

## PATIENTS CHARACTERISTICS AND PROGNOSTIC IMPLICATIONS OF TYPE 2 DIABETES MELLITUS IN HEART FAILURE WITH PRESERVED, MID-RANGE REDUCED AND REDUCED EJECTION FRACTION

### KARAKTERISTIKE BOLESNIKA I PROGNOSTIČKE IMPLIKACIJE TIP 2 DIJABETESA MELITUSA U SRČANOJ INSUFICIJENCIJI SA OČUVANOM, UMERENO REDUKOVANOM I REDUKOVANOM EJEKCIJOM

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#### Abstract

**Introduction:** Type 2 diabetes mellitus (T2DM) is frequent in patients with heart failure (HF) and correlated with an increased morbidity and mortality. The features and outcomes of patients with and without T2DM, depending on the HF type (HF with preserved: HFpEF, mid-range: HFmrEF; and reduced ejection fraction: HFrEF), are inefficiently explored.

**Aim:** To explore the impact of T2DM on clinical features and one-year overall mortality in patients with HFrEF, HFmrEF and HFpEF.

**Material and methods:** A prospective, observational study was conducted, including patients with HF at the Department of Cardiology, Clinical Center of Serbia, Belgrade. The enrollment occurred between November 2018 and January 2019. The study outcome was one-year all-cause mortality.

**Results:** Study included 242 patients (mean-age, 71 ± 13 years, men 57%). T2DM was present in 31% of patients. The proportion of T2DM was similar amid patients with HFrEF, HFmrEF, and HFpEF. Regardless of the HF type, patients with T2DM were probably older and had a higher prevalence of myocardial infarction, other types of coronary disorder or peripheral arterial disorder (all  $p < 0.001$ ). Also, chronic kidney disease was more prevalent in T2DM ( $p < 0.001$ ). In HFpEF, T2DM patients were commonly female, and usually had hypertension and atrial fibrillation (all  $p < 0.001$ ). Estimated one-year total mortality rates were significantly higher in T2DM patients. It also emerged as a unique predictor of higher mortality in HFrEF (HR; 1.33; 95% CI; 1.34 – 2.00), HFmrEF (HR; 1.13; 95% CI; 1.0 – 1.24) and HFpEF (HR; 1.21; 95% CI; 1.09 – 1.56), all  $p < 0.05$ .

**Conclusion:** Compared with non-diabetics, patients with HF and T2DM are older, with higher prevalence of comorbidities and greater one-year mortality, regardless of HF type. Heart failure is a unique predictor of mortality in all HF types in multivariate analysis. Considering the increased risk, T2DM requires meticulous screening/diagnosis and contemporary treatment to improve outcomes.

#### Keywords:

heart failure,  
ejection fraction,  
diabetes mellitus,  
clinical features,  
mortality

## Sažetak

**Uvod:** Tip 2 dijabetesa melitusa (T2DM) čest je u srčanoj insuficijenciji (SI) i povezan je sa povišenim morbiditetom i mortalitetom. Karakteristike i ishodi bolesnika sa i bez T2DM, u zavisnosti od tipa SI, definisane kao SI sa očuvanom ejskcionom frakcijom (EF) leve komore (engl. *heart failure with preserved EF, HFpEF*), umereno redukovanom EF (engl. *midrange EF, HFmrEF*) i redukovanom EF (engl. *reduced EF, HFrfEF*) nisu detaljno proučeni. **Cilj:** Ispitati kliničke karakteristike i jednogodišnji ukupni mortalitet kod bolesnika sa *HFrfEF, HFmrEF* i *HFpEF*, u zavisnosti od prisustva T2DM.

**Materijal i metode:** Sprovedena je prospektivna, opservaciona studija u koju su uključeni bolesnici sa SI lečeni na Klinici za kardiologiju, Kliničkog centra Srbije u Beogradu (novembar 2018 - januar 2019). Primarni cilj studije je ukupni mortalitet tokom 12 meseci praćenja.

