Cardiovascular Diabetology

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Sex differences in the diagnostic algorithm of screening for heart failure by symptoms and NT-proBNP in patients with type 2 diabetes

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Abstract

Objectives This study aimed to assess the guideline recommended diagnostic tools NT-proBNP and NYHA classification, with a focus on sex-specific differences.

Background Patients with Type 2 Diabetes (T2D) face a heart failure (HF) risk up to four times higher than those without T2D, particularly affecting women more than twice as much as men. Despite distinct pathophysiological differences between men and women, there are currently no sex-specific recommendations for the diagnostic algorithm of HF in diabetic patients.

Methods A total of 2083 patients with T2D were enrolled, and the primary endpoint was heart failure during hospitalization within a 5-year timeframe. The secondary endpoint was all-cause death.

Results In female patients, frequency of HF diagnosis prior to or during hospitalization and mortality did not differ significantly between NYHA II and III, in contrast to male patients. Additionally, there was no notable difference in mean NT-proBNP levels between NYHA stage II and III only in female patients. The multivariable regression analysis highlighted NYHA classification not to be a predictor of NT-proBNP levels in female but solely in male patients. On multivariable Cox regression NYHA score was also no significant risk factor for occurence of HF in female patients. Furthermore, there was no significant disparity in mortality between men with NT-proBNP levels between 125 and 400 pg/ml and those below 125 pg/ml, whereas in women mortality was significantly higher in the group with NT-proBNP levels between 125 and 400 pg/ml than below 125 pg/ml.

Conclusion These findings suggest that NYHA classification may not be the most suitable tool for assessing the diagnosis of HF in female patients with T2D. Moreover, the need for consideration of a more symptom-independent screening for HF in female patients with T2D and re-evaluation of current guidelines especially regarding sex-specific aspects is highlighted.

Keywords Type 2 diabetes, Heart failure, Sex, Gender, NYHA, NT-proBNP, Mortality

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Introduction

Type 2 Diabetes (T2D) is one of the most frequent chronic diseases worldwide with a prevalence rate of 11% [1, 2]. Uncontrolled hyperglycemia leads to an increased cardiovascular (CV) risk and mortality [3–6]. Furthermore, risk of heart failure (HF) in patients with T2D is up to 4 times higher than in patients without T2D [7–11]. Looking at sex differences, men are more often diagnosed with HF with reduced (HFrEF) ejection fraction while women more often feature HF with preserved ejection fraction (HFpEF). Pathophysiology of HFpEF is not clarified so far. Obesity and insulin resistance are hypothesized to play a critical role in the development of HFpEF, causing myocardial hypertrophy, collagen deposition and fibrosis [12, 13]. Independent of ejection fraction, T2D is associated with worse clinical status and increased CV mortality in HF patients [14].

The higher prevalence of HFpEF in women [15–17] may also be due to misclassification since women tend to have a higher LVEF compared to men [18–21]. Higher stroke volume of the heart might be explained by lower afterload due to estrogen-mediated stimulation of the production of nitric oxide, resulting in a lower total peripheral resistance [22, 23]. Despite a preserved systolic ejection fraction (EF), risk of HF and decompensation seems to be higher in female T2D patients compared to male T2D patients [16, 24–27]. Diabetes may represent a more crucial role in the pathophysiology of HF in women, since diabetes more than doubles the HF risk in women compared to men (5 times higher risk in women versus 2 times higher risk in men) [24], which highlights the importance of HF screening in patients with T2D.

ESC Guidelines state that "Plasma concentrations of NPs are recommended as initial diagnostic tests in patients with symptoms suggestive of HF to rule out the diagnosis" [28, p-3617]. More and more studies describe differences in symptoms and B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels for diagnosing HF between men and women [29–34]. Especially pretest probability of symptoms depending on sex was never tested in a chronic setting. Therefore, the aim of this study is to analyze sex-specific differences in the diagnostic algorithm recommended by the guidelines.

Methods

Study design

Study population and procedure was explained in detail earlier in [35]. In summary, this is a post hoc analysis of a prospective study performed at the Medical University of Vienna investigating heart failure risk in T2D patients. Patients were enrolled from December 2005 to January 2010 from four diabetes outpatient departments in a prospective registry. At baseline, medical history (including comorbidities, diabetes duration, medication, NYHA class), anthropometric data (including body weight, height, body mass index and blood pressure) and blood samples were collected. The observation period was 5 years. Approval of the local Ethics Committee of the Medical University of Vienna and written informed consent of all patient was obtained. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Study population

Inclusion criteria were diagnosed type 2 diabetes, minimum age of 18 years and willingness to participate.

Laboratory analysis

For laboratory analysis fasting samples were used and included lipid parameters, creatinine, parameters of the glucose metabolism and NT-proBNP levels. NT-proBNP levels were measured using a point-of-care system (COBAS H232, Roche Diagnostics Rotkreuz, Switzerland). Limit of detection was 59 pg/ml.

Endpoints

The primary endpoint was unplanned hospitalization for heart failure or manifest heart failure during hospitalization in the period of 5 years, which was used to estimate the event-free survival. Secondary endpoint was all-cause-death at 5 years. Mortality data was obtained from the Austrian Death Registry.

