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Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

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Siniša Stanković[1,2,♣], Dragana Šobić-Šaranović[3,4], Valentina Soldat-Stanković[1,5], Vera Artiko[3,4], Zvezdana Rajkovača[1,2], Gostimir Mikač[6], Nataša Egeljić-Mihailović[1,2], Marina Majkić[1,2]

Correlation between myocardial perfusion imaging findings and future cardiac events in patients with type 2 diabetes mellitus

Корелација између налаза перфузионе сцинтиграфије миокарда и будућих срчаних догађаја код оболелих од дијабетеса типа 2

[1]University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[2]University Clinical Center of the Republic of Srpska, Department of Nuclear Medicine and Thyroid Gland Diseases, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[3]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[4]University Clinical Center of Serbia, Center for Nuclear Medicine, Belgrade, Serbia;
[5]University Clinical Center of the Republic of Srpska, Clinic of Internal Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[6]Specialist Center for Thyroid Gland Diseases, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

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♣Correspondence to:
Siniša STANKOVIĆ
Department of Nuclear Medicine and Thyroid Gland Diseases, University Clinical Center of the Republic of Srpska, 12 beba bb, 78000 Banja Luka, Republic of Srpska, Bosnia and Herzegovina
E-mail: **sinisa.stankovic@med.unibl.org**

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SUMMARY

Introduction/Objective Myocardial perfusion imaging (MPI) is clinically useful for the evaluation of coronary artery disease (CAD) in patients with diabetes mellitus (DM). However, the prevalence of ischemia and its ability to predict future cardiac events is less clear. The aim was to determine the incidence of cardiac events in diabetic patients and relationship between them and MPI findings.

Methods Two cohorts of patients, 98 diabetics and 100 non-diabetics, with medium- to high-risk of CAD without previous coronary revascularization were studied prospectively. All of them were outpatients underwent ^{99m}Tc-sestamibi MPI with dipyridamole. The data about cardiac events were collected during follow-up period of two years.

Results Cardiac events occurred in 17.3% diabetics and in 8% non-diabetics (p = 0.048). Diabetics had shorter estimated event-free time 24.7 months (95% CI 23.2–26.2) versus non-diabetics 28.5 months (95% CI 27.4–29.5) (p = 0.046). The independent predictors of cardiac events were male sex (p = 0.010), previous myocardial infarction (p < 0.001), presence of the symptoms of angina (p = 0.014) and all variables derived from MPI findings. After adjustment for variables derived from MPI findings, the significant predictors in diabetics were size of stress perfusion defect (p = 0.022), summed stress score (p = 0.011) and summed difference score (p = 0.044).

Conclusion In diabetic patients, the cumulative rate of cardiac events was higher and the event-free survival was worse. MPI could help in prediction of cardiac events in diabetics and the most important predictors were size of stress perfusion defect, summed stress score and summed difference score.

Keywords: myocardial perfusion imaging, diabetes mellitus, coronary artery disease, cardiac events

САЖЕТАК

Увод/Циљ Перфузиона сцинтиграфија миокарда (ПСМ) је корисна у евалуацији коронарне артеријске болести (КАБ) код оболелих од типа 2 дијабетеса (Т2Д). Ипак, преваленца исхемије код њих и могућност предвиђања будућих срчаних догађаја су нејасни. Циљ је био одредити инциденцу срчаних догађаја код оболелих од Т2Д и везу између њих и налаза ПСМ.

Методе Проспективно су испитиване две групе болесника са средњим до високим ризиком за КАБ, 98 са Т2Д и 100 без, који нису имали ранију коронарну реваскуларизацију. Свима је урађена *^{99m}Tc-sestamibi* ПСМ са дипиридамолом. Подаци о срчаним догађајима су сакупљени током двогодишњег праћења.