**Rezultati:** U studiju su uključena 242 bolesnika (srednja starost  $71 \pm 13$ , muškarci 57%). Učestalost T2DM je bila 31%. Nije registrovana razlika u učestalosti T2DM kod *HFrfEF, HFmrEF* i *HFpEF*. Kod sve tri grupe dijabetičari su bili stariji i češće su imali infarkt miokarda, drugi oblik koronarne bolesti, perifernu arterijsku bolest i hroničnu bubrežnu slabost (sve vrednosti  $p < 0,001$ ). Bolesnici sa *HFpEF* i T2DM češće su bili ženskog pola i češće su imali hipertenziju i atrijalnu fibrilaciju (sve vrednosti  $p < 0,001$ ). U sve tri grupe procenjena jednogodišnja stopa mortaliteta bila je značajno viša kod dijabetičara. Tip 2 DM je nezavisni prediktor povišenog rizika od smrti u *HFrfEF* (*HR*; 1,33; 95% *CI*; 1,34 - 2,00), *HFmrEF* (*HR*; 1,13; 95% *CI*; 1,0 - 1,24) i *HFpEF* (*HR*; 1,21; 95% *CI*; 1,09 - 1,56), sve vrednosti  $p < 0,05$ .

**Zaključak:** Bolesnici sa T2DM i SI su stariji, sa više komorbiditeta i većom stopom ukupnog mortaliteta u odnosu na osobe bez T2DM. Tip 2 DM je nezavisni prediktor povišenog ukupnog mortaliteta u *HFrfEF, HFmrEF* i *HFpEF* u multivarijantnoj analizi. S obzirom na povišen rizik, T2DM zahteva revnosno dijagnostikovanje i savremeno lečenje kako bi se poboljšalo preživljavanje.

### Ključne reči:

srčana  
insuficijencija,  
ejskciona frakcija,  
dijabetes melitus,  
kliničke  
karakteristike,  
mortalitet

## Introduction

Heart failure (HF) is a complex cardiovascular syndrome caused by structural heart disease and/or by interrupted cardiac function, which results in a reduction in contractility or disruption of ventricular filling (1, 2). It frequently occurs in the following cases: 1 - 3% of the general population expands HF (1) and it is expressly pronounced in older individuals - the incidence is beyond 10% in patients over 80 years of age (3). Despite significant advances in the treatment, HF is accompanied by high rates of morbidity and mortality, with a five-year survival rate of circa 50% (4, 5).

In accordance with the Clinical Practice Guidelines of the European Society of Cardiology (ESC), there are three types of HF, defined on the foundation of the left ventricle (LV) ejection fraction (EF): HF with reduced EF (EF LV  $< 40\%$ , heart failure with reduced EF, *HFrfEF*), HF with moderately reduced EF (EF LV 40 - 49%, heart failure with midrange EF, *HFmrEF*) and HF with preserved EF LV (EF LV  $\geq 50\%$ , heart failure with preserved EF, *HFpEF*) (6). These types diverge in etiology and pathogenesis, demographic characteristics, clinical presentation, comorbidities and therapy (7, 8).

One of the most frequent comorbidities in patients with heart failure is type 2 Diabetes Mellitus (T2DM), which is present in around 30% of patients with chronic HF (9, 10). It is an independent forecaster of elevated morbidity and mortality portends worse outcomes in the

population of patients with heart failure (11, 12). However, the clinical features and prognostic implications of T2DM depending on the HF type (*HFrfEF, HFmrEF* and *HFpEF*) have not been thoroughly studied to date. Therefore, it is important to establish the relation between T2DM and specific clinical features and outcomes in *HFrfEF, HFmrEF*, and *HFpEF* respectively, thereby opening up the prospects of improving treatment for these patients.

The aim of this research is to compare the clinical characteristics and one-year mortality rates in patients with *HFrfEF, HFmrEF* and *HFpEF*, depending on the presence of T2DM.