Statistical analysis

Metric data was presented as mean and ±standard error (SE) and discrete data as frequency and percentages. For comparison of not normally distributed data Mann–Whitney-U-test was used and for normally distributed data t-test. For comparison of more than two groups Kruskal-Wallis was performed. The Spearman correlation rank test was applied for correlation analyses. Linear regression models were calculated for multivariable adjustment. For evaluation of prognostic utility of recommended cut-off levels of NT-proBNP and New York Heart Association (NYHA) classification, patients were divided into groups according to the NYHA score and by NT-proBNP thresholds of ≥400 pg/ml and ≥125 pg/ml, which are recommended by the National Institute for Health and Care Excellence (NICE) and the European Society of Cardiology (ESC) for patients with suspected heart failure, respectively [28, 36]. Observed 5-year mortality and event-free survival (survival free from the primary endpoint) were presented using Kaplan-Maier curves and estimates. Differences between groups were compared using the log-rank test. Cox proportional hazard regression model was used to estimate hazard ratios. Sensitivity and specificity analysis was done using

R version 4.3.2 and repeated with log-transformed NT-proBNP values to reduce the impact of extreme values. Cut-off values were calculated as: Youden index (YI) = sensitivity + (1−specificity). A two-sided p-value of <0.05 was considered as statistically significant. All other statistical analyses were performed with IBM SPSS version 27.

Table 1 Baseline characteristics of female and male patients with T2D of the study population

	All	Men	Women	*p*-value
N (%)	2083	1148 (55.1%)	935 (44.9%)	
Age (years)	60.92 (±0.29)	60.29 (±0.37)	61.68 (±0.44)	**0.009**
BMI (kg/m^2)	29.19 (±0.13)	28.9 (±0.16)	29.55 (±0.19)	**0.007**
HbA1c (%)	7.37* (±0.03)	7.26* (±0.04)	7.48 (±0.04)	**<0.001**
NT-proBNP (pg/ml)	244.75 (±8.88)	248.29 (±13.08)	240.41 (±11.54)	**<0.001**
Creatinine (mg/dl)	1.04 (±0.01)	1.12 (±0.01)	0.94 (±0.01)	**<0.001**
eGFR (ml/min)	73.27 (±0.1)	76.78 (±0.56)	68.94 (±0.57)	**<0.001**
DM duration (years)	13.64 (±0.27)	13.43 (±0.37)	13.89 (±0.4)	0.346
LDL (mg/dl)	104.63 (±0.78)	103.84 (±1.15)	105.60 (±1.02)	**0.029**
Arterial Hypertension (%)	1437 (69.0%)	784 (65.2%)	653 (69.8%)	0.448
AF (%)	52 (2.5%)	32 (2,8%)	20 (2.1%)	0.340
CABG (%)	74 (3.6%)	63 (5.5%)	11 (1.2%)	**<0.001**
PCI (%)	74 (3.6%)	53 (4.6%)	21 (2.2%)	**0.014**
NYHA class				**<0.001**
NYHA I (%)	1782 (85.5%)	1015 (88.4%)	767 (82.0%)	
NYHA II (%)	234 (11.2%)	107 (9.3%)	127 (13.6%)	
NYHA III (%)	63 (3.0%)	26 (2.3%)	37 (4.0%)	
NYHA IV (%)	4 (0.2%)	0	4 (0.4%)	
RAS inhibitors (%)	1212 (58.2%)**	669 (58.3%)	543 (58.1%)	0.958
Beta-blocker (%)	599*** (28.9%)	329 (28.7%)	270 (29.1%)	0.847
Diuretics (%)	695**** (33.4%)	357 (31.1%)	338 (36.3%)	**0.014**
Aldosterone antagonist (%)	65***** (3.1%)	30 (2.6%)	35 (3.8%)	0.220
Insulin (%)	1138 (54.6%)	640 (55.8%)	498 (53.3%)	0.257
Statin (%)	918 (44.1%)	496 (43.2%)	422 (45.1%)	0.656
PAD (%)	189 (9.1%)	94 (8.2%)	95 (10.2%)	0.119
CVD (%)	111 (0.5%)	74 (6.4%)	37 (4.0%)	**0.012**

Data is presented as mean ± standard error or percentages

BMI: body mass index, HbA1c: glycated haemoglobin, eGFR: estimated glomerular filtration rate, DM: Diabetes mellitus, LDL: low-density lipoprotein, AF: atrial fibrillation, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, NYHA: New York Heart Association, RAS: renin-angiotensin system, PAD: Peripheral artery occlusive disease, CVD: Cerebrovascular disease

*Missing data from 19 patients

**Missing data from 5 patients

***Missing data from 9 patients

****Missing data from 5 patients

*****Missing data from 15 patients

Results

Baseline characteristics of the study population

A total of 2186 patients with T2D were enrolled in the study, 103 patients were excluded from the analysis due to missing outcome data. The study population included 1148 (55.1%) men with a mean age of 60.29 ± 0.37 years and 935 (44.9%) women with a mean age of 61.68 ± 0.44 years ($p=0.011$). Detailed description of the baseline characteristics is shown in Table 1. Note that in the following we report comparisons between males and females that were not adjusted for these differences in age. Female patients tended to a higher rate of obesity (body mass index (BMI) (29.55 ± 0.199 kg/m^2 vs. 28.9 ± 0.16 kg/m^2) and were diagnosed more frequently with cerebral vascular disease (CVD) (6.4% vs. 4.0%). Men suffered more frequently from coronary artery bypass graft (CABG) (5.5% vs. 1.2%) and percutaneous coronary intervention (PCI) (4.6% vs. 2.2%). In terms of laboratory parameters, female patients had higher low-density lipoprotein (LDL) (105.60 ± 1.02 mg/dl vs. 103.84 ± 1.15 mg/dl) and HbA1c values (7.48 ± 0.04% vs. 7.26 ± 0.04%) than male patients. NT-proBNP levels showed a strongly right-skewed distribution (SD much higher than mean) that were significantly higher in men (248.29 ± 13.08 vs. 240.41 ± 11.54). Regarding medication, diuretic use was more frequent in female patients (36.3% vs. 31.1%). There was no significant difference in the frequency of renin-angiotensin system (RAS) inhibitors, beta-blockers, aldosterone antagonists, insulin and statin use. Women were more likely to score a higher NYHA class than men ($p<0.001$) in the unadjusted analysis.

