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Long-term mortality is increased in patients with undetected prediabetes and type-2 diabetes hospitalized for worsening heart failure and reduced ejection fraction

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Abstract

Background: We assessed the prevalence of newly diagnosed prediabetes and type-2 diabetes mellitus (T2DM), and their impact on long-term mortality in patients hospitalized for worsening heart failure with reduced ejection fraction (HFrEF).

Methods: We included patients hospitalized with HFrEF and New York Heart Association (NYHA) functional class II–III. Baseline two-hour oral glucose tolerance test was used to classify patients as normoglycaemic or having newly diagnosed prediabetes or T2DM. Outcomes included post-discharge all-cause and cardiovascular mortality during the median follow-up of 2.1 years.

Results: At baseline, out of 150 patients (mean-age 57 ± 12 years; 88% male), prediabetes was diagnosed in 65 (43%) patients, and T2DM in 29 (19%) patients. These patients were older and more often with NYHA class III symptoms, but distribution of comorbidities was similar to normoglycaemic patients. Taking normoglycaemic patients as a reference, adjusted risk of all-cause mortality was significantly increased both in patients with prediabetes (hazard ratio, 2.6; 95% confidence interval (CI), 1.1–6.3; $p = 0.040$) and in patients with T2DM (hazard ratio, 5.3; 95% CI, 1.7–15.3; $p = 0.023$). Likewise, both prediabetes (hazard ratio, 2.9; 95% CI, 1.1–7.9; $p = 0.041$) and T2DM (hazard ratio, 9.7; 95% CI 2.9–36.7; $p = 0.018$) independently increased the risk of cardiovascular mortality compared with normoglycaemic individuals. There was no interaction between either prediabetes or T2DM and heart failure aetiology or gender on study outcomes (all interaction p-values > 0.05).

Conclusions: Newly diagnosed prediabetes and T2DM are highly prevalent in patients hospitalized for worsening HFrEF and NYHA functional class II–III. Importantly, they impose independently increased long-term risk of higher all-cause and cardiovascular mortality.

Keywords

Heart failure with reduced ejection fraction, diabetes, prediabetes, all-cause mortality, cardiovascular mortality

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Introduction

Heart failure with reduced ejection fraction (HFrEF) is a complex clinical entity affecting over 23 million people worldwide and is associated with a high annual mortality rate of 8.8%, despite recent improvements in treatment.[1,2] Evidence suggests that patients with HFrEF commonly have type-2 diabetes mellitus (T2DM) or prediabetes.[3–5] According to current

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guidelines, prediabetes is defined by the presence of impaired fasting glucose and/or impaired glucose tolerance and/or haemoglobin A_{1c} (HbA_{1c}) levels of 5.7–6.4%.[6] However, both prediabetes and T2DM are often undetected in HFrEF and there is a wide variation in the reported incidence of these conditions, ranging between 17–55% and 18–35%, respectively.[3–5,7] In chronic HFrEF, previously known T2DM has been shown to predict poor prognosis,[8–10] but data on the prognostic impact of undetected prediabetes or T2DM are limited and inconclusive.[10,11] Of note, in the GISSI-HF trial (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure), known T2DM, but not prediabetes, was associated with an increased risk of all-cause death in unselected patients with chronic heart failure.[11] In the CHARM trial (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity), despite a trend towards a higher mortality in patients with prediabetes and newly diagnosed T2DM, only known T2DM significantly increased the risk of mortality and heart failure hospitalization.[4] In the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), besides known T2DM, prediabetes and newly diagnosed T2DM emerged as independent predictors of higher risks for mortality and heart failure hospitalization.[12] In acute or worsening chronic heart failure, some studies, but not all, have demonstrated that known T2DM increases the risk of in-hospital and post-discharge mortality.[7,13,14] However, the prognostic relevance of prediabetes or newly diagnosed T2DM has not been sufficiently explored in acute or worsening chronic heart failure. Determining an independent association between these conditions and long-term mortality risk in patients hospitalized for worsening chronic HFrEF would confirm their importance for heart failure progression and decreased survival. Furthermore, this would provide a rationale for investigating preventive interventions aimed to improve outcomes in patients with HFrEF and prediabetes or newly diagnosed T2DM.

The aim of the present study was to assess the prevalence and long-term prognostic impact of prediabetes and newly diagnosed T2DM on all-cause and cardiovascular mortality after hospitalization for worsening HFrEF in patients without known dysglycaemia.