## Material and methods

This research was conducted as a prospective, observational and cohort study involving the HF patients treated at the Cardiology Clinic of the Clinical Center of Serbia in Belgrade. Diagnosing of heart failure and its distinction into HF with reduced EF (EF LV  $< 40\%$ , heart failure with reduced EF, *HFrfEF*), HF with moderate reduced EF (EF LV 40 - 49%, heart failure with midrange EF, *HFmrEF*) or HF with preserved EF LV (EF LV  $\geq 50\%$ , heart failure with preserved EF, *HFpEF*) was determined according to the guidance of the European Society of Cardiology 2016. Those three main phenotypes describe HF according to the measurement of left ventricular ejection fraction (LVEF) taken during an echocardiogram. Normal LVEF is considered as  $\geq 50\%$ , so patients with

HFpEF have enough percentage of blood that left ventricle pumps out of the heart with each contraction. A new term is HFmrEF where patients have LVEF in the “gray area”, in the range of 40 – 49% (13). The study involved patients hospitalized between November 2018 and the end of January 2019 and those patients were randomly selected for the study. The included patients provided both demographic (age, gender) and clinical data (associated cardiovascular diseases and comorbidities), an electrocardiogram and a standard transthoracic echocardiographic examination, using Vivid e90 (2D cardiovascular ultrasound), all performed alongside pharmacological and non-pharmacological therapies that were recorded. The presence of T2DM was initially established according to the ADA (American Diabetes Association) criteria as: a) a previously known diagnosis of T2DM and/or proven use of glycemic regulation drugs: b) in other patients, glycemic status was assessed by determining serum glycosylated hemoglobin A1c levels, and in the case of elevated values, the diagnosis was certified after a standard 2 h glucose loading test, according to the current recommendations (14).

The primary objective of the study was to estimate the one-year total mortality (all cause case fatality, cardiovascular included), representing the end-point of this study. Mortality data were collected by telephone contact with family (or other close persons) and by access to available medical records in case of in-hospital death.

### Statistical analysis

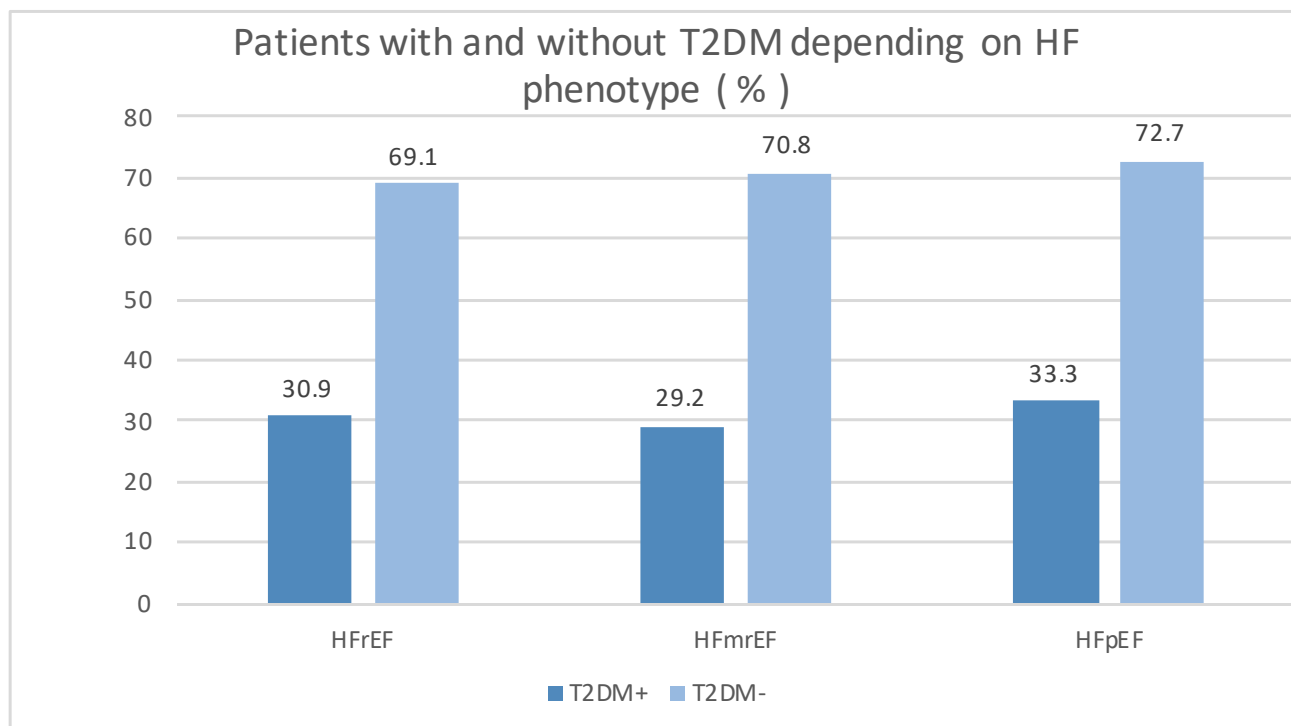
The categorical variables are presented as absolute and relative numbers (percentages) and compared using the  $X^2$  test or the Fisher exact probability test in the case of < 5 observations. Continuous variables are presented as mean  $\pm$  standard deviation and compared using t-test.