Sex-specific differences in NT-proBNP levels

NT-proBNP levels significantly correlated with age in female and male patients ($r=0.48$ vs. 0.49 respectively, p-value <0.001). In Fig. 1 mean NT-proBNP levels of female and male patients divided into subgroups with a 10-year interval are presented. Mean NT-proBNP levels rise significantly with increasing age.

The univariable and multivariable predictors of NT-proBNP in both groups are reported in Tables 2 and 3. There was no significant correlation between NT-proBNP level and BMI or HbA1c in both groups. Multivariable analysis showed independent associations of NT-proBNP levels with creatinine, diagnosis of atrial fibrillation (AF) and CABG after adjusting for other possible confounders in both sexes. A significant independent association with the diagnosis of peripheral artery occlusive disease (PAD) was identified only in women. The significant independent association with NYHA classes remained evident only in the male group, while in the female group NYHA class did not predict NT-proBNP levels.

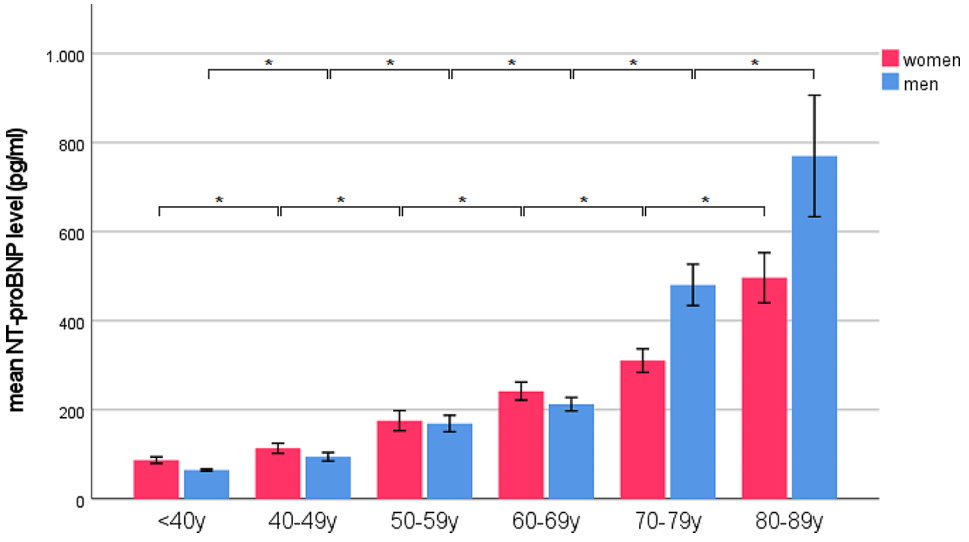

Fig. 1 Mean NT-proBNP levels and SE of female and male patients divided into subgroups with a 10-year interval

Table 2 Univariable and Multivariable predictors of NT-proBNP in male patients

	Men			
	Univariable model		Multivariable model**	
	β-Coefficient	*p* value	β-Coefficient	*p* value
Age (years)	11.115	**< 0.001**	6.424	**< 0.001**
Creatinine (mg/dl)	450.096	**< 0.001**	344.395	**< 0.001**
DM duration (years)	2.159*	**0.046**	− 0.812	0.384
Arterial Hypertension	96.503	**< 0.001**	− 12.131	0.628
AF	896.053	**< 0.001**	702.171	**< 0.001**
CABG	396.938	**< 0.001**	124.160	**0.016**
PCI	264.865	**< 0.001**	42.172	0.443
NYHA classes				
NYHA II	255.519	**< 0.001**	90.592	**0.029**
NYHA III	653.323	**< 0.001**	371.320	**< 0.001**
PAD	266.072	**< 0.001**	39.506	0.378
CVD	223.857	**< 0.001**	76.308	0.101
BMI (kg/m^2)	− 0.610	0.796		
HbA1c (%)	15.103	0.123		
LDL (mg/dl)	− 0.593	0.079		

DM: Diabetes mellitus, AF: atrial fibrillation, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, NYHA: New York Heart Association, PAD: Peripheral artery occlusive disease, CVD: Cerebrovascular disease, BMI: body mass index, HbA1c: glycated haemoglobin, LDL: low-density lipoprotein

*Missing data from 19 patients

**Adjusted for all significant univariable predictors (age, creatinine, DM duration, history of arterial hypertension, atrial fibrillation, coronary artery bypass graft, percutaneous coronary intervention, peripheral artery occlusive disease, cerebrovascular disease, NYHA class)