Material and methods

Study design and population

This was a prospective observational cohort study, in which 244 adult patients (≥18 years), hospitalized for worsening HFrEF, were screened at the Department of Cardiology, Clinical Centre of Serbia and 150 patients were included. These patients met the following criteria: 1) hospitalization for worsening symptoms of chronic HFrEF consistent with the New York Heart Association (NYHA) functional class II–III; 2) HFrEF diagnosed for more than six months prior to the inclusion according to the definition of the European Guidelines for the diagnosis and management of acute or chronic heart failure;[15] and 3) no previous medical record or patient's knowledge of abnormality in glucose metabolism or treatment with glucose-lowering medications.

Out of 244 screened patients, 94 were not enrolled because of the exclusion criteria: acute heart failure with NYHA class IV and/or haemodynamic compromise requiring inotropic support; evidence of organ damage including acute hepatic injury (i.e. elevated liver transaminases and/or bilirubin levels) or acute kidney injury; acute myocardial dysfunction due to acute coronary syndrome, inflammatory or toxic aetiology; acute valve insufficiency or pericardial tamponade; percutaneous coronary intervention or coronary artery by-pass surgery within six weeks prior to admission; chronic HFrEF with NYHA class I symptoms; hypertrophic cardiomyopathy, congenital heart disease, significant valvular disease or previous valvular surgery, known chronic kidney disease grade IV, known active malignancy or infection. The exclusion criteria were chosen to prevent inclusion of haemodynamically unstable heart failure patients and/or patients with other conditions in which stress hyperglycaemia could be erroneously considered as prediabetes or T2DM. The study flow-chart is presented in Figure 1.

The study has been conducted in accordance with the 1975 Declaration of Helsinki. Prior to initiation of the study, the Ethics Committee of the Clinical Centre of Serbia provided approval. All patients signed the informed consent.

Baseline clinical assessment

Heart failure was defined as ischaemic in cases of a prior myocardial infarction, coronary revascularization, and/or coronary artery stenosis >50% verified by coronary angiography prior to, or at inclusion. In cases of non-ischaemic heart failure aetiology, dilated cardiomyopathy was defined as ventricular dilatation and HFrEF in the absence of abnormal loading conditions or significant coronary artery stenosis.[16]

Demographic characteristics, detailed medical history, NYHA class, physical examination, routine laboratory findings, standard 12-lead electrocardiogram, chest X-ray, standard two-dimensional and Doppler transthoracic echocardiography with left

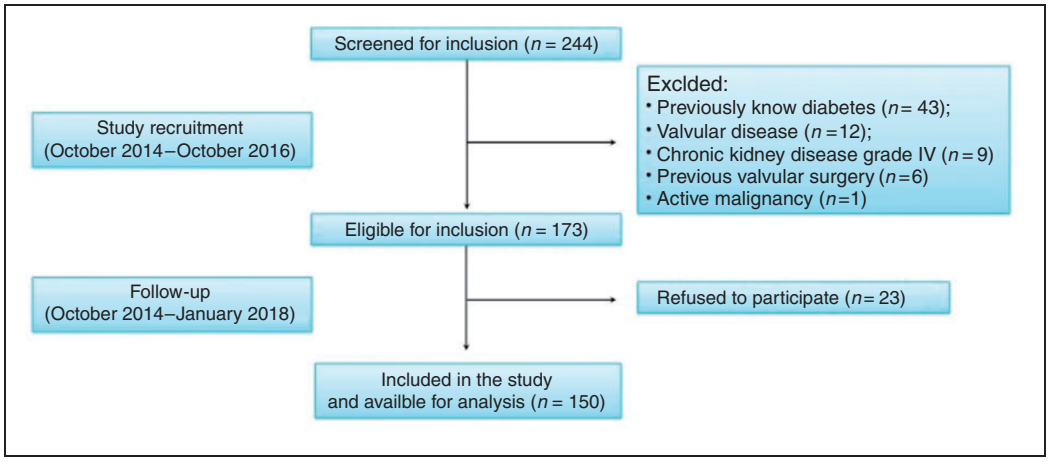

Figure 1. The study flow-chart.

ventricular ejection fraction (LVEF) assessment,[17] and medical treatment data were recorded for every participant at baseline. The following cardiovascular risk factors were assessed: hypertension (previous antihypertensive treatment and/or blood pressure >140/90 mmHg at admission), hyperlipidaemia (previous lipid lowering drug treatment), cerebrovascular disease (documented in medical records as a previous stroke verified by computed tomography and/or transient ischaemic attack), peripheral vascular disease (previously verified significant peripheral arterial stenosis >50% by colour Doppler scan, ischaemic limb pain, peripheral revascularization procedure and/or non-traumatic limb amputation), previous deep vein thrombosis, atrial fibrillation (documented by electrocardiogram prior to or at inclusion), chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2)[18] and smoking status.