Резултати Срчани догађаји су настали код 17,3% испитаника са Т2Д и 8,0% испитаника без Т2Д (p = 0,048). Испитаници са Т2Д су имали краће време преживљавања без срчаног догађаја 24,7 месеци (95% *CI* 23,2–26,2) према 28,5 месеци (95% *CI* 27,4–29,5) код оних без Т2Д (p = 0,046). Независни предиктори настанка срчаних догађаја су су били мушки пол (p = 0,010), ранији инфаркт миокарда (p < 0,001), присуство ангинозних тегоба (p = 0,014) и све варијабле добијене из налаза ПСМ. Код испитаника са Т2Д, након корекције и прилагођавања са варијаблама добијеним из налаза ПСМ, значајни предиктори су били величина испада перфузије у оптерећењу (p = 0,022), *summed stress score* (*SSS*)(p = 0,011) и *summed difference score* (*SDS*) (p = 0,044).

Закључак Код оболелих од Т2Д, кумулативна стопа срчаних догађаја је била виша, а време преживљавања до настанка срчаног догађаја краће. ПСМ може помоћи у предвиђању будућих срчаних догађаја код оболелих од Т2Д, а најважнији предиктори су били величина испада перфузије у оптерећењу, *SSS* и *SDS*.

Кључне речи: перфузиона сцинтиграфија миокарда; дијабетес; коронарна артеријска болест; срчани догађаји

INTRODUCTION

Coronary artery disease (CAD) has now become a common cause of mortality and morbidity worldwide [1]. Furthermore, caring for patients with known or suspected CAD poses tremendous economic pressure on healthcare resources, not only due to costs related to testing and treatment, but also those associated with loss of productivity in afflicted individuals [1]. The worldwide prevalence of diabetes mellitus (DM) is increasing, concurrently with obesity and other comorbid conditions [2]. Despite significant advances in medical and invasive therapy, CAD is the leading cause of morbidity and mortality in patients with DM [3]. The diagnosis of CAD is complicated by the often atypical presentation of patients with DM attributable to concomitant autonomic neuropathy and other disorders. It is important to identify CAD early in these patients to optimize medical therapy and lifestyle modifications, and especially important to identify and aggressively treat those at the highest risk of events. The value of single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in the evaluation of diabetic patients has been widely investigated [4, 5]. MPI is clinically useful for the evaluation of CAD in patients with DM. In diabetic patients with suspected or known CAD, a strong evidence base has been accumulated that MPI provides diagnostic and incremental prognostic information [4, 6, 7, 8]. The prognostic impact of ischemia together with other clinical and stress variables has previously been reported [4]. However, the prevalence of ischemia and its ability to predict those who experience future cardiac events is less clear in patients with DM with or without symptoms referred for MPI.

The aim of the study was to determine the incidence of cardiac events in diabetic patients and relationship between them and MPI findings.

METHODS

Patient selection

The study population consisted of two cohorts of patients with medium- to high-risk of CAD without previous coronary revascularization. In study group, there were 98 patients

with diabetes mellitus type 2 and 100 patients without diabetes in control group. All of them were outpatients underwent ^{99m}Tc-sestamibi SPECT MPI with pharmacologic stress using dipyridamole. The test was requested for assessment of myocardial ischemia in all patients. The patients in study group had previously diagnosed DM and were treated with insulin or oral hypoglycemic agents. Selection of patients was performed so that the groups were matched with no significant differences between them regarding classical risk factors of CAD (age, sex, body mass index, smoking, arterial hypertension, previous myocardial infarction and symptoms of angina). The study was conducted prospectively under the rules of the Declaration of Helsinki. The informed consent was obtained from all subjects before testing. The local medical ethics committee approved the study protocol. Before the test, a structured interview was performed and a clinical history was obtained, including assessment of cardiac risk factors. Furthermore, the measurements of patient height and weight were performed. Hypertension was defined as blood pressure above 140/90 mmHg or need for antihypertensive medication. Dyslipidemia was defined as need for lipid-lowering medication. Subjects were considered symptomatic if they were experiencing chest pain or shortness of breath thought to be of possible cardiac origin.