Table 3 Univariable and Multivariable predictors of NT-proBNP in female patients

	Women			
	Univariable model		Multivariable model*	
	β-Coefficient	*p* value	β-Coefficient	*p* value
Age (years)	7.575	**< 0.001**	3.400	**< 0.001**
Creatinine (mg/dl)	548.683	**< 0.001**	416.254	**< 0.001**
LDL (mg/dl)	− 1.057	**0.004**	− 0.643	**0.047**
Arterial Hypertension	77.297	**0.002**	− 2.227	0.924
AF	803.170	**< 0.001**	689.106	**< 0.001**
CABG	356.236	**< 0.001**	219.686	**0.02**
NYHA classes				
NYHA II	159.937	**< 0.001**	56.971	0.064
NYHA III	215.599	**< 0.001**	92.019	0.081
NYHA IV	43.281	0.804	− 198.084	0.201
PAD	192.660	**< 0.001**	104.147	**0.003**
CVD	52.816	0.372		
BMI (kg/m^2)	− 1.619	0.409		
HbA1c (%)	12.142	0.169		
DM duration (years)	1.617	0.103		
PCI	108.038	0.138		

LDL: low-density lipoprotein, AF: atrial fibrillation, CABG: coronary artery bypass graft, NYHA: New York Heart Association, PAD: Peripheral artery occlusive disease, CVD: Cerebrovascular disease, BMI: body mass index, HbA1c: glycated haemoglobin, DM: Diabetes mellitus, PCI: percutaneous coronary intervention

*Adjusted for all significant univariable predictors (age, creatinine, low-density lipoprotein, history of arterial hypertension, atrial fibrillation, coronary artery bypass graft, peripheral artery occlusive disease, NYHA class)

Symptoms do not reflect cardiac risk in women as accurate as in men

Dividing patients into subgroups according to NYHA stages, as expected NT-proBNP levels were significantly higher with higher NYHA scores (I vs. II vs. III) in male patients (209.68 ± 11.13 vs. 465.20 ± 69.92 vs. 863.00 ± 199.68; $p = 0.021$) (Fig. 2).

Interestingly, there was no significant difference in the NT-proBNP levels between NYHA stage II and III in female patients (369.91 ± 48.02 vs. 425.57 ± 94.38; $p = 0.572$), which highlights that NYHA classification

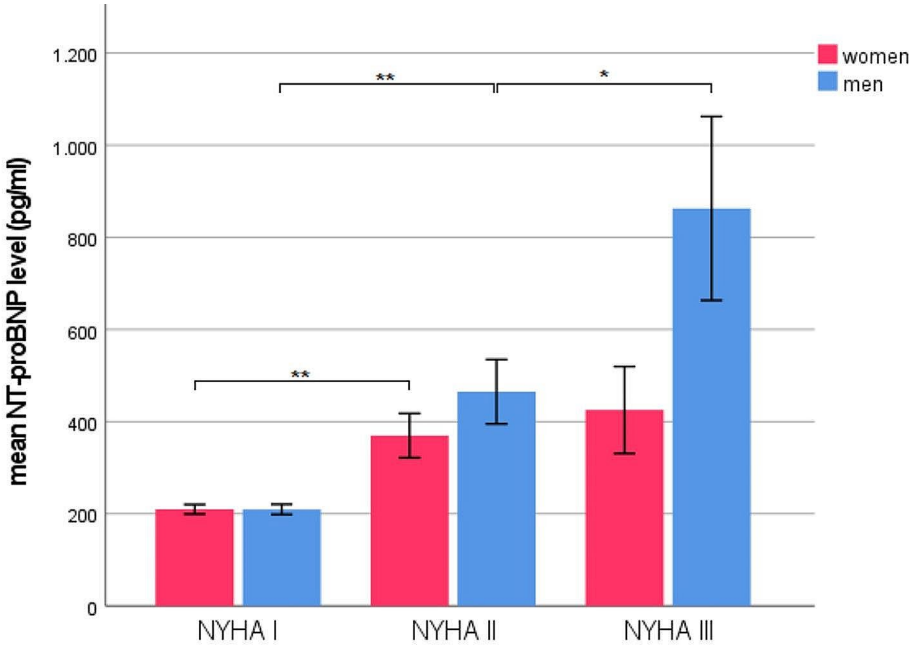

Fig. 2 Mean NT-proBNP levels ± SE of male and female patients stratified according to NYHA classification

might not reflect severity of cardiac risk mirrored by NT-proBNP levels in female patients as accurate as in male patients. It appears that especially severe symptoms (NYHA III) is not fully covered by a cardiac risk but severe symptoms might be also due to non-cardiac reasons.

Subgroup analysis of female and male patients with NYHA class II and III showed no significant difference in possible confounders such as BMI or HbA1c (Table S1 and S2).

NT-proBNP to rule out a risk for heart failure

During the 5-year observation period, 68 (7.3%) female and 74 (6.4%) male patients suffered from hospitalized manifest HF. There was no significant difference in HF occurrence between men and women over the total study population (log-rank, $p=0.428$).

Dividing women and men according to recommended NT-proBNP threshold levels, there was no significant sex-specific difference concerning the occurrence of HF at or during hospitalization (NT-proBNP level < 125 pg/ml: log-rank, $p=0.182$; 125–400 pg/ml: log-rank, $p=0.245$; ≥400 pg/ml: log-rank, $p=0.909$). With rising NT-proBNP level, risk for HF was significantly higher in both men and women (Fig. 3).