The rate of one-year mortality was evaluated by Kaplan-Meier analysis, with the outcome defined as time to death, while in other cases time was censored at 12 months. Mortality rates are presented per 100 patient-years with 95% confidence intervals, and rates were compared for patients with and without T2DM. The correlation between T2DM and total mortality in patients with HFrEF, HFmrEF and HFpEF was performed using univariate Cox regression analysis, which was subsequently controlled, i.e. adjusted according age, gender, previous myocardial infarction, EF LV (continuous variable), atrial fibrillation, chronic kidney failure (CKD) and differences in used medications. These characteristics were used to control (adjust) multivariate Cox regression analyses because they were significantly statistically correlated ( $p < 0.05$ ) with mortality in the univariate analysis. The statistical software STATA MP 14 was used for all analyses, and the significance of the difference was defined by a probability level of  $p < 0.05$ .

## Results

### Demographic and clinical characteristics of eligible patients

The study included 242 patients with HF, mean age  $71 \pm 13$  years. There were more males in the study population - 138 (57%), in relation to females - 104 (43%),  $p < 0.001$ . Distribution of patients, according to HF type indicates that HFrEF was present in 152 (62.8%) patients (mean EF LV in HFrEF:  $31.4 \pm 5.8\%$ ), HFmrEF was found in 39 (16.1%) patients (mean EF LV at HFmrEF:  $44.1 \pm 3.7\%$ ), while HFpEF occurred in 51 (21.1%) patients (mean EF LV at HFpEF:  $58.2 \pm 8.7\%$ ). A number of 75 (31%) patients suffered from T2DM. Among patients with T2DM, 59 (78.7%) were found to have the disease previously known,



**Figure 1.** Frequency (%) of patients with and without T2DM depending on HF phenotype (HFrEF, HFmrEF and HFpEF)

**Table 1.** Demographic and clinical characteristics and therapy for patients with HFrEF and with HFpEF, with and without T2DM