Stress protocol and SPECT MPI

Stress testing and stress/rest gated SPECT MPI was performed as per guidelines of the EANM (European Association of Nuclear Medicine) [9]. Patients underwent intravenous vasodilator stress using dipyridamole (0.56 mg/kg over 4 minutes). At 4 minutes after completion of the dipyridamole infusion, a bolus of 550 MBq ^{99m}Tc-sestamibi (technetium-99m methoxy-isobutyl-isonitrile) was intravenously injected. In the event of chest pain, significant ST depression or other symptoms, a dose of 125 mg of aminophylline was administered intravenously 2 minutes after injection of the radiotracer. SPECT MPI was performed using 2-day protocol. Each participant had gated stress using 8 frames per R-R cycle and non-gated rest SPECT MPI. For resting studies, 550 MBq of the same tracer was injected at least 24 hours after the stress test. Image acquisition was performed with a commercially available SPECT camera system (Optima™ NM/CT 640, GE Healthcare). Radiopharmaceutical dosing, SPECT acquisition, and image processing were performed within previously mentioned guidelines established by EANM [9]. All images were obtained

60 minutes after radiotracer injection using rotating dual-head gamma camera equipped with low-energy, high-resolution, parallel hole collimator with 30% (± 15%) symmetric energy window centered at 140 keV. Sixty-four projections (40 seconds per projection), with a 64x64 matrix were obtained over a 180º orbit. No attenuation or scatter correction was used.

Image interpretation

Relative perfusion distribution was analyzed semiquantitatively using standardized segmentation of 17 myocardial segments. Each segment was scored by the consensus of two experienced observers using a 5-point scoring system (0 = normal; 1 = equivocal; 2 = moderate; 3 = severe reduction; and 4 = absence of tracer uptake in a segment). The summed stress score (SSS) was obtained by adding the scores of the 17 segments of the stress images. The summed rest score (SRS) was obtained by similarly adding the scores of the 17 segments of the rest images. The sum of the differences between each of the 17 segments on the stress and rest images was defined as the summed difference score (SDS), a variable representing the amount of ischemia present. A scan was considered normal if the SSS was 3 or lower, mildly abnormal if the SSS was between 4 and 8, moderately abnormal if the SSS was between 9 and 13 and severely abnormal if the SSS was more than 13, as previously reported [10, 11]. The SDS < 2 were considered as no ischemia; 2 to 4 mild ischemia; 5 to 8 moderate ischemia; and > 8 severe ischemia [10, 11]. An automated software program the Emory Cardiac Toolbox™ (ECTb™, Emory University School of Medicine, Atlanta, Georgia, USA) was used to calculate left ventricular ejection fraction (LVEF) and the variables incorporating both the extent and severity of perfusion defects.

Patient follow-up

Collection of follow-up data was obtained by reviewing hospital records, by contacting the patient's general practitioner and/or by contacting the patient by phone during the period of approximately two years. The date of the last review or consultation was used to determine follow-up time. End points were developments of cardiac events: cardiac mortality, nonfatal

myocardial infarction (MI) or coronary revascularization by percutaneous coronary intervention or coronary artery bypass grafting. Cardiac mortality was defined as a death caused by acute MI, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac mortality. Nonfatal MI and coronary revascularization were confirmed by reviewing hospital records. Patients with other-cause mortality were excluded from the study.

Statistical analysis

Baseline characteristics of patients were compared by Student t or Mann-Whitney U tests for continuous variables and chi-square or Fisher exact tests for categorical variables where appropriate. Univariate Cox proportional hazard regression model was used to identify independent predictors of cardiac events. The risk of a variable was expressed as a hazard ratio with corresponding 95% confidence interval (CI). Univariate Cox regression model was used to investigate association between cardiac events and DM, after adjustment for variables derived from MPI findings LVEF, end diastolic volume (EDV), end systolic volume (ESV), systolic volume (SV), presence of stress defect, presence of ischemia, SSS, SRS, and SDS. Survival curves as a function of time (months) were generated with the Kaplan-Meier method. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using the statistical software platform IBM® SPSS® Statistics (Version 22).