Using a threshold of ≥125 pg/ml as recommended by ESC, sensitivity for occurrence of HF over 5-years was 97.1% in female patients and 89.2% in male patients ($p=0.067$). Specificity was significantly lower in female patients (54.3% vs. 64.6%; $p<0.001$). Sensitivity in females was 51.5% (Specificity 90.0%) and 64.9% (Specificity 89.0%) in males using the cut-off level of ≥400 pg/ml according to the NICE (Sensitivity: $p=0.106$; Specificity: $p=0.497$). Using receiver operating characteristic (ROC) curve, area under the curve (AUC) of NT-proBNP value was 0.8611 and 0.8554 in female and male patients, respectively. YI value achieved the maximum at a NT-proBNP cut-off value of 190 pg/ml in female patients (Sensitivity: 93.1%, Specificity 69.7%). In male patients, the maximum value of YI was reached at a higher NT-proBNP value of 316 pg/ml (Sensitivity 72.5%, Specificity 85.6%) (Figure S1). Repeated analysis using log-transformed NT-proBNP levels confirmed higher NT-proBNP thresholds in male patients.

In univariate Cox regression analysis, a NT-proBNP level between 125 and 400 ng/ml was a risk factor for heart failure occurrence compared with the group with a NT-proBNP level < 125 ng/ml in men (HR 5.92, 95% CI: 2.57–13.61; $p<0.001$) and in women (HR 22.62, 95% CI: 5.42–94.7; $p<0.001$). HR for patients with a NT-proBNP level above 400 pg/ml was 5.33 (CI: 3.09–9.21; $p<0.001$) in male and 3.71 (CI: 2.29 − 6.03; $p<0.001$) in female patients, when compared to patients with NT-proBNP level between 125 and 400 pg/ml.

Women with a NT-proBNP level between 125 and 400 pg/ml had a higher mortality when compared to women with a NT-proBNP level below 125 pg/ml (HR 3.22, $p<0.001$) (Fig. 4). However, there was no significant difference comparing men with a NT-proBNP level between 125 and 400 pg/ml and below 125 pg/ml (HR 1.486,

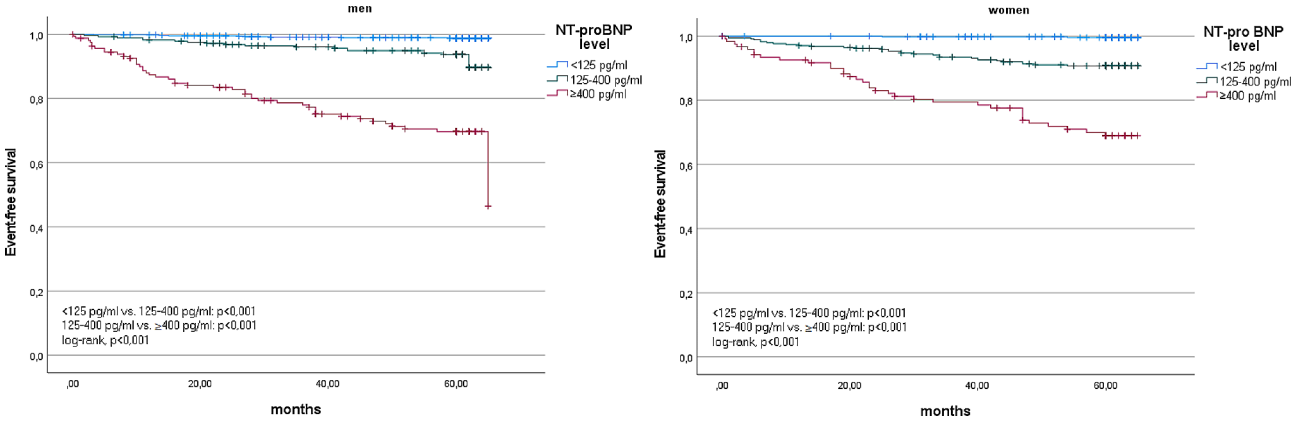

Fig. 3 Event-free survival (survival free from the primary endpoint) of male (left) and female (right) patients stratified according to the European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) recommended NT-proBNP threshold levels of 125 and 400 pg/ml, respectively

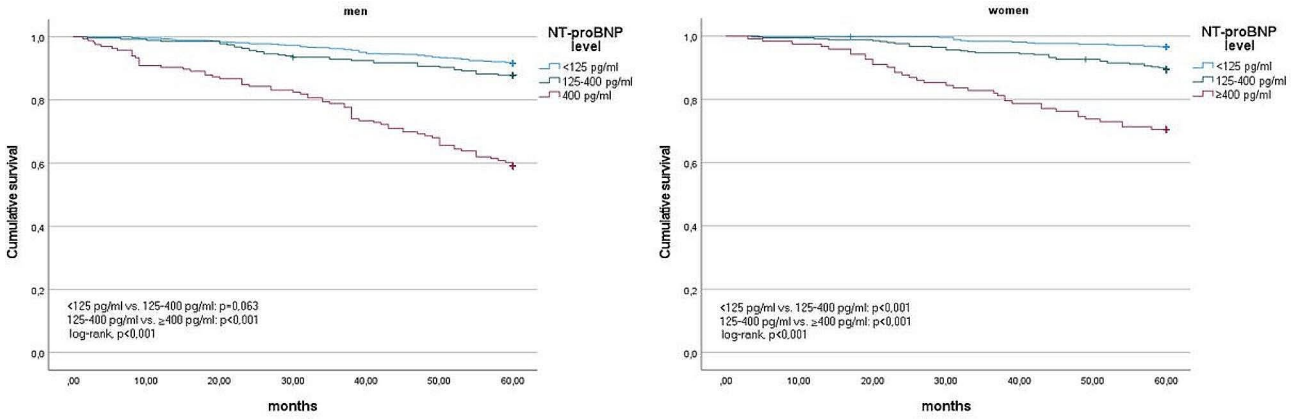

Fig. 4 Cumulative survival of male (left) and female (right) patients stratified according to the European Society of Cardiology (ESC) and the National Institute for Health and Care Excellence (NICE) recommended NT-proBNP threshold levels of 125 and 400 pg/ml, respectively

95%CI: 0.97–2.27; $p=0.066$) in mortality. In univariate Cox regression analysis, a NT-proBNP level≥400 ng/ml was a risk factor for all-cause death compared with the group with a NT-proBNP level<125 ng/ml in men (HR 6.02 95% CI: 4.25–8.54; $p<0.001$) and in women (HR 10.35, 95% CI: 5.74–18.66; $p<0.001$).