Assessment of glycaemic status

In all participants, fasting plasma glucose (FPG) was measured within five days from inclusion, following initial stabilization and after a mandatory overnight fasting of at least 8 h.[19] FPG and a standard 2-h oral glucose tolerance test (OGTT) with 75 g of glucose were used for diagnosing prediabetes or T2DM in accordance with diagnostic criteria used by the American Diabetes Association.[19] Plasma glucose was measured prior to glucose load intake, and at the 120th minute of OGTT. Patients were classified as: 1) normoglycaemic (FPG < 5.6 mmol/L and 2-h OGTT <7.8 mmol/L); 2) prediabetes, which included impaired fasting glucose (FPG ≥ 5.6 mmol/L and <7.0 mmol/L, and normal response to the 2-h OGTT) and impaired glucose tolerance (normal FPG, or FPG ≥ 5.6 mmol/L and <7.0 mmol/L, and 2-h OGTT ≥ 7.8 mmol/L and <11.1 mmol/L); and 3) newly diagnosed T2DM (FPG ≥ 7.0 mmol/L and/or 2-h OGTT ≥ 11.1 mmol/L), Figure 2.[6,20] Newly diagnosed T2DM patients were referred to the diabetologist and initiated treatment with metformin according to current guidelines.[20]

Follow-up and study outcomes

All patients were prospectively followed in an outpatient clinic at six-monthly intervals. In the case of a patient not attending the scheduled visit, telephone follow-up was performed and data on study outcomes, including all-cause and cardiovascular mortality, were collected. The cause of death was determined from medical records provided by the patient's next-of-kin. Cardiovascular mortality included fatal myocardial infarction (death within the first 30 days), worsening heart failure, sudden cardiac death, fatal cerebrovascular insult, and death related to myocardial revascularization procedures (percutaneous or surgical). All-cause mortality included cardiovascular death or other causes (i.e. malignancy, infection). No patient was lost to follow-up.

Statistical analysis

Descriptive data are presented as a mean with standard deviation for continuous variables and as a count with proportion for categorical variables. Variables were compared using analysis of variance for continuous variables or a chi-square test for categorical variables.

Incidence rates of study outcomes for patients with and without dysglycaemia (including prediabetes and T2DM) were calculated and expressed in units per 100 patient-years. Incidence rate ratios between patients with prediabetes, T2DM and normoglycaemia were calculated for all-cause and cardiovascular mortality. The Kaplan–Meier survival curves were estimated and compared according to glycaemia status

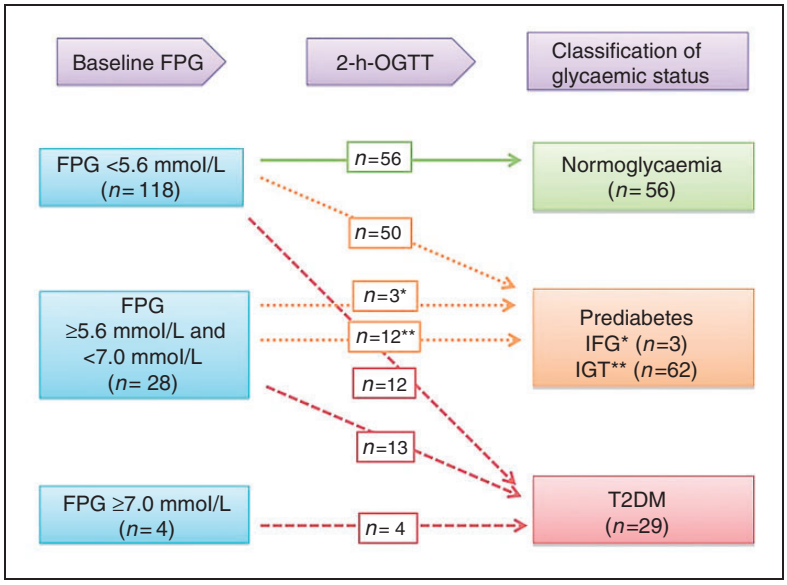

Figure 2. Classification of glycaemia status based on fasting plasma glucose and two-hour oral glucose tolerance test in accordance with the American Diabetes Association Standards of Medical Care in Diabetes Criteria.
*IFG: fasting plasma glucose ≥5.6 mmol/L and <7.0 mmol/L and normal 2-h OGTT.
**IGT: 2-h OGTT ≥ 7.8 mmol/L and <11.0 mmol/L.
IFG: impaired fasting glucose; IGT: impaired glucose tolerance; FPG: fasting plasma glucose; 2-h OGTT: two-hour oral glucose tolerance test; T2DM: type 2 diabetes mellitus