RESULTS

Study population and MPI findings

The demographics, clinical characteristics and MPI results among diabetics and non-diabetics are shown in Table 1 and Table 2 respectively. There were no significant differences of the prevalence of classical risk factors between the groups except of dyslipidemia and family history of diabetes, which were higher among diabetics ($p = 0.004$ and $p < 0.001$). Perfusion and non-perfusion variables were obtained from MPI for all

patients. Diabetics had lower LVEF (p = 0.018), higher ESV (p = 0.039) and higher proportion of them were with abnormal ESV (p = 0.049). There were no significant differences of perfusion variables between the groups.

Follow-up, outcomes, and survival analysis

Median of follow-up period did not differ significantly between the 2 groups (26 vs. 24 months; p = 0.184). During this period of time, cardiac events occurred in 17.3% diabetics and in 8% nondiabetics (p = 0.048) (Table 3).

Event-free survival curves were constructed using the Kaplan-Meier method to account for censored survival times (Figure 1). Diabetics had shorter estimated event-free time 24.7 months (95% CI 23.2–26.2) versus non-diabetics 28.5 months (95% CI 27.4–29.5) (p = 0.046).

Predictors of cardiac events

The results of the univariate Cox proportional hazards analysis predicting cardiac events are given in Table 4. The independent predictors were male sex (p = 0.010), previous myocardial infarction (p < 0.001), presence of the symptoms of angina (p = 0.014) and all variables derived from MPI findings. DM was not significant, but borderline predictor of cardiac events in univariate Cox proportional hazards analysis. The association between cardiac events and DM was determined using univariate Cox regression model after adjustment for variables derived from MPI findings (Table 5). The significant predictors were size of stress perfusion defect (p = 0.022), SSS (p = 0.011) and SDS (p = 0.044).

DISCUSSION

In our study the groups were matched and there were no significant differences between them regarding classical risk factors of CAD (age, sex, body mass index, smoking, arterial hypertension, previous MI and symptoms of angina) except of prevalence of dyslipidemia and family history of diabetes, which were higher among diabetics ($p = 0.004$ and $p < 0.001$). These were expected since diabetics have higher prevalence of dyslipidemia and 2 to 4 times higher prevalence of family history of diabetes than non-diabetics [12, 13].

We found that diabetics had lower LVEF ($p = 0.018$), in accordance with some other studies. Ehl et al. showed that diabetics had a lower LVEF determined by MPI than non-diabetics ($p = 0.001$) and this difference could be demonstrated regardless of CAD extent (no significant differences of SSS, SRS and SDS) and might in part explain their generally worse cardiac survival compared with non-diabetics [14]. Chareonthaitawee et al. found that 1 of 6 asymptomatic diabetic patients without known CAD referred for MPI had reduced LVEF. The annual mortality rates of the groups with and without reduced LVEF were 7% and 4%, respectively [15].

In recent years, a large body of literature has established the prognostic significance of MPI in general population [7, 16, 17]. It was shown that patients with normal stress MPI studies had remarkably low cardiac event rates (< 1% per year) and the event rate was proportional to the extent of stress-induced hypoperfusion. In patients with a normal MPI SPECT, there was an annual death rate of 0.3% compared with 2.9% in patients with severely abnormal scans [10]. The nonfatal MI rate in another study also increased in relation to the SSS [3].

Diabetic patients have multitude of characteristic features including higher prevalence of multi-vessel and small vessel CAD, frequent silent myocardial ischemia and infarction with higher cardiac event rates, and the presence of autonomic dysfunction. This together with the prevalence of diabetic cardiomyopathy contributes to a higher cardiovascular mortality [18, 19]. Furthermore, diabetic patients have higher prevalence of cardiovascular co-morbidities as compared to patients without diabetes [20, 21]. Two-thirds of diabetic patients will die of heart or vascular disease, and patients with CAD and diabetes mellitus

have worse outcomes and a much higher cardiac event rate than their nondiabetic counterparts [22, 23].