NYHA stage does not correlate with HF diagnosis in women

Female and male patients were divided into subgroups according to the NYHA classification. In male patients, HF diagnosed prior to or during hospitalization was significantly higher in groups with a higher NYHA score (log-rank, $p=0.021$) (Fig. 5). On unadjusted Cox regression analysis, HR for HF occurrence in male patients with a NYHA score III was 2.52 when compared to male patients with NYHA stage II (95%CI: 1.12–5.68; $p=0.026$). HF occurrence was significantly lower in female patients with a NYHA score I when compared to group NYHA II, but surprisingly there was no significant difference between NYHA II and III (log-rank, $p=0.352$) (Fig. 5). Sensitivity using NYHA score I compared to NT-proBNP cutoff of 125 pg/ml for HF diagnosis was significantly lower in male and female patients (men: 64.9% vs. 89.2% $p<0.001$; women: 57.4% vs. 97.1% $p<0.001$).

History of cardiovascular diseases and risk factors were analyzed using logistic regression (Table S3 and S4). Significant predictors for HF were further included in an age adjusted multivariable COX regression analysis and showed that NYHA score is no independent predictor for HF diagnosis in female patients and remained significant only in male patients (Table 4 and 5).

Looking at all-cause mortality, there was as well no significant difference between female patients with NYHA stage II and III (log-rank, p = 0.866) (Fig. 6). Comparing NYHA stage groups of male patients, all-cause mortality was significantly higher with rising NYHA stage (NYHA I vs. NYHAII log-rank p < 0.001, NYHA II vs. NYHA III log-rank, p = 0.011)

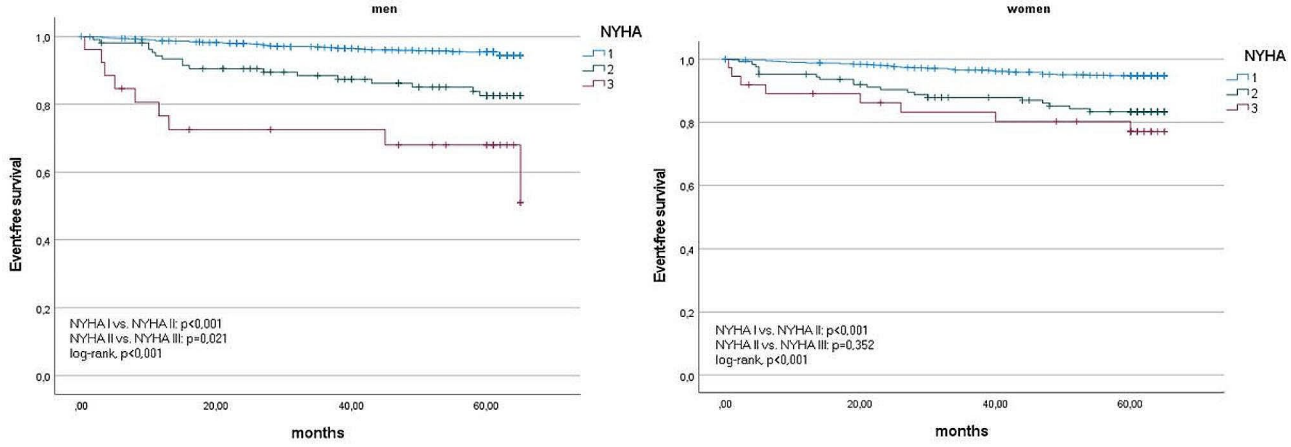

Fig. 5 Event-free survival (survival free from the primary endpoint) of male (left) and female (right) patients stratified according to the NYHA classification

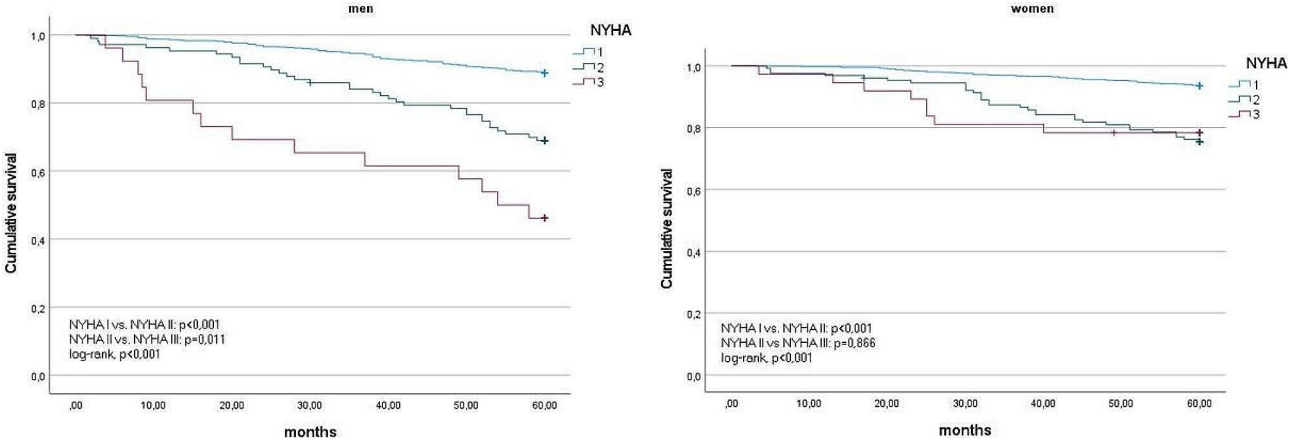

Fig. 6 Cumulative survival of male (left) and female (right) patients stratified according to the NYHA classification