using the log-rank test for both outcomes. The Cox proportional hazard models were used to estimate the hazard ratios for all-cause and cardiovascular mortality in patients with prediabetes and T2DM with normoglycaemic patients serving as a reference. The adjusted Cox regression models were formed in a 'two-step' process. First, we used univariable regression analysis in which study outcomes (i.e. all-cause and cardiovascular mortality) were regressed on explanatory variables, including age, sex, heart failure aetiology, LVEF, hypertension, hyperlipidaemia, cerebrovascular disease, peripheral vascular disease, previous deep vein thrombosis, atrial fibrillation, chronic kidney disease, anaemia and smoking status (not presented). Then we used five covariates with the strongest association with study outcomes (LVEF, NYHA class, peripheral arterial disease, chronic kidney disease and anaemia) to adjust Cox regression models for the association between prediabetes and diabetes and all-cause/cardiovascular mortality. This was a necessary approach to prevent overfitting the Cox adjusted models, taking into account the relatively small number of outcome events due to a small sample size (i.e. adjusted analysis can produce reliable results only if there are at least 5–10 events per an explanatory variable).[21,22] Interaction analyses on study outcomes (cardiovascular and all-cause mortality) were assessed between glycaemia status (prediabetes and T2DM) and heart failure aetiology (ischaemic versus non-ischaemic), as well as between glycaemia status and gender (male versus female). The proportionality of hazard was estimated using Schoenfield residuals, and time to death or time to the end of follow-up was used in all survival analyses. Data were analysed using the STATA MP 14. A two-sided p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The study included 150 patients hospitalized for worsening HFrEF (NYHA class II–III) without known prediabetes or T2DM at baseline. Baseline characteristics of the study population are presented in Table 1. The mean age was 57 ± 12 years, and the majority of patients were male (88%). Ischaemic heart failure aetiology was present in 53% of patients, while the most prevalent comorbidities were hypertension and hyperlipidaemia.

At baseline, out of 150 participants, 118 had normal FPG levels, whereas 32 had elevated FPG, as presented in Figure 2. Following the 2-h OGTT, 56 patients with normal FPG and normal response to the 2-h OGTT were classified as normoglycaemic. Prediabetes was diagnosed in 65 (43%) patients, including three patients with impaired fasting glucose and 62 patients with impaired glucose tolerance. T2DM was diagnosed in 29 (19%) patients.

Table 1. Baseline clinical characteristics of all patients, and according to glycaemia status.