Characteristics of patients with HFrEF, n = 152 and with HFpEF, n = 51	HFrEF			HFpEF		
	With T2DM, n = 47 (with T2DM - %)	Without T2DM, n = 105 (without T2DM - %)	P-value	With T2DM, n = 17 (with T2DM - %)	Without T2DM, n = 34 (without T2DM - %)	P-value
Age	69 ± 14	64 ± 11	< 0.001	75 ± 10	68 ± 7	< 0.001
Gender (male)	24 (51)	55 (52.3)	0.867	10 (58.8)	24 (70.6)	< 0.001
<b>Comorbidities</b>						
Arterial hypertension	35 (74.4)	80 (76.2)	0.645	15 (88.2)	27 (79.4)	< 0.001
Previous myocardial infarction	31 (65.9)	39 (37.1)	< 0.001	5 (29.4)	5 (14.7)	< 0.001
Another form of coronary artery disease*	6 (12.8)	11 (10.5)	< 0.001	1 (5.9)	2 (5.9)	< 0.001
Mitral regurgitation	15 (31.9)	28 (26.7)	0.221	1 (5.9)	2 (5.9)	0.255
Atrial fibrillation	13 (27.6)	27 (25.7)	0.221	8 (47)	10 (29.4)	< 0.001
Dilated cardiomyopathy	10 (21.3)	18 (17.1)	0.422	0	0	---
<b>Non - cardiovascular comorbidities</b>						
Chronic kidney disease**	12 (25.5)	10 (9.5)	< 0.001	9 (52.9)	7 (20.6)	< 0.001
Anemia***	5 (10.6)	10 (9.5)	0.117	2 (11.8)	4 (11.8)	0.076
<b>Echocardiography</b>						
Left ventricular ejection fraction	30.1 ± 5.5	32.3 ± 4.1	0.433	58.3 ± 8.8%	57.6 ± 9.1%	0.922
Left Ventricular End-Systolic Dimension	6.7 ± 3.1	6.5 ± 4.1	0.378	5.0 ± 2.1	5.2 ± 1.6	0.433
Left ventricular End-Diastolic dimensions	4.7 ± 3.1	4.5 ± 3.2	0.346	3.0 ± 1.7	3.2 ± 1.8	0.566
Right ventricle	3.0 ± 1.8	2.9 ± 1.8	0.855	2.3 ± 1.1	2.4 ± 1.2	0.544
Left atrium	4.7 ± 2.5	4.8 ± 2.3	0.433	4.8 ± 2.1	4.7 ± 2.5	0.466
<b>Therapy</b>						
ACE inhibitor / AT1 receptor antagonist	39 (83)	82 (78)	0.211	13 (76.5)	27 (79.4)	0.433
Mineralocorticoid receptor agonist	28 (59.6)	59 (56.2)	0.332	9 (52.9)	19 (55.9)	0.911
Beta-blockers	33 (70.2)	69 (65.7)	0.188	9 (52.9)	19 (55.9)	0.911
Henle loop diuretic	47(100)	105 (100)	---	13 (76.5)	25 (73.5)	0.822
Another diuretic	14 (29.8)	34 (32.4)	0.023	0	0	---
Statin	33 (70.2)	60 (57.1)	< 0.001	11 (64.7)	10 (29.4)	< 0.001
Antiplatelet therapy	40 (85.1)	50 (47.6)	< 0.001	10 (58.8)	8 (23.5)	< 0.001
Anticoagulant therapy	11 (23.4)	28 (26.7)	0.031	8 (47)	10 (29.4)	< 0.001
ICD****	8 (17)	27 (25.7)	< 0.001	0	0	---
CRT-P / CRT-D*****	5 (10.6)	19 (18)	< 0.001	0	0	---
T2DM drug therapy	32 (68)	---	---	9 (52.9)	---	---

\* Patients who have not had myocardial infarction but who have a haemodynamically significant coronary artery stenosis confirmed by angiography, coronary artery bypass graft, or coronary stent; \*\* Persistent reduced glomerular filtration strength (eGRF) < 60 mL / min; \*\*\* Hemoglobin < 120 g/L in women and > 130 g/L in men; \*\*\*\* ICD - implantable cardioverter defibrillator; \*\*\*\*\* CRT-D / CRT-P - cardiac resynchronization therapy / bypass or coronary stent.

whereas newly discovered T2DM occurred in 16 (21.3%) patients. No difference in the incidence of T2DM was observed in patients with HFrEF, HFmrEF, and HFpEF, p = 0.874.

Characteristics of patients with HFrEF with and without associated T2DM

Among the HFrEF patients (n = 152), there were 47

(30.9%) patients with T2DM. The demographic and clinical features of these patients are presented in Table 1 (**table 1**). The T2DM population was older (69 ± 14 years) compared to patients without T2DM (64 ± 11 years), p < 0.001. The incidence of comorbidities was higher in T2DM patients, including earlier myocardial infarction (n = 31; 65.9% vs. n = 39; 37.1%), p < 0.001. Among the non-cardiovascular comorbidities, a significantly higher incidence of chronic

**Table 2.** Demographic and clinical characteristics and treatment management for patients with HFmrEF, with and without T2DM

