diagnostic accuracy of the markers of interest. Logistic regression analysis was performed to assess the independent impact of each study variable on the study outcome. All results were reported with a p-value of less than 0.05 considered statistically significant.

**Results.** In this study, a total of 97 patients with STEMI and T2DM and 34 patients with STEMI were analyzed. The results showed that patients with STEMI and T2DM were significantly younger (60.96±8.64 years) compared to those with STEMI alone (64.53±8.35 years, p=0.038). The prevalence of multivessel disease (atherosclerotic lesions in >1 coronary artery) was higher in patients with STEMI and T2DM (73.2%) compared to patients with STEMI alone (41.2%, p=0.003). Additionally, patients with STEMI and T2DM had a higher BMI (31.06±8.45 kg/m²) and a higher prevalence of obesity (45.4%) compared to patients with STEMI alone (26.56±7.10 kg/m² and 20.6% respectively, p=0.006 and 0.014). The results showed that patients with STEMI and T2DM had higher levels of leukocytes (10.86 (10.27;11.69) vs 8.90 (7.93;9.72) 10⁹/L, p<0.001), neutrophils (9.34 (8.82;9.99) vs 7.36 (6.50;8.22) 10⁹/L, p<0.001), and platelets (269.00 (247.00;291.00) vs 230.00 (213.75;244.00) 10⁹/L, p<0.001), and lower levels of lymphocytes (1.20 (1.08;1.36) vs 1.09 (0.87;1.27) 10⁹/L, p=0.005). It was also found, that the SII (2074.50 (1838.45;2331.05) vs 1504.85 (1342.00;1943.38)), NLR (7.80 (7.10;8.60) vs 6.30 (5.80;8.60), p=0.002), and AISI (699.45±433.53 vs 531.80±217.27, p=0.033) were significantly higher in patients with STEMI and T2DM compared to patients with STEMI alone. Also, the levels of fibronectin (2.76±0.33 vs 2.53±0.44 ng/mL, p=0.002) and sST2 (23.06±1.19 vs 20.93±1.63 ng/mL, p=0.000) were higher in patients with STEMI and T2DM compared to patients with STEMI alone. The PLR (226.01±48.58 vs 224.19±59.61) and SIRI (2.59±1.54 vs 2.34±0.98) were not significantly different between the two groups (table 1). Age was found to be significantly associated with the 1st group, with a decrease in odds of occurrence with decreasing age (odds ratio (OR) = 0.953, 95% confidence interval [CI] = 0.909-0.998, p = 0.041). Male sex did not show a significant association with the 1st group (OR = 1.186, 95% CI = 0.534-2.63, p = 0.675). Multivessel disease was positively associated with the 1st group (OR = 2.289, 95% CI = 1.344-3.898, p = 0.002).

BMI was also significantly associated with the 1st group, with an increase in odds of occurrence with increasing BMI (OR = 1.084, 95% CI = 1.021-1.152, p = 0.008). Obesity showed a stronger association with the 1st group (OR = 3.202, 95% CI = 1.273-8.055, p = 0.013). Leukocytes, neutrophils, lymphocytes, monocytes, and platelets, with leukocytes (OR = 5.110, 95% CI = 2.843-9.183, p < 0.001), neutrophils (OR = 6.967, 95% CI = 3.512-13.822, p < 0.001), and lymphocytes (OR = 25.145, 95% CI = 3.269-193.390, p = 0.002) showed significant positive associations with the 1st group, while monocytes did not (OR = 0.457, 95% CI = 0.040-5.183, p = 0.527). Platelets were also positively associated with the 1st group (OR = 1.057, 95% CI = 1.034-1.080, p < 0.001).

Of analyzed markers of inflammation, SII showed a very significant association with the 1st group (OR = 1.004 (1.002-1.005), p<0.001), NLR showed a significant positive association with the 1st group (OR = 1.647, 95% CI = 1.138-2.382, p = 0.008). The other markers showed no significant associations. Finally, fibronectin (OR = 4.524, 95% CI = 1.646-12.430, p = 0.003) and sST2 (OR = 3.594, 95% CI = 2.203-5.864, p < 0.001) were both positively associated with the 1st group.

These results suggest that the presence of these factors may contribute to the development of STEMI + T2DM. The results of the univariable regression analysis are presented in table 2.

The results of the ROC analysis in table 3 showed the...
effectiveness of various markers of inflammation in predicting the presence of T2DM in patients with STEMI.

The findings of the study indicate that among the markers of inflammation analyzed, SII, sST2, and Fibronectin were found to have significant statistical differences in their ability to predict the presence of T2DM in STEMI patients. In particular, SII was found to be highly accurate, with an AUC of 0.806 (CI 95%: 0.710-0.903) and a p value less than 0.001. This suggests that SII may be a valuable tool for identifying patients with T2DM in the setting of STEMI. sST2 was similarly effective, with an AUC of 0.862 (CI 95%: 0.786-0.938) and a p value less than 0.001. Meanwhile, Fibronectin showed moderate accuracy, with an AUC of 0.638 (CI 95%: 0.518-0.759) and a p value of 0.017. The results also indicate that NLR and AISI had moderate accuracy, with AUCs of 0.675 (CI 95%: 0.536-0.814) and 0.607 (CI 95%: 0.509-0.705), respectively, and p values of 0.002 and 0.064 (fig.1, fig.2).