Our study demonstrates that the two-year cumulative rate of cardiac events was higher (17.3% vs 8%) and the event-free survival was worse in diabetics (24.7 vs 28.5 months) than that seen in patients without DM. We found that the independent predictors of cardiac events were male sex, previous myocardial infarction, presence of the symptoms of angina and all variables derived from MPI findings, but in diabetics the most important predictors were size of stress perfusion defect, SSS and SDS. There are a lot of similar evidences in previous work of many authors. Kang et al. showed that diabetics had a higher event rate than nondiabetics with the same SSS [24]. Giri et al. showed in a multicenter trial that diabetics with ischemic defects had increased cardiac events than nondiabetics with the same level of ischemia. Despite this, an abnormal scan was an independent predictor of cardiac death and MI in both diabetic and nondiabetic groups [4].

In the previous analyses of perfusion imaging, the cardiac event rates in diabetic patients were significantly higher compared with nondiabetic patients, and the event rates in diabetic patients were related to the presence or absence of perfusion abnormalities. Kang et al. showed a higher cardiac event rate in diabetic patients than in nondiabetic patients, and the severity and size of the perfusion abnormalities as evaluated by the SSS, were significantly related to the probability of a cardiac event [24]. Giri et al. demonstrated the incremental value of perfusion imaging in predicting cardiac events [4], and De Lorenzo et al. showed that risk is related to the number of territories involved, and the extent and severity of the stress defects in both men and women [6]. Similarly, Berman et al. further demonstrated that the SSS predicted outcome in both diabetic men and women. Outcome was significantly higher in diabetic patients than in nondiabetics, and the severity of the defect predicted the event rates [25]. Cardiac events are, however, significantly higher in diabetic patients with an abnormal scan, resulting in a three- to eightfold increased risk compared with diabetic patients with a normal scan, and the severity of the perfusion abnormality in the diabetic population is proportionately related to outcome [26]. These findings are consistent with the assumption that diabetes contributes to an accelerated path of CAD complications. Diabetic patients are predisposed to a more aggressive form of vascular disease with diffuse coronary atherosclerosis and significantly higher incidence of cardiac events [4].

CONCLUSION

Our study adds to the body of evidence that the MPI continues to have an important diagnostic and prognostic value in evaluation of CAD, particularly in diabetics. In diabetic patients, the cumulative rate of cardiac events was higher and the event-free survival was worse than in patients without DM. We found that MPI could help in prediction of cardiac events in diabetics and the most important predictors were size of stress perfusion defect, summed stress score and summed difference score.

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Table 1. Baseline characteristics of the cohorts

Baseline characteristics	DM (n = 98)	non-DM (n = 100)	p
Male, n (%)	55 (56.1)	45 (45)	0.118
Age, years	66.8 ± 7.2	66.9 ± 7.7	0.952
Body mass index, kg/m^2	30.2 ± 4.8	29.2 ± 5	0.137
Hypertension, n	96	97	NS
Previous MI, n (%)	18 (18.4)	18 (18)	0.947
Smokers (anytime), n (%)	50 (51)	51 (51)	0.998
Smokers (current), n (%)	11 (11.2)	15 (15)	0.432
Dyslipidemia, n (%)	72 (73.5)	54 (54)	**0.004**
Family history of DM, n (%)	61 (62.2)	28 (28)	**< 0.001**
Family history of CAD, n (%)	73 (74.5)	76 (76)	0.806
Symptoms of angina, n (%)	61 (62.2)	64 (64)	0.798

DM – diabetes mellitus; MI – myocardial infarction; CAD – coronary artery disease

