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ORIGINAL RESEARCH ARTICLE

6 min walk test is a strong independent predictor of death in outpatients with heart failure

Morten Grundtvig[1,2]*, Torfinn Eriksen-Volnes[1,3], Stein Ørn[4,5], Eva Kjøl Slind[1] and Lars Gullestad[6,7]

[1]*Department of Medicine and Health Care, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway;* [2]*Division Lillehammer, Department of Medicine, Innlandet Hospital Trust, Lillehammer, Norway;* [3]*Norwegian University of Science and Technology, NTNU, Trondheim, Norway;* [4]*Department of Cardiology, Division of Medicine, Stavanger University Hospital, Stavanger, Norway;* [5]*Department of Electrical Engineering and Computer Science, Faculty of Science and Technology, University of Stavanger, Stavanger, Norway;* [6]*Department of Cardiology, Division of Cardiovascular and Pulmonary Diseases, Oslo University Hospital, Rikshospitalet, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway;* [7]*KG Jebsen Cardiac Research Center and Center for Heart Failure Research, Oslo University Hospital, Postbox 4956 Nydalen, Oslo, 0424, Norway*

Abstract

Aims The aim of this study was to examine the prognostic value of the 6 min walk test (6MWT) in a large cohort of outpatients with heart failure.

Methods and results A total of 5519 outpatients with heart failure from the National Norwegian Heart Failure Registry (NNHFR), which is part of the Norwegian Cardiovascular Disease Registry, were included in this analysis. The NNHFR recommended the use of the 6MWT for prognostic assessment of all patients included in the registry. Patients were categorized according to the 6MWT: Category 1 walked the longest and Category 3 the shortest. During a median (25th–75th percentiles) follow-up of 24 (14–36), 12.9% of the patients died. Patients in Category 3 had the overall worst outcome than had patients in Categories 1 and 2. 6MWT used as a continuous variable was a highly significant independent predictor for mortality in a multivariate Cox regression model adjusted for 16 other variables with a hazard ratio of 0.979 [(95% confidence interval 0.972–0.986), $P < 0.001$]. The four most important predictors for mortality were active cancer in the last 5 years, age, 6MWT, and natriuretic peptides (all $P < 0.001$).

Conclusions 6MWT is a strong independent predictor of mortality in outpatients with HF. The findings support the use of the 6MWT in the prognostic assessment of patients with HF irrespective of HF aetiology.

Keywords Exercise testing; 6 min walk test; Heart failure; Mortality; Registry; Natriuretic peptides

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**Correspondence to: Morten Grundtvig, St. Olavs Hospital HF, Seksjon for medisinske kvalitetsregistre, Norsk hjertesviktregister, Postboks 3250 Torgarden, 7006 Trondheim, Norway. Tel: +47 92218497; Fax: +47 61272039.*
Email: morten-g@online.no

Introduction

Exercise capacity is one of the strongest predictors of survival in patients with heart failure (HF).[1,2] However, an objective assessment of exercise capacity has not been included in current guidelines to assess prognosis.[3]

Maximal functional capacity can be accurately measured as peak VO_2 by cardiopulmonary exercise testing.[4,5] The 6 min walk test (6MWT) is a readily available test reflecting the general capacity to perform activities of daily living.[6] The 6MWT is reproducible and sensitive to change in the quality of life.[7,8] Previous studies have been conflicting on the prognostic usefulness of the 6MWT; some studies demonstrated a prognostic impact,[9–13] whereas others found no association between the 6MWT and its outcomes.[14–17] Former studies were small and performed before contemporary HF treatment. However, on the basis of previous results, we hypothesized that 6MWT would be of prognostic importance when tested in a large cohort of patients with HF. The aim of the present study was therefore to assess the prognostic implication of 6MWT in a large sample of outpatients with contemporary HF treatment.