Table 4 Multivariable COX regression analysis predicting HF diagnosis in male patients

	Men *p* value	Hazard ratio	95% CI for Hazard ratio	
			Lower	Upper
Age (years)	**< 0.001**	1.051	1.025	1.077
AF	**0.017**	2.601	1.184	5.712
NYHA I	**0.020**	0.485	0.264	0.892
PAD	**0.001**	2.780	1.509	5.121
CVD	0.454	1.302	0.652	2.598
HbA1c (%)	**0.007**	1.220	1.057	1.410
CABG	0.366	1.388	0.682	2.823

AF: atrial fibrillation, NYHA: New York Heart Association, PAD: Peripheral artery occlusive disease, CVD: Cerebrovascular disease, HbA1c: glycated haemoglobin, CABG: coronary artery bypass graft

Table 5 Multivariable COX regression analysis predicting HF diagnosis in female patients

	Women *p* value	Hazard ratio	95% CI for Hazard ratio	
			Lower	Upper
Age (years)	**< 0.001**	1.106	1.077	1.136
AF	**0.027**	2.612	1.114	6.122
NYHA I	0.115	0.687	0.379	1.111
PAD	**< 0.001**	2.817	1.564	5.076
CVD	0.687	1.189	0.513	2.754
HbA1c (%)	**< 0.001**	1.355	1.145	1.602
PCI	0.783	1.180	0.36	3.823

AF: atrial fibrillation, NYHA: New York Heart Association, PAD: Peripheral artery occlusive disease, CVD: Cerebrovascular disease, HbA1c: glycated haemoglobin, PCI: percutaneous coronary intervention

Discussion

The aim of this study was to evaluate the diagnostic value of NT-proBNP and NYHA classification in terms of sex-specific differences. The findings from this study underscored several critical nuances in the relationship between NT-proBNP levels, NYHA classification, and their respective associations with future HF diagnosis (i.e. HF hospitalization) and showed that dyspnea estimated by NYHA classification might not be suitable at all for the evaluation of diagnosis of HF in female patients with T2D.

In this study population, frequency of HF diagnosis and mortality did not differ between NYHA II and III in female patients, whereas in males there was a significant stepwise risk elevation between all stages. Furthermore, on Cox regression analysis adjusted for age and cardiovascular diseases NYHA score>I was no significant risk factor for HF diagnosis in women with T2D. Sensitivity using NYHA score I compared to NT-proBNP cutoff of 125 pg/ml for HF diagnosis was significantly lower in both sexes (men: 64.9% vs. 89.2% $p<0.001$; women: 57.4% vs. 97.1% $p<0.001$). There was no significant difference in mean NT-proBNP levels between NYHA stage II and III in female patients, in contrast to male patients and in multivariable Cox regression analysis NYHA classification was a significant predictor of NT-proBNP level only in male patients. With rising NT-proBNP level, mortality in female patients of this study population aligned with male mortality. Women with a NT-proBNP level between 125 and 400 pg/ml had a higher mortality when compared to women with a NT-proBNP level below 125 pg/ml. However, there was no significant difference comparing men with a NT-proBNP level between 125 and 400 pg/ml and below 125 pg/ml in mortality.

These findings reveal a noteworthy sex difference in how NT-proBNP levels reflect symptomatic variations. While NT-proBNP levels in male patients significantly increased with higher NYHA scores, indicating a potential alignment with symptom severity, this trend was not observed in female patients. This discrepancy suggests that the relationship between NYHA classification and NT-proBNP levels may not be as consistent in female patients as in their male counterparts.

NYHA classification is commonly used for diagnosis and prognosis estimation of HF, but does not include sex-specific considerations. Current ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, as well as diabetes-specific ESC Guidelines for the management of cardiovascular disease in patients with diabetes, recommend further evaluation such as measurement of NT-proBNP and echocardiography only in the presence of HF symptoms or signs [28, 37]. Furthermore, triage regarding the referral to an advanced HF centre of patients with advanced HF is recommended depending on the NYHA score [28]. Despite the widespread utilization of NYHA classification, our findings underscored its potential limitations, particularly when applied to women scoring higher NYHA classes. Unlike male patients, where higher NYHA stages correlated with increased frequency of HF diagnosis and mortality, NYHA stage did not exhibit a consistent association with adverse outcomes in female patients. This raises questions about the universality of NYHA classification as a prognostic tool in women with T2D and with and without HF. These observations appear inconsistent with other studies analyzing patient outcomes, disregarding their diabetes status [38, 39]. Notably, several studies have reported a more pronounced symptomatic profile in female HF patients compared to their male counterparts, despite similar survival rates [40–42], raising questions about the relationship between symptoms and prognosis in female patients.