Table 2. Myocardial perfusion imaging findings

Characteristics		DM (n = 98)	non-DM (n = 100)	p
LVEF US, %		54.7 ± 9.9	57.8 ± 6.9	**0.013**
LVEF SPECT, %		64 ± 14.3	68.6 ± 12.3	**0.018**
LVEF SPECT ≥ 50%, n (%)		84 (85.7)	92 (92)	0.159
EDV, ml		104 (43–318)	97 (41–214)	0.133
ESV, ml		34 (4–245)	29.5 (6–140)	**0.039**
SV, ml		67.5 ± 16.4	67.5 ± 16.8	0.983
Abnormal ESV, n (%)		27 (27.6)	16 (16)	**0.049**
SSS		0 (0–19)	0 (0–23)	0.093
SRS		0 (0–18)	0 (0–20)	0.606
SDS		0 (0–15)	0 (0–18)	0.094
Abnormal stress MPI (SSS ≥ 4), n (%)		33 (33.7)	24 (24)	0.133
Severity of stress defect, n (%)	SSS < 4 – no defect	65 (66.3)	76 (76)	0.095
	SSS 4–8 – mild	13 (13.3)	13 (13)	
	SSS 9–13 – moderate	12 (12.2)	7 (7)	
	SSS >13 – severe	8 (8.2)	4 (4)	
Ischemia (SDS≥2), n (%)		18 (18.4)	12 (12)	0.212
Severity of ischemia, n (%)	SDS < 2 – no ischemia	80 (81.6)	88 (88)	0.145
	SDS 2–4 – mild	0 (0)	6 (6)	
	SDS 5–8 – moderate	6 (6.1)	2 (2)	
	SDS >8 – severe	12 (12.2)	4 (4)	

DM – diabetes mellitus; LVEF – left ventricular ejection fraction; US – ultrasound; SPECT – single photon emission computed tomography; EDV – end diastolic volume; ESV – end systolic volume; SV – systolic volume; SSS – summed stress score; SRS – summed rest score; SDS – summed difference score; MPI – myocardial perfusion imaging

Table 3. Follow-up period and outcomes

Characteristics		**DM (n = 98)**		**non-DM (n = 100)**		**p**
Follow-up, months		26 (2–28)		24 (3–30)		0.184
Cardiac event n (%)	Cardiac death	2 (2)	17 (17.3)	1 (1)	8 (8)	**0.048**
	Non-fatal MI	2 (2)		2 (2)		
	Revascularization	13 (13.3)		5 (5)		

DM – diabetes mellitus; MI – myocardial infarction

Table 4. Predictors of cardiac events in the univariate Cox analysis

Variable	HR (95% CI)	p
DM	2.3 (0.99–5.3)	0.053
Sex (f/m)	0.3 (0.1–0.8)	**0.010**
Body mass index	1 (0.9–1.1)	0.867
Hypertension	0.6 (0.1–4.2)	0.574
Previous myocardial infarction	5.9 (2.7–12.9)	< **0.001**
Smokers (anytime)	2.7 (1.1–6.4)	**0.027**
Smokers (current), n (%)	0.9 (0.3–3)	0.877
Dyslipidemia	1.3 (0.5–2.9)	0.596
Family history of DM	1.7 (0.7–3.6)	0.213
Family history of CAD	1 (0.4–2.6)	0.938
Symptoms of angina	4.5 (1.4–15.1)	**0.014**
LVEF SPECT, %	0.9 (0.9–1)	< **0.001**
Presence of normal LVEF SPECT	0.2 (0.1–0.4)	< **0.001**
EDV, mL	1.01 (1.01–1.02)	< **0.001**
ESV, mL	1.01 (1.01–1.02)	< **0.001**
Presence of normal ESV	0.2 (0.1–0.4)	< **0.001**
SV, mL	1.02 (1.00–1.05)	**0.025**
Presence of stress perfusion defect	119.1 (4–3574.9)	**0.006**
Size of stress perfusion defect, %	1.1 (1.1–1.2)	< **0.001**
Presence of ischemia	82.4 (19.3–351.1)	< **0.001**
Size of ischemia, %	1.2 (1.1–1.2)	< **0.001**
SSS	1.2 (1.2–1.3)	< **0.001**
SRS	1.1 (1.1–1.2)	< **0.001**
SDS	1.3 (1.2–1.4)	< **0.001**
Abnormal stress MPI (SSS≥4)	498.2 (3.6–69325.6)	**0.014**
Severity of stress defect	5.2 (3.5–7.8)	< **0.001**
Ischemia (SDS≥2)	112.5 (26.3–481)	< **0.001**
Severity of ischemia	4.6 (3.2–6.6)	< **0.001**