Characteristic	All patients $N = 150$	Normoglycaemic patients $n = 56$ (37%)	Prediabetes $n = 65$ (43%)	T2DM $n = 29$ (20%)	p
Age, years	57 ± 12	54 ± 12	60 ± 11	59 ± 12	0.045
Male sex	132 (88)	48 (86)	60 (92)	24 (83)	0.34
HF aetiology, ischaemic	79 (53)	26 (46)	36 (55)	17 (59)	0.47
NYHA class III	73 (49)	17 (30)	40 (62)	16 (55)	0.002
Physical examination characteristics					
BMI, kg/m^2	27.2 ± 4.4	26.6 ± 4.3	26.8 ± 4.3	29.2 ± 4.4	0.020
Heart rate, beats/min	80 ± 19	79 ± 19	79 ± 21	84 ± 17	0.44
Systolic BP, mmHg	120 ± 19	123 ± 23	120 ± 18	115 ± 18	0.20
Diastolic BP, mmHg	75 ± 11	77 ± 11	74 ± 10	72 ± 11	0.17
Medical history					
Hypertension	89 (60)	33 (59)	42 (66)	14 (48)	0.28
Hyperlipidaemia	67 (45)	26 (46)	30 (47)	11 (38)	0.69
Current smoker	29 (19)	15 (27)	9 (14)	5 (17)	0.41
Atrial fibrillation	49 (33)	16 (29)	23 (35)	10 (34)	0.70
Cerebrovascular disease	12 (8)	5 (9)	4 (6)	3 (10)	0.74
Peripheral artery disease	24 (16)	7 (12)	14 (21)	3 (10)	0.26
Prior deep vein thrombosis	10 (7)	2 (4)	6 (9)	2 (7)	0.46
Metabolic assessment					
Fasting glycemia, mmol/L	5.0 ± 0.9	4.6 ± 0.5	5.0 ± 0.7	5.8 ± 1.1	<0.001
Total cholesterol, mmol/L	4.6 ± 1.5	4.7 ± 1.4	4.6 ± 1.6	4.4 ± 1.3	0.63
Laboratory assessment					
Haemoglobin, g/L	140 ± 17	145 ± 16	138 ± 19	136 ± 12	0.037
Creatinine, mmol/L	100 ± 43	86 ± 21	112 ± 49	101 ± 54	0.004
eGFR, mL/min per 1.73 m^2	95 ± 43	105 ± 39	82 ± 32	105 ± 59	0.004
CKD ≥ grade III, %	26 (17)	6 (11)	15 (23)	5 (17)	0.20
Na^+, mmol/L	137 ± 11	138 ± 3	135 ± 17	137 ± 2	0.46
Echocardiography assessment					
LVEF, %	27 ± 9	27 ± 8	27 ± 8	25 ± 10	0.67
LVEDD, cm	7.3 ± 5.1	6.7 ± 0.7	7.9 ± 7.8	6.9 ± 0.8	0.46
LVESD, cm	6.1 ± 4.6	5.6 ± 1.0	6.6 ± 6.9	5.8 ± 0.8	0.51
LAD, cm	5.1 ± 3.2	4.6 ± 0.8	5.4 ± 4.7	5.1 ± 0.9	0.34
Therapy					
ACEi/ARB	126 (84)	45 (80)	55 (85)	26 (90)	0.53
Beta blocker	122 (83)	50 (89)	48 (77)	24 (83)	0.23
Loop diuretics	135 (92)	51 (91)	57 (92)	27 (93)	0.94
Digitalis	23 (16)	8 (14)	9 (14)	6 (21)	0.70
Ca^{2+}channel antagonists	3 (2)	1 (2)	1 (2)	1 (3)	0.83
Aspirin	96 (65)	33 (59)	42 (68)	21 (72)	0.40
Nitrates	28 (19)	9 (16)	13 (21)	6 (21)	0.79
Amiodaron	55 (38)	22 (40)	26 (42)	7 (24)	0.24
Lipid-lowering treatment	75 (50)	24 (43)	31 (50)	19 (65)	0.14

Data are n (%) or mean ± SD.

T2DM: type 2 diabetes mellitus; HF: heart failure; NYHA: New York Heart Association; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LAD: left atrial anteroposterior dimension; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

Compared with normoglycaemic individuals (54 ± 12 years), patients with prediabetes (60 ± 11 years) and T2DM (59 ± 12 years) were older ($p = 0.045$) with more frequent NYHA class III symptoms (prediabetes 62% *vs.* T2DM 55% *vs.* normoglycaemia 30%, $p = 0.002$), lower haemoglobin levels (prediabetes 138 ± 19 g/L *vs.* T2DM 136 ± 12 g/L *vs.* normoglycaemia 145 ± 16, $p = 0.037$) and lower estimated glomerular filtration rate (prediabetes 82 ± 32 *vs.* T2DM 105 ± 59 *vs.* normoglycaemia 105 ± 39 ml/min per 1.73 m^2, $p = 0.004$). There were no differences in sex, heart failure aetiology, or the distribution of comorbidities or treatment allocation between patients with and without dysglycaemia (Table 1).

Study outcomes

Over the median follow-up of 2.1 years (range 0.1–3.1 years), there were 26 cases of all-cause death and 21 cases of cardiovascular death. Compared with normoglycaemic patients, patients with both prediabetes and T2DM had higher incidence rates of all-cause and cardiovascular mortality (Table 2).

The cumulative Kaplan–Meier survival curves illustrating all-cause and cardiovascular mortality according to glycaemic status are presented in Figure 3.

In unadjusted Cox proportional hazard analysis, the risk of death from any cause was significantly higher in patients with prediabetes (hazard ratio, 3.8; 95% confidence interval (CI), 1.6–8.8; $p = 0.002$) as well as in patients with T2DM (hazard ratio, 6.7; 95% CI, 1.1–15.9; $p = 0.032$) relative to normoglycaemic patients (Table 3). Following adjustment, these associations remained significant for both prediabetes (adjusted hazard ratio, 2.6; 95% CI, 1.1–6.3; $p = 0.040$) and T2DM (adjusted hazard ratio, 5.3; 95% CI, 1.7–15.3; $p = 0.023$). Similarly, in a univariable analysis, the risk

Table 2. Incidence rate and incidence rate ratio of outcome events according to glycaemia status.