Characteristics of patients with HFmrEF, n = 39	With T2DM, n = 11 (with T2DM - %)	Without T2DM, n = 28 (without T2DM - %)	P-value
Age	72 ± 14	66 ± 10	< 0.001
Gender (male)	6 (54.5)	15 (53.6)	0.387
<b>Comorbidities</b>			
Arterial hypertension	9 (81.9)	21 (75)	0.321
Previous myocardial infarction	4 (36.4)	7 (25)	< 0.001
Another form of coronary artery disease *	2 (18.2)	5 (17.9)	< 0.001
Mitral regurgitation	4 (36.4)	9 (32.1)	0.358
Atrial fibrillation	3 (27.3)	9 (32.1)	0.261
Dilated cardiomyopathy	0	1 (3.6)	0.121
<b>Non - cardiovascular comorbidities</b>			
Chronic kidney disease **	5 (45.5)	7 (25)	< 0.001
Anemia***	1 (9)	3 (10.7)	0.276
<b>Echocardiography</b>			
Left ventricular ejection fraction	43.2 ± 2.7	44.0 ± 3.3	0.288
Left Ventricular End-Systolic Dimension	5.6 ± 1.5	5.6 ± 1.4	0.378
Left ventricular End-Diastolic dimensions	4.0 ± 2.2	4.1 ± 2.2	0.381
Right ventricle	2.8 ± 1.8	2.7 ± 1.7	0.592
Left atrium	4.7 ± 2.1	4.6 ± 2.2	0.788
<b>Therapy</b>			
ACE inhibitor / AT1 receptor antagonist	6 (54.5)	19 (67.9)	0.677
Mineralocorticoid receptor agonist	5 (45.5)	15 (53.6)	0.822
Beta-blockers	6 (54.5)	16 (57.1)	0.455
Henle loop diuretic	11 (100)	28 (100)	---
Another diuretic	0	0	---
Statin	11 (100)	19 (67.9)	< 0.001
Antiplatelet therapy	10 (90)	16 (57.1)	< 0.001
Anticoagulant therapy	3 (27.3)	9 (32.1)	0.261
ICD****	0	1 (3.6)	0.245
CRT-P / CRT-D*****	0	0	---
T2DM drug therapy	7 (63.7)	---	---

\* Patients who have not had myocardial infarction but who have a haemodynamically significant coronary artery stenosis confirmed by angiography, coronary artery bypass graft, or coronary stent;

\*\* Persistent reduced glomerular filtration strength (eGRF) < 60 mL/min;

\*\*\* Hemoglobin < 120 g / L in women and > 130 g / L in men;

\*\*\*\* ICD - implantable cardioverter defibrillator;

\*\*\*\*\* CRT-D / CRT-P - cardiac resynchronization therapy;

kidney disease (CKD) was observed in T2DM patients (n = 12; 25.5% vs. n = 10; 9.5%, p < 0.001). Patients with T2DM were more often treated with statins n = 33; 70.2% vs. n = 60; 57.1%) and antiplatelet drugs (n = 40; 85.1% vs. n = 50; 47.6%, p < 0.001); and significantly less frequently with anticoagulant therapy (n = 11; 23.4% vs. n = 28; 26.7%; p = 0.031) (**table 1**).

### Characteristics of patients with HFpEF with and without associated T2DM

Among the HFpEF patients (n = 51), there were 17 (33.3%) individuals with T2DM. The demographic and clinical features of these patients are presented in Table 1. The T2DM patients were older (75 ± 10 years) and there were more women (n = 24; 70.6%) compared to patients without T2DM (68 ± 7 years), p < 0.001. The T2DM population had a higher prevalence of comorbidities, including arterial hypertension (n = 15; 88.2% vs. n = 27; 79.4%), p < 0.001. People with T2DM were more likely to receive statins (n = 11; 64.7% vs. n = 10; 29.4%) and antiplatelet drugs (n = 10; 58.8% vs. n = 8; 23.5%), all p values < 0.001 (**table 1**).