Methods

Study design

The National Norwegian Heart Failure Registry (NNHFR) has collected data on outpatients referred to HF clinics in Norwegian hospitals since 2013. The patients are enrolled successively after being diagnosed with chronic HF of any aetiology according to the ESC HF Guidelines from 2012[18] and 2016[3] when this latest Guidelines were available. All participating hospitals have specially trained nurses working in close collaboration with cardiologists. The NNHFR registry uses a web-based system, and data entered into the system are demographic data, aetiology of HF, left ventricular ejection fraction (LVEF), ECG parameters including heart rate, systolic blood pressure, blood tests, and the 6MWT. All data pertinent to this study were recorded at the first registered visit. LVEF was registered according to local practice (echocardiography, ventriculography using isotopes, or cardiac magnetic resonance imaging). Patients with HF primarily due to chronic obstructive pulmonary disease (COPD) or pulmonary hypertension, secondary to pulmonary disease, were not included in the registry. COPD/asthma was therefore only registered as a co-morbidity.

The 6MWT was conducted following a standardized protocol. Patients were instructed to walk at a self-selected pace in a suitable space (for example a corridor) of 20 to 50 m length for 6 min. The result of the test may be influenced by the encouragement of bystanders; the protocol therefore specifies that only phrases like 'You are doing well' and 'Keep up the good work' may be used to inspire performance. The total distance covered was measured to the nearest metre.

Mortality data were obtained continuously from the Norwegian national registry and automatically recorded in the NNHFR. This study is pursuant to the Norwegian regulation of the register of Cardiovascular diseases from 2012 §2-2. The National Institute of Public Health has responsibilities for correct information and shall ensure that the data processed in the registry are correct, relevant, and necessary. The study complies with the Declaration of Helsinki. The study is exempt from being assessed by the Regional Committee for Health Research ethics owing to it being the done on an anonymized data set. The study complies with the EU 2016/679 General Data Protection Regulation. No patient has been lost to follow-up with regard to mortality.

Statistical analyses

Continuous variables are presented as mean ± standard deviation or median with interquartile range represented by the 25th and 75th percentiles, as appropriate and categorical variables as percentages (%). The 6MWT was divided into tertiles and assigned Categories 1 (longest distance) to 3 for the presentation of patient characteristics. Category 1 was used as the reference for all analyses of the 6MWT. New York Heart Association (NYHA) functional class was assigned categorical variables 1–4 and smoking history 0–2 (non-smoker, ex-smoker, and current smoker).

Renal function was expressed as an estimated glomerular filtration rate (eGFR) and calculated using Chronic Kidney Disease Epidemiology Collaboration equation. Use of diuretics was calculated as daily dose (mg per 24 h) of furosemide + 40 mg × bumetanide + thiazide × 10 mg or 0 (yes or no). The natriuretic peptides were divided into tertiles for both N-terminal pro-B-type natriuretic peptide (NT-proBNP) and BNP, and the resulting tertiles were combined. Anaemia was defined as Hgb < 12 g/100 mL in women and Hgb < 13 g/100 mL in men. Cancer was defined as any cancer within the last 5 years except localized prostatic cancer and cervical carcinoma *in situ*.

Differences in continuous variables were compared by Student *t*-test, and differences in categorical variables were compared by Pearson's χ^2 test. The two-tailed significance level test was set to $P < 0.05$.

Cox proportional regression models (univariate and multivariable) were used to develop predictors for all-cause mortality. Multivariate regression was done by the backward Wald method to identify independent predictors of all-cause mortality from available variables (*P*-value for entry was <0.05; *P*-value for removal was >0.1). The 6MWT was examined as a continuous variable. The risk of mortality for the variables was expressed as the hazard ratio and their 95% confidence intervals (CIs). Survival curves were presented using Kaplan–Meier statistics according to the patient's tertile categories of the 6MWT. Intergroup differences were assessed by the log-rank test. A ROC curve was produced for the 6MWT with sensitivity and 1 − specificity to predict death; and the highest sum of sensitivity and specificity measurements were chosen to give an estimate of the 6MWT for the prediction. All statistical analyses were performed using IBM SPSS Statistics Version 25 (IBM SPSS Statistics, New York, USA).