	No. of events (%)	Incidence rate per 100 patient-years (95% CI)	Incidence rate ratio (95% CI) Dysglycaemia *vs.* normoglycaemia[a]	*p*-value
All-cause mortality				
Normoglycaemia $n = 56$	3 (5.1)	2.5 (0.8–7.7)	–	–
Prediabetes $n = 65$	18 (29)	17.3 (10.9–27.4)	3.9 (1.6–10.3)	0.001
T2DM $n = 29$	5 (18)	9.7 (4.0–23.2)	12.6 (1.4–60.3)	0.009
Cardiovascular mortality				
Normoglycaemia $n = 56$	1 (1.7)	0.8 (0.1–5.9)	–	–
Prediabetes $n = 65$	15 (24)	14.4 (8.6–23.9)	4.3 (1.6–13.5)	<0.001
T2DM $n = 29$	5 (3.3)	9.7 (4.0–23.2)	10.2 (1.1–50.1)	0.026

[a]Comparison between dysglycaemia and normoglycaemia includes: prediabetes *vs.* normoglycaemia; T2DM *vs.* normoglycaemia.
CI: confidence interval; T2DM: type 2 diabetes mellitus

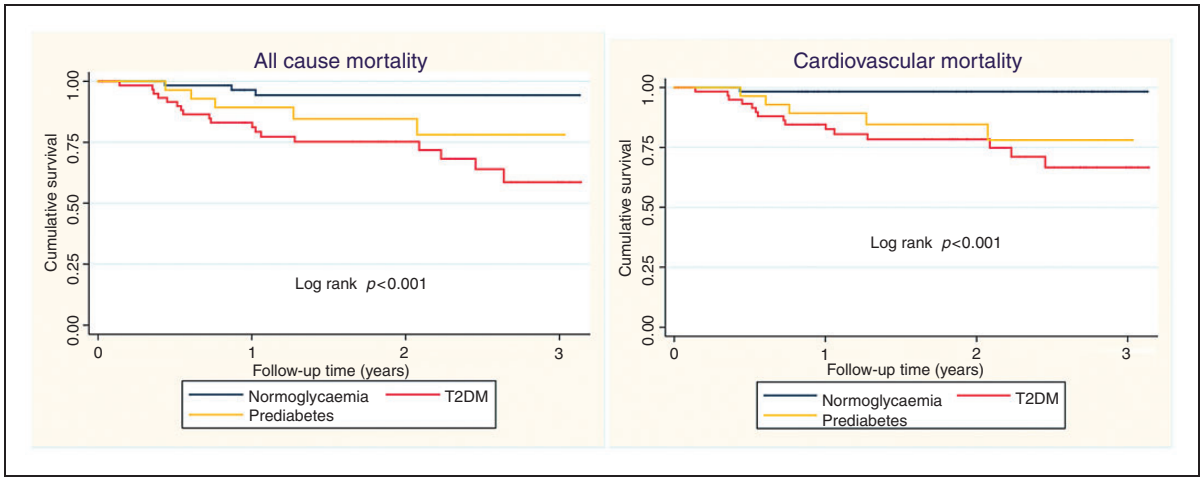

Figure 3. Kaplan–Meier curves for all-cause and cardiovascular mortality according to glycaemia status.
T2DM: type 2 diabetes mellitus

Table 3. Cox proportional hazards models of all-cause and cardiovascular mortality according to glycaemia status.

	All-cause mortality				Cardiovascular mortality			
	Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Normoglycaemia	1 (reference)	–	1 (reference)	–	1 (reference)	–	1 (reference)	–
Prediabetes	3.8 (1.6–8.8)	0.002	2.6 (1.1–6.3)	0.040	4.2 (1.6–10.9)	0.003	2.9 (1.1–7.9)	0.041
T2DM	6.7 (1.1–15.9)	0.032	5.3 (1.7–15.3)	0.023	16.5 (2.2–76.2)	0.016	9.7 (2.9–36.7)	0.018

HR: hazard ratio; CI: confidence interval; T2DM: type 2 diabetes mellitus

of cardiovascular death was significantly higher in patients with prediabetes (hazard ratio, 4.2; 95% CI, 1.6–10.9; $p = 0.003$) and T2DM (hazard ratio, 16.5; 95% CI, 2.2–76.2; $p = 0.016$) compared with normoglycaemic patients. After adjustment, both prediabetes (adjusted hazard ratio, 2.9; 96% CI, 1.1–7.9; $p = 0.041$) and T2DM (adjusted hazard ratio, 9.7; 95% CI, 2.9–36.7; $p = 0.018$) remained significantly associated with cardiovascular mortality (Table 3).