**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC (CI 95%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SII</td>
<td>0.806 (0.710-0.903)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLR</td>
<td>0.515 (0.394-0.636)</td>
<td>0.801</td>
</tr>
<tr>
<td>NLR</td>
<td>0.675 (0.536-0.814)</td>
<td>0.002</td>
</tr>
<tr>
<td>SIRI</td>
<td>0.521 (0.417-0.624)</td>
<td>0.717</td>
</tr>
<tr>
<td>AISI</td>
<td>0.607 (0.509-0.705)</td>
<td>0.064</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>0.638 (0.518-0.759)</td>
<td>0.017</td>
</tr>
<tr>
<td>sST2</td>
<td>0.862 (0.786-0.938)</td>
<td>&lt;0.001</td>
</tr>
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</table>

The markers PLR and SIRI had lower AUC values and p values, indicating that they were not as effective in predicting the presence of STEMI + T2DM. The AUC for PLR was 0.515 (CI 95%: 0.394-0.636), and the p value was 0.801, indicating that it had limited accuracy in distinguishing between the two groups. The AUC for SIRI was 0.521 (CI 95%: 0.417-0.624), and the p value was 0.717, indicating that it had limited accuracy in distinguishing between the two groups.

**Discussion.** In the current study, the results showed that patients with STEMI and T2DM had higher levels of sST2, fibronectin, and indices of inflammation compared to patients with STEMI alone. This is in line with previous studies that have shown an increased incidence of inflammation and oxidative stress in patients with T2DM and cardiovascular disease.

A study by C. Lucci et al. found that patients with T2DM and acute coronary syndrome had higher levels of high-sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation, compared to those without T2DM (5.32 vs. 3.24 mg/L; P < 0.0001). The results of this study suggest that T2DM is associated with a state of chronic
low-grade inflammation, which may contribute to the increased risk of cardiovascular disease in this population [11].

Several studies have investigated the use of inflammation indices as predictors of cardiovascular events and outcomes. For instance, a study by Z. Ji et al. found that NLR was an independent predictor of major adverse cardiac events in patients with STEMI (the hazard ratio (HR) for death in patients with or without diabetes were 6.586 and 3.375, respectively), while another study by K. Han et al. found that SIRI was associated with a higher risk of major adverse cardiovascular events in patients with T2DM [12].

A study by Ya-Ling Yang et al found that the SII was a stronger predictor of major cardiovascular events in patients with Coronary Artery Disease (CAD) compared to traditional risk factors. An optimal SII cut-off point was identified and verified in two CAD patient cohorts. The
results showed that a higher SII score was independently linked to increased risk of cardiac death (HR: 2.02), nonfatal myocardial infarction (HR: 1.42), nonfatal stroke (HR: 1.96), and major adverse cardiovascular events (HR: 1.65) [13]. In our study, we also found that SII is a reliable method for evaluation of STEMI + T2DM.

Urbanowicz et al conducted a study to assess the influence of postoperative inflammation on mortality risk after off-pump coronary artery bypass surgery in diabetic patients. The results showed that postoperative SII was a significant predictor for long-term prognosis in these patients, with a sensitivity of 68.75% and specificity of 71.07%. The findings suggest that SII could serve as a valuable tool in predicting mortality risk in diabetic patients with atherosclerotic cardiovascular disease [14].

In a study by Fan et al, the predictive value of A1SI, SIRI, and NLRP in patients with acute coronary syndromes (ACS) undergoing PCI was evaluated. The study included 1558 patients and found that higher values of A1SI, SIRI, and NLRP were associated with an increased risk of MACE. The association between these indices and prognosis in ACS patients was found to be stable across various subgroups. The study concluded that A1SI, SIRI, and NLRP may be suitable markers for identifying high-risk ACS patients after PCI [15]. But in our study, we found that, these indices are less reliable in STEMI patients with concomitant T2DM.

Additionally, a study by M. Celik et al. (2018) evaluated the prognostic value of inflammation indices in patients with STEMI, and found that in patients with STEMI, the PLR, NLR, and SII have been found to be significant independent predictors of the occurrence of no-reflow phenomenon. Furthermore, the SII has been shown to have a better predictive capability for no-reflow compared to NLR and PLR in STEMI patients [16].

In addition to inflammation, oxidative stress has also been shown to play a role in the development of cardiovascular disease in patients with T2DM. A review conducted by Y. Kayama et al. stated, that patients with T2DM and coronary artery disease had higher levels of oxidative stress markers compared to those without T2DM. This suggests that T2DM may cause an increase in oxidative stress, which in turn may contribute to the development of cardiovascular disease [17].

Several studies have investigated the relationship between sST2 and cardiovascular disease in patients with type 2 diabetes (T2DM). In a study by D. Jha et al. it was found that levels of the sST2 protein were not different between patients with ACS + T2DM vs acute coronary syndromes only (36.76±29.20 vs 32.35±21.18, p=0.370), but had higher predictive value for future MACE (AUC 0.80 [p=0.03; 95% CI(0.60-0.97)] vs AUC 0.72 [p=0.04; 95% CI (0.58-0.91)] [18].