Results

Study population

A total of 5519 patients in the NNHFR from 40 hospital outpatient HF clinics were included in this analysis. Data were collected from 2013, but >95% of the data were collected in 2015 until the end of December 2018. Two-thirds of patients had been hospitalized within the previous 6 months before the first visit. The median age was 70 (61–77) years. The main HF aetiologies were ischaemic heart disease in 48%, tachycardia 15%, non-ischaemic dilated cardiomyopathy 13%, valvular

7%, hypertension 6%, and others and unknown 18%. The majority of patients were in NYHA functional class II (52%) and class III (35%). The LVEF was <40% in 71% (HF with reduced ejection fraction), 40–49% in 20.7% (HF with mid-range ejection fraction), and ≥50% in 8.3% [HF with preserved ejection fraction (HFpEF)] of the patients. Missing values in the registry were none for medications, co-morbidities, LVEF, age, and sex; 0.9% for the natriuretic peptides; and <1% for other variables.

6 min walk test and baseline characteristics

The 6MWT studied was done by the patients on the day of the first registered visit or the latest within 2 weeks if time to do the test was not sufficient at the first visit. The 6MWT was done by the nurses in the 40 hospitals. The median 6MWT was 420 (320–503) m. For presentation purposes, the 6MWT was divided into tertiles ≥480, 361–479, and ≤360 m. In Categories 1, 2, and 3, the median 6MWTs were 540, 420, and 275 m, respectively.

The number of patients in the middle tertile counts fewer patients than in the other tertiles. This is due to many patients with the same recorded 6MWT of 480 m in the first tertile and 360 m the third tertile.

At the first visit, >90% of the patients received a beta-blocker and an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) with doses of 44% and 50% of the recommended doses, respectively (*Table 1*). During follow-up, a further titration of the treatment during the next weeks occurred with 95% of the patients receiving a beta-blocker, 90% received an ACEi or an ARB in combination with a beta-blocker, and 31% received a mineralocorticoid receptor antagonist (MRA). Baseline characteristics are given in *Table* 1. As compared with patients who walked the longest (Category 1), patients who walked the shortest (Category 3) had the following significant difference in their characteristics: they were on average 12 years older; more frequently women; had a higher combination of ex-smokers and smokers; more frequently had ischaemic HF or anaemia; more frequently had history of stroke; had higher frequency of cancer in the last 5 years; more frequently had diabetes mellitus; more frequently had obstructive lung disease; had lower systolic blood pressure; had higher heart rate; had wider QRS; more frequently had pacemaker stimulation in the ventricle; had higher LVEF; had higher NYHA functional class; had lower serum sodium; had higher uric acid; had higher NT-proBNP or BNP; frequently used more daily diuretics; frequently used higher beta-blocker doses; frequently used less and smaller doses of ACEi or ARBs; frequently used more MRAs; and had a higher crude mortality. They had more frequently stroke, diabetes mellitus, COPD or asthma, cancer, and pacemaker; they used higher doses of diuretics and more frequently

Table 1 Baseline characteristics of patients attending the first visit at specialized hospital outpatient heart failure clinics in relation to tertiles of categories of the 6 min walk test (n = 5519)