In sensitivity analyses, there were no interactions between dysglycaemia and heart failure aetiology (ischaemic versus non-ischaemic) or gender on the study outcomes (all interaction p values > 0.05) (Supplementary Material Table S1 online).

Discussion

There are two main findings of the present study. In well-characterized, chronic HFrEF patients hospitalized for worsening heart failure, previously undetected prediabetes and T2DM were highly prevalent, affecting 63% of the cohort. During the follow-up, compared with normoglycaemic individuals, patients with prediabetes, as well as patients with newly diagnosed T2DM, had an independently increased long-term risk for both all-cause and cardiovascular mortality, even after adjustment for multiple potential confounders.

The first finding reveals a high proportion (63%) of patients hospitalized for worsening chronic HFrEF with previously unrecognized prediabetes (43%) or T2DM (19%). In the present study both FPG and 2-h OGTT were used for diagnosing dysglycaemia, which has improved both diagnostic specificity and sensitivity as reflected in identification of 62 (52%) new cases of prediabetes or T2DM among patients with normal FPG. In comparison, in the post hoc analysis of the PARADIGM HF trial, prediabetes and newly diagnosed T2DM were established based on HbA_{1c} levels in 39% and 21% of chronic stable HFrEF patients, respectively, which is similar to our results.[12] Conversely, in the GISSI-HF trial, a lower proportion of chronic heart failure patients had prediabetes and newly diagnosed T2DM (29% and 13%, respectively) compared with our findings.[11] In a large cohort of HFrEF outpatients in Denmark, without previously established T2DM, 19% presented with overt T2DM, whereas 22% had prediabetes.[3] The reasons behind differences in the frequency of dysglycaemia across studies are currently unresolved and could be attributed to several factors, including geographic variations and differences in the severity and clinical presentation of heart failure.[23] Accordingly, there is a positive correlation between heart failure severity, as indicated by a higher NYHA functional class, and insulin resistance.[24] This supports the high prevalence of prediabetes and newly diagnosed T2DM amongst our patients with NYHA class II–III symptoms. Likewise, in several studies, T2DM was more prevalent in acute or worsening heart failure than in stable chronic heart failure, which is also in line with our findings.[7,25–27] In addition, in contrast to the use of HbA_{1c} in most trials, patients in our study were stratified according to the 2-h OGTT, which has comparable sensitivity but an imperfect concordance with HbA_{1c}.[19] Importantly, the feasibility of the 2-h OGTT in heart failure patients has been previously confirmed.[3]

The relevance of undetected prediabetes or T2DM is reflected in substantially increased mortality rates associated with dysglycaemia in our study. Despite being treated with modern agents, patients with newly diagnosed prediabetes or T2DM had higher rates of all-cause (~10–17 per 100 patient-years) and cardiovascular (~10–14 per 100 patient-years) mortality compared with normoglycaemic individuals. In addition, mortality rates attributed to prediabetes and T2DM exceeded reports from earlier studies. In the PARADIGM HF trial, crude incidence rates of all-cause (8–9 per 100 patient-years) and cardiovascular (~8 per 100 patient--years) mortality in patients with prediabetes and newly diagnosed T2DM were lower than in our study.[12] Likewise, in the CHARM and GISSI-HF trials, mortality rates associated with prediabetes were lower than in our cohort.[4,11] The observed discrepancies could be related to differences in study populations. Namely, these trials have enrolled chronic stable HFrEF patients, whereas our study included patients

hospitalized for worsening chronic HFrEF with NYHA class II–III symptoms. Worsening heart failure is considered a critical point in the course of heart failure associated with a sharp increase in short-term and long-term mortality.[28–30] This is corroborated by a post hoc analysis of the EVEREST trial (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan), in which the rates of all-cause and cardiovascular mortality were significantly higher in patients with than without diabetes, with acute or worsening heart failure, which supports our findings.[7]

The high mortality rates in patients with prediabetes and T2DM translated into a substantially higher long-term risk of all-cause and cardiovascular death compared with normoglycaemic individuals in our study, even after adjusting for relevant confounders. The observed hazard ratios were high, which could be explained by the small sample size of our study.