Furthermore, diastolic dysfunction, especially elevated LV end-diastolic pressure, correlates with dyspnea [43, 44] and seems to be more predominant in female patients [45–48], offering a potential explanation for more pronounced and earlier onset of breathing disorders such as orthopnea, resulting in higher NYHA scores among women with HF.

In addition, depression prevalence in patients with T2D and HF is high, especially in women [42, 49–51], which might explain higher NYHA scoring in female patients of this study population without a worse HF prognosis or mortality, since fatigue or loss of energy seems to be more frequently reported by women than men with depressive disorders [52].

Using a NT-proBNP threshold level of ≥125 pg/ml as recommended by ESC, sensitivity for occurrence of HF during the 5-year observation period was higher in female than in male patients of this study population (97.1% vs. 89.2%). Compared to men, maximum YI assessing the diagnostic accuracy of NT-proBNP for HF was lower in women (190 pg/ml vs. 316 pg/ml). With rising NT-proBNP level, risk for HF was significantly higher in both men and women. All-cause mortality was significantly higher in male patients with a NT-proBNP level below 400 pg/ml compared to women with a similar NT-proBNP level. There was no sex-specific difference in the groups with NT-proBNP level≥400 pg/ml. In general, women with or without HF have a survival advantage over men [53, 54]. Within our study population, this advantage was discernible in female patients with an NT-proBNP level below 400 pg/ml. As NT-proBNP levels rose, the mortality of women converged towards that of men. Cardiovascular disease is still undertreated in female patients [55], which could contribute to the increased mortality of women with a NT-proBNP level above 400 pg/ml. In agreement with other studies, significantly higher HbA1c and LDL levels in female patients of this study population might also point out an undertreatment for diabetes and cardiovascular diseases in women [56, 57].

Inconsistent with other studies, BMI did not correlate with NT-proBNP level in this study population [58, 59]. Higher BMI is associated with lower NT-proBNP levels and raises concerns about underestimated NT-proBNP levels in obese patients. These concerns were not substantiated in this study. A possible explanation for the missing correlation in this study population might be the

high frequency of obesity of patients with T2D resulting in smaller BMI range in T2D populations.

Women with a NT-proBNP level between 125 and 400 pg/ml had a higher mortality when compared to women with a NT-proBNP level below 125 pg/ml. However, there was no significant difference comparing men with a NT-proBNP level between 125 and 400 pg/ml and below 125 pg/ml in mortality. Together this could indicate a stronger association of NT-proBNP level with mortality in female than in male patients and confirms the lower recommended NT-proBNP of 125 pg/ml, especially in women with T2D. Supporting our findings Rudolf et al. [60] found a stronger association between NT-proBNP level and mortality in women compared to men and Daubert et al. [61] demonstrated that an early NT-proBNP goal of ≤1000 pg/mL might have a greater prognostic value in female patients than in male patients. This contradicts with the findings of Cesaroni et al. [62] and Willeit et al. [63], who described a more pronounced association of logNT-proBNP with HF risk in male patients.

Limitations

The limitations of this study include restricted generalizability, as the study population consisted solely of T2D patients from Vienna. Additionally, the NYHA classification is designed to assess dyspnea in patients with heart failure, which may limit its applicability and lead or contribute to inconsistent results in studies analyzing patients already diagnosed with HF [38, 39], compared to this study population. Furthermore, prognostic evaluations of HF, including NYHA classification and NT-proBNP levels, were only collected at baseline. This, combined with the higher prevalence of HFpEF in women, may explain the limitations of the NYHA classification as a diagnostic tool for HF in women over a five-year observation period, as women with HFpEF often present with acute rather than chronic symptoms. Another limitation is the challenge in distinguishing between NYHA class II and III [64]. Moreover, the absence of data on left ventricular ejection fraction and other HF signs, such as edema, neck vein distension, nocturia, or paroxysmal nocturnal dyspnea, represents another limitation. The inclusion of additional diagnostic tools, such as the six-minute walking test and the Kansas City Cardiomyopathy Questionnaire, might also provide further insights into sex-specific differences in the clinical presentation of HF as well as offering advanced and deeper understanding regarding efficiency and effectiveness of them as diagnostic tools.

In summary, our study serves as a critical contribution to the understanding of diagnositic and prognostic markers in the context of HF and sex disparities. We emphasize the potential limitations of NYHA classification, particularly in female patients, and illuminate the correlation between NT-proBNP levels and mortality, with an emphasis on the female cohort. These findings highlight the importance of a more symptom-independent screening for heart failure in female patients with T2D and underscore the need for tailored prognostic approaches, considering the multifaceted aspects of sex-specific differences in HF patients with T2D.

Abbreviations

AF	Atrial fibrillation
AUC	Area under the curve
BMI	Body mass index
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass graft
CVD	Cerebrovascular disease
DM	Diabetes mellitus
ESC	European Society of Cardiology
EF	Ejection fraction
HbA1c	Glycated haemoglobin
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LDL	Low-density lipoprotein
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PAD	Peripheral artery occlusive disease
PCI	Percutaneous coronary intervention
RAS	Renin-angiotensin system
ROC	Receiver operating characteristic
SD	Standard deviation
SE	Standard error
T2D	Type 2 diabetes
YI	Youden index

Supplementary Information

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Supplementary Material 1

Author contributions

S.H.-Z. wrote the manuscript and prepared figures and tables. A.K.-W., M.L., M.H. and S.H.-Z. interpreted the data. P.K. and S.H.-Z. performed the statistical analyses. All authors reviewed the manuscript.

Data availability

The datasets used in the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

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