### One-year total mortality in patients with and without T2DM

A number of 54 patients (22.4%) died within 12 months of follow-up, 31 of who had T2DM. Comparison of Kaplan-Meier mortality rates in all three studied groups (HFrEF, HFmrEF and HFpEF) showed higher mortality in patients with T2DM compared to those without T2DM, as shown in Table 3 (**table 3**). Univariate Cox regression analysis, as also Cox analysis after controlling (adjusting) the most important demographic data (age and gender), clinical data (early myocardial infarction, EFLV, atrial fibrillation, CKD) and therapeutic differences, indicates that T2DM is a statistically unique predictor of increased one-year mortality in HF. Compared with patients without T2DM, 33% higher overall mortality (risk ratio; 1.33; 95% confidence interval; 1.04 - 2.00; p < 0.001) was registered in patients with HFrEF and T2DM after adjusting demographic and clinical characteristics. Similarly, 13% higher total mortality (risk ratio 1.13; 95% confidence interval; 1.06 - 1.24; p = 0.021) was registered in patients with HFmrEF and T2DM in an adjusted Cox analysis. In patients with HFpEF and T2DM in the adjusted analysis, mortality was 21% higher (risk ratio 1.21; 95% confidence interval; 1.09 - 1.56, p < 0.001), as shown in Table 3.

## Discussion

The most significant results of this prospective, observational study involving 242 patients with HF indicate are the following: a) a high prevalence of T2DM, which is current in about 30% of patients with HF regardless of clinical HF type (HFrEF, HFmrEF or HFpEF); b) in all three types of HF, T2DM occurs more often in the elderly and is accompanied by vascular and renal comorbidities; and c) the presence of T2DM is an unique predictor of increased

**Table 3.** Estimated Kaplan-Meier total mortality rates depending on the presence of T2DM and the results of Cox regression analysis in patients with HFrEF, HFmrEF and HFpEF dependent on the presence of T2DM

	Estimated mortality rate / 100 patient years (95% confidence interval)	Univariate Cox regression analysis HR (95% CI)	Multivariate Cox regression analysis HR (95% CI) *	p-value**
<b>HFrEF</b>				
With T2DM	8.5 (7.6 – 9.9)			
Without T2DM	7.9 (6.8 – 10.3)	1.67 (1.21 – 2.24)	1.33 (1.04 – 2.00)	< 0.001
<b>HFmrEF</b>				
With T2DM	9.1 (8.3 – 11.2)			
Without T2DM	8.8 (7.8 – 10.9)	1.56 (1.08 – 1.99)	1.13 (1.06 – 1.24)	0.021
<b>HFpEF</b>				
With T2DM	11.8 (9.2 – 13.1)			
Without T2DM	9.0 (7.9 – 10.4)	1.34 (1.19 – 1.89)	1.21 (1.09 – 1.56)	< 0.001

HR - Hazard Ratio; CI - Confidence Interval;

\* Multivariate Cox regression analysis was controlled (adjusted) for age, gender, previous myocardial infarction, left ventricular ejection fraction, atrial fibrillation, chronic kidney disease, statin administration, antiplatelet and anticoagulant drugs; \*\* p-value for multivariate Cox regression analysis

mortality in HFrEF, HFmrEF, and HFpEF at one-year follow-up.

Results of this study comply with the previous studies that showed that T2DM is a repeated comorbidity in HF, current in almost one third of patients (15). Our results extend the findings to date, pointing to the association of T2DM with various comorbidities, as well as with an independent effect on mortality in HFrEF, HFmrEF and HFpEF. In our study, the T2DM patients were older than those without T2DM, which is consistent with previous researches showing that the combined presence of T2DM and HF is explicitly pronounced in patients older than 75 years (4). In some studies, the presence of T2DM in patients with HF grows by nearly 4% per year (4). Hence, the prevention and proper treatment of T2DM are highly important in HF patients (4, 16). It is related with a systemic inflammatory response, oxidative stress, and left ventricular hypertrophy that may be linked to the development of HF (1). Diabetes has been accepted as one of the leading risk factors for HF, independent of other diseases and nearly was equivalent to the presence of three other established atherosclerotic risk factors (1, 4). Surely, this correlation is additionally influenced by more repeated presence of other risk factors such as old age, obesity, hypertension, KCD, sleep apnea, dyslipidemia and anemia (15).