Notwithstanding the high frequency of prediabetes and newly diagnosed T2DM in heart failure, its impact on heart failure progression and survival outcomes has remained unresolved. Most evidence is derived from clinical trials and registries of patients with chronic stable HFrEF, in whom known T2DM has been consistently associated with higher risks of death and heart failure hospitalization, although in some older trials, the risk was higher in patients with ischaemic heart failure and in females.[31–35] These disparities were not corroborated in subsequent analyses, and the results of interaction analysis in the present study also suggest that dysglycaemia confers a worse prognosis independently of heart failure aetiology or gender. Unlike chronic HFrEF, available data in patients with acute or worsening chronic HFrEF are inconsistent, and mostly confined to the assessment of known T2DM. In the Italian IN-HF (Italian Network on Heart Failure) registry, known T2DM and hyperglycaemia at admission were strong predictors of in-hospital mortality, but had no effect on one-year risk of death.[36] Conversely, post hoc analysis of several clinical trials, as well as data from a large pan-European long-term heart failure registry indicate that known T2DM is a strong predictor of impaired survival, one-year and beyond following hospitalization for acute or worsening chronic heart failure.[7,27,35,37]

Our findings confirm and extend these observations by demonstrating that, in addition to known T2DM, prediabetes and newly diagnosed T2DM are not only common in patients hospitalized with worsening HFrEF, but also independently associated with impaired long-term survival following heart failure hospitalization. Although common, these abnormalities often remain clinically undetected or underappreciated, and consequently expose the patients to the long-standing risk of heart failure progression.[38] In addition, following an episode for acute or worsening HFrEF, patients may become more vulnerable to the harmful effects of dysglycaemia, as suggested by our findings. As compared with normoglycaemic individuals, patients with prediabetes not treated with glucose lowering medications had a substantially higher mortality rate, which strongly supports the notion of a detrimental effect of dysglycaemia per se on heart failure progression.

Based on our results, and concordant with current guidelines,[15,23,39] there are several lines of preventive measures worthy of consideration. First, adopting a widespread screening of heart failure patients without known T2DM with either 2-h OGTT or HbA_{1c} could decrease the burden of these conditions and enable a timely application of preventive strategies.[23] Although optimal management of prediabetes in heart failure remains to be defined, a benefit could be expected from lifestyle modifications (e.g. healthy eating pattern and increased physical activity) with a proven ability to delay the progression to overt T2DM.[40] Notably, in a randomized trial assessing the effects of exercise training in patients with HFrEF, patients with diabetes exhibited lower functional capacity and attenuated response to exercise compared with normoglycaemic individuals.[41] Despite these limitations, there was no interaction between T2DM and exercise on clinical outcomes (i.e. mortality and hospitalization).[41] Recent data suggest that exercise training following an episode of worsening heart failure could be safe and effective in improving functional capacity and endothelial function in heart failure.[42–44] It is plausible that patients with prediabetes and HFrEF may be more responsive to the benefits of exercise, but this remains to be determined. In addition, it might be worth assessing whether enhanced glycaemic control with sacubitril/valsartan observed in diabetics with HFrEF could be extended to patients with prediabetes.[45] Finally, our results stress the importance of better understanding the role of treatment across a broader range of glucometabolic abnormalities in heart failure, aiming to achieve timely and effective prevention of adverse events.

There are several limitations of our study. Most importantly, this was a single-centre study with a small number of enrolled patients, which has reduced the statistical power and resulted in high hazard ratios with wide CIs. Exclusion of patients with established T2DM precluded comparing the risk across the whole range of glucometabolic impairments in patients with worsening HFrEF. Also, HbA_{1c} levels in our patients could not be provided because of a significant proportion of missing data. Furthermore, considering that the assessment of glycaemic status was performed only once, there is a possibility that, in some patients, prediabetes and T2DM were misclassified due to the effects

of stress-induced hyperglycaemia and/or reduced insulin sensitivity. Certainly, repeating 2-h OGTT after discharge would have increased the diagnostic accuracy for dysglycaemia. Still, our results are consistent with previous studies in similar patient populations and provide clinically relevant information that needs to be confirmed in a larger study.

In conclusion, unrecognized prediabetes and T2DM are common in patients hospitalized for worsening chronic HFrEF with NYHA class II–III symptoms and are independently associated with a higher long-term risk of all-cause and cardiovascular mortality. Our results highlight the importance of screening for unrecognized prediabetes and T2DM in the setting of worsening HFrEF. In addition, development of strategies to prevent and/or treat a broader spectrum of glucometabolic abnormalities deserves further consideration with a prospect to improve outcomes in HFrEF.

Author contribution

AP, AR, JPS, GK, MA and PMS contributed to the conception or design of the work. AP, MP, JPS, IV, IM and IOP contributed to the acquisition, analysis or interpretation of data for the work. AP, MP, AR, JPS and PMS drafted the manuscript. AR, MP and PMS critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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