A study by X. Hu et al. analyzed the relationship between sST2 and carotid intima-media thickness (CIMT) in patients with T2DM. The study found that elevated sST2 levels were associated with increased CIMT in T2DM patients and also with indicators of glucose and lipid metabolism. The results suggest that sST2 may be a potential novel marker to assess the progression of diabetic macrovascular complications [19]. This highlights association between sST2, T2DM and atherosclerosis, that explains higher prevalence of patients with multivessel disease in patients with T2DM.

The study by G. Miñana et. al assesses the relationship between sST2 and left ventricular remodeling after a first STEMI. 109 patients with STEMI were evaluated and results showed that higher levels of ST2 were associated with larger infarct size and a decrease in myocardial salvage index. The study also found that higher baseline ST2 levels were linked to progressive LV volume dilation and LVEF deterioration, especially in patients with severe structural damage. These findings suggest that ST2 may be a predictor of LV remodeling after a first STEMI [20].

A study by J. Sabbatielli et al. found that soluble suppression of tumorigenesis 2 (sST2), high-sensitivity cardiac troponin I (hs-cTnl), and N-terminal pro-brain natriuretic peptide (NT-proBNP) were associated with all-cause mortality and onset of cardiovascular events in patients with type 2 diabetes (T2DM) over a median follow-up of 16.8 years. The results showed that sST2 followed an increasing trend from healthy controls to uncomplicated T2DM patients and to patients with complications, while hs-cTnl was higher in T2DM patients with complications. A "cardiac score" based on the combination of sST2, hs-cTnl, and NT-proBNP was found to be associated with all-cause mortality and development of cardiovascular events. The study suggests that sST2, hs-cTnl, and NT-proBNP could have long-term prognostic value in T2DM and support the implementation of sST2 into routine clinical practice [21].

W. Jenkins et al. conducted a study to investigate the relationship of sST2 with long-term outcomes after myocardial infarction in a geographically defined community. The study enrolled 1401 patients who experienced a first-ever myocardial infarction between 2002 and 2012 and measured their sST2 levels. Results showed that sST2 was elevated in 51% of patients and was associated with increased age, female sex, and comorbidities. After 5 years of follow-up, higher values of sST2 were found to be significantly associated with increased risk of both death and heart failure, independently of other prognostic indicators such as age, sex, comorbidities, and troponin T levels. The study concludes that sST2 elevation is present in half of myocardial infarctions and that measurement of sST2 should be considered for risk stratification after myocardial infarction [22].

A study by I. Valiente-Alandi et al. explored the potential of inhibiting fibronectin (FN) polymerization as a therapeutic strategy for treating cardiac fibrosis and heart failure. They found that administering an FN polymerization inhibitor (pUR4) in vitro reduced FN and collagen deposition in cardiac myofibroblasts, resulting in decreased cell proliferation, migration, and extracellular matrix deposition. In vivo, daily administration of pUR4 for 7 days after an ischemia/reperfusion injury improved myocardial function, reduced cardiac remodeling, and fibrosis. Additionally, inducible ablation of FN in cardiac myofibroblasts after injury resulted in significant functional
The findings suggest that inhibiting FN polymerization may be a promising approach for treating heart failure [23].

The results of our study support previous findings that T2DM is associated with increased levels of inflammation and oxidative stress, which may contribute to the development of cardiovascular disease. Further studies are needed to determine the mechanisms by which T2DM may lead to increased inflammation and oxidative stress, and to explore potential interventions to reduce the risk of cardiovascular disease in this population.

Conclusions. 1. Age, multivessel disease, body mass index (BMI), obesity, leukocytes, neutrophils, lymphocytes, platelets, and fibronectin were significantly associated with the T2DM in patients with STEMI.

2. SII, sST2, and NLR are significantly associated with T2DM in patients with STEMI.

3. sST2 and SII are better predictors of T2DM in patients with STEMI compared to other markers of inflammation like PLR, NLR, SIRI, and AIsI.

4. These results highlight the importance of considering various factors, including age, obesity, and markers of inflammation, when evaluating the risk of T2DM in patients with STEMI.

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Відомості про авторів

Бєлінський Микита Вадимович – аспірант каф. внутрішньої медицини №2 та медсестринства, Івано-Франківський національний медичний університет, м. Івано-Франківськ, Україна.

Середюк Нестор Миколайович – д-р мед. наук, професор, зав. каф. внутрішньої медицини №2 та медсестринства, Івано-Франківський національний медичний університет, м. Івано-Франківськ, Україна.

Information about the authors

Bielinskyi M. V. – MD, PhD candidate, Department of Internal Medicine №2 and Nursing, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine. ORCID ID: 0000-0001-5013-3838.

Seredyuk N. M. – MD, PhD, DSc, Professor, head of the Department of Internal Medicine №2 and Nursing, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine. ORCID ID: 0000-0002-3616-2445.

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