Examining the clinical types of HF, our study showed the highest incidence of HFrEF (62.8%), which is consistent with literature data, showing that in the present-day HF population, the prevalence of HFrEF is about 57% (17). The second most frequently reported both in our study and in the literature, is HFpEF, while the prevalence of HFmrEF is the lowest (17). Our study showed no differences in the incidence of T2DM among HF phenotypes.

In our research, among patients with HFrEF, the T2DM patients were older than the patients without T2DM. No gender difference was registered, and the most common comorbidities were a previous myocardial infarction, other forms of coronary diseases, peripheral arterial

disease and CKD with a frequency higher than compared to patients without T2DM. In the literature, among patients with HFrEF, individuals with T2DM were more likely to be male, with higher NYHA class, and had a higher incidence of comorbidities, most commonly ischemic heart disease and hypertension (17, 18).

In the group of patients with HFmrEF, people with T2DM were older than patients without T2DM, no gender difference was registered, and the most common comorbidity was CKD, whose incidence was higher than in patients without T2DM. The literature has described that patients with HFmrEF and T2DM have higher NYHA class and more comorbidities, including ischemic heart disease, hypertension, and COPD (17, 19).

Among the HFpEF patients, individuals with T2DM were more often older and female. The accompanying more often included: atrial fibrillation, arterial hypertension, CKD, and previous myocardial infarction. These results are somewhat different from earlier publications showing that patients with HFpEF and T2DM were younger, usually male, and the most common comorbidities were hypertension, ischemic heart disease, COPD, and obesity (17). It is possible that reason of such discrepancies lies in different population structure of the HFpEF patients characterized by high heterogeneity (20, 21).

Type 2 Diabetes Mellitus stimulates atherosclerosis, causing myocardial ischemia and leading to microvascular dysfunction which may explain higher incidence of comorbidities such as myocardial infarction and arterial hypertension (1, 22). In the presence of T2DM, renal function is impaired due to changes in the glomerulus level as well as in the kidney blood vessels, resulting in fluid loading of the organism, which can bind CKD in patients with HF (1).

Significantly, the results of our research showed that the overall mortality rate was remarkably higher in individuals with T2DM, independently of the HF clinical type and that T2DM was a unique predictor of enlarged

mortality in HF<sub>r</sub>EF, HF<sub>m</sub>rEF, and HF<sub>p</sub>EF. In patients with HF<sub>r</sub>EF, the risk of mortality is 33% higher in diabetics, followed by patients with HF<sub>p</sub>EF at 22% higher risk, and patients with HF<sub>m</sub>rEF at 13% higher risk. These results are all in line with previous studies (12, 21). According to recent results from a large pan-European registry of patients with acute HF (n = 6,926), T2DM is a predictor of elevated intrahospital mortality, one-year overall mortality, and hospitalization risk due to HF (6). Similarly, the results of this registry in patients with chronic HF (n = 9428) indicate that T2DM is present in about one-third of patients and is related with a 28% increase in overall one-year mortality (3, 23). Our results expand these findings by suggesting that mortality is uplifted independently of the HF phenotype. This is particularly significant in the era of improved treatment options for T2DM with the use of the latest drugs that remarkably decrease the risk of hospitalization due to HF and, some of them, the overall and cardiovascular mortality of patients (24).

### Study limitations

Important limitations of the study are related to the small size of the sample, possible bias in patient involvement (tertiary care), and the fact that only overall mortality was monitored.

### Conclusion

Type 2 Diabetes Mellitus is important and repeated comorbidity in patients with HF, independently of the HF clinical type (HF<sub>r</sub>EF, HF<sub>m</sub>rEF, and HF<sub>p</sub>EF). Patients with T2DM and HF are older, with more comorbidities and higher overall mortality rates than those without T2DM. It is an independent predictor of increased one-year total mortality in HF<sub>r</sub>EF, HF<sub>m</sub>rEF, and HF<sub>p</sub>EF. Given the increased risk, T2DM requires purposeful diagnosis and modern treatment to improve the survival of these patients.

### Literature

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