HR – hazard ratio; CI – confidence interval; DM – diabetes mellitus; CAD – coronary artery disease; LVEF – left ventricular ejection fraction; SPECT – single photon emission computed tomography; EDV – end diastolic volume; ESV – end systolic volume; SV – systolic volume; SSS – summed stress score; SRS – summed rest score; SDS – summed difference score; MPI – myocardial perfusion imaging

Table 5. Association between cardiac events and diabetes mellitus using univariate Cox regression model after adjustment for variables derived from myocardial perfusion imaging findings

Adjusting variable	HR (95% CI)	p
LVEF SPECT, %	1.8 (0.8–4.2)	0.180
Presence of normal LVEF SPECT	2.1 (0.9–4.8)	0.094
EDV, mL	1.9 (0.8–4.5)	0.148
ESV, mL	1.9 (0.8–4.4)	0.153
Presence of normal ESV	1.8 (0.8–4.3)	0.167
SV, mL	2.3 (1–5.3)	0.054
Presence of stress perfusion defect	1.9 (0.8–4.5)	0.129
Size of stress perfusion defect, %	2.8 (1.2–6.6)	**0.022**
Presence of ischemia	1.6 (0.7–3.8)	0.263
Size of ischemia, %	2.2 (0.9–5.3)	0.069
SSS	3.2 (1.3–7.9)	**0.011**
SRS	2.3 (1–5.3)	0.052
SDS	2.4 (1–5.8)	**0.044**
Abnormal stress MPI (SSS ≥ 4)	1.8 (0.8–4.2)	0.161
Severity of stress defect	1.7 (0.7–4)	0.223
Ischemia (SDS ≥ 2)	2.2 (0.9–5.1)	0.079
Severity of ischemia	0.9 (0.4–2.2)	0.802

HR – hazard ratio; CI – confidence interval; LVEF – left ventricular ejection fraction; SPECT – single photon emission computed tomography; EDV – end diastolic volume; ESV – end systolic volume; SV – systolic volume; SSS – summed stress score; SRS – summed rest score; SDS – summed difference score; MPI – myocardial perfusion imaging

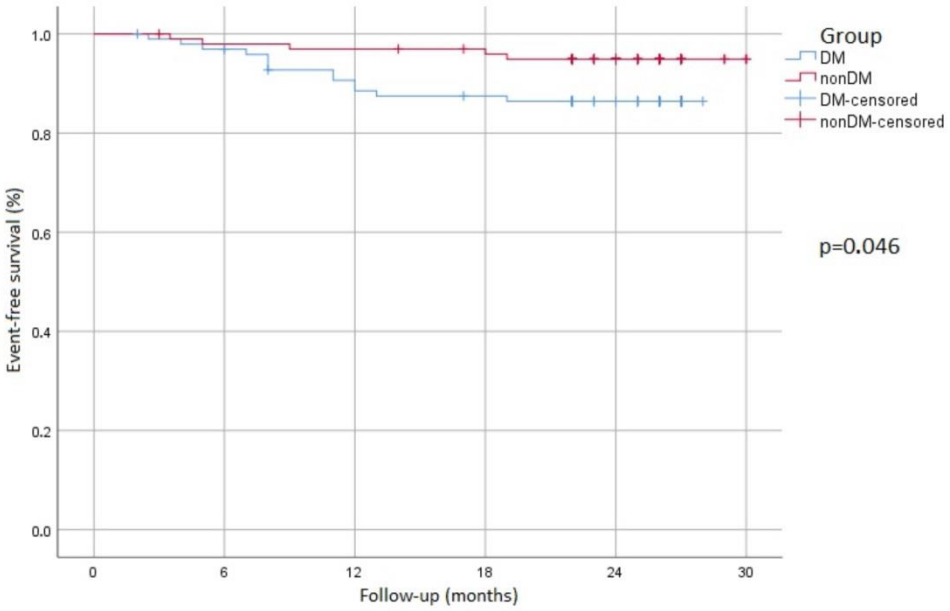

Figure 1. Kaplan–Meier event-free survival curves