		Categories of 6MWT (1–3)		
Variable	All	1	2	3
n of patient	5519	1851	1794	1874
6MWT (m)	410 (136)	552 (61)	422 (31)	258 (81)
Age (years)	68.6 (12.1)	62.4 (11.5)	68.5 (11.1)	74.3 (10.4)***
Female sex (%)	26	17	24***	39***
BMI (kg/m^2)	27.2 (5.2)	27.1	27.3	27.2
Smoker (%)	67.6	53.7	69.9***	69.5***
Ischaemic HF (%)	48	45	47	50**
Anaemia (%)	21	11	19***	33***
Stroke (%)	10	7	8*	14***
Cancer (%)	5	5	6*	7**
DM (%)	23	15	23***	28***
COPD or asthma (%)	18	10	18***	26***
Systolic BP (mmHg)	122 (110–139)	124 (111–139)	122 (110–139)	120 (109–138)***
Heart rate/min	73.4 (16.5)	69.9 (15.5)	73.6 (17.0)***	76.3 (17.3)***
QRS width (ms)	116.1 (34.8)	113 (33)	116 (33)***	118 (35)***
PM (%)	11	8	11*	15***
LVEF (%)	33.4 (10)	33 (9)	33 (10)	35 (11)***
HFrEF (%)	71.0	72.0	74.9*	66.2***
HFmrEF (%)	20.7	23.6	17.7***	20.8*
HFpEF (%)	8.3	4.5	7.4***	13.0***
NYHA (1–4)	2.2 (0.7)	1.8 (0.6)	2.2 (0.6)***	2.6 (0.6)***
S-sodium (mmol/L)	140.3 (2.9)	140.6 (2.5)	140.4 (2.9)*	139.9 (3.4)***
S-potassium (mmol/L)	4.43 (0.44)	4.44 (0.39)	4.43 (0.44)	4.40 (0.49)
eGFR (mL/min/1.73 m^2)	65.8 (23.2)	76 (20)	66 (21)***	54 (21)***
Uric acid (μmol/L)	439 (123)	418 (104)	436 (116)***	472 (140)***
NT-ProBNP (pg/mL)	1712 (796–3398)	1093 (478–212)	1712 (847–3262)***	2588 (1271–5102)***
BNP (pg/mL)	287 (119–607)	206 (87–409)	303 (136–605)***	403 (199–837)***
Diuretics (mg/day)	40 (0–40)	20 (0–40)	40 (0–40)***	40 (20–80)***
Beta-blocker (%)	91.0	90.8	91.9	90.2
Beta-blocker dose (%)	44 (35)	40 (32)	45 (36)***	46 (36)***
ACEi/ARB (%)	90.0	94.1	91.8**	84.3***
ACEi/ARB dose (%)	49 (34)	51 (33)	52 (34)	42 (34)***
MRA (%)	29.1	26.6	29.7*	31.0**
ICD	11	10.9	12.7	10.7
CRT	6	5.3	6.6	5.9
Crude mortality (%)	13	4	9***	25***

Values are expressed as mean and standard deviation (SD), median and 25th–75th percentiles, or per cent. Categories 2 and 3 were compared with Category 1.
6MWT, 6 min walk test; ACEi/ARB dose (%), per cent of the recommended dose of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; Beta-blocker dose (%), per cent of the recommended dose; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; Cancer, any cancer within the last 5 years except localized prostatic cancer and cervical carcinoma *in situ*; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; Diuretics, daily doses of furosemide

mg + 40 × bumetanide and 10 mg was added if using thiazide; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; PM, pacemaker stimulation in the ventricle; Smoker, combined ex-smoker and current smoker.
$^{*}P < 0.05$.
$^{**}P < 0.01$.
$^{***}P < 0.001$.

used MRA. The 6MWT had a positive correlation with eGFR (r = 0.41, P < 0.001) and a negative correlation with age (r = −0.44, P < 0.001), while there was very weak correlation with LVEF (r = −0.06, P < 0.001) and weak correlation with NT-proBNP (r = −0.29, P < 0.001) (*Figure 1*).

6 min walk test and mortality

During a median follow-up of 24 (14–36) months in survivors, 12.9% of the patients died. The lowest mortality was in Category 1 of 4%, increasing to 9% in Category 2, and 25% in Category 3. *Figure 2* shows the Kaplan–Meier survival curves during the first 48 months for the categories of the 6MWT. The distribution was highly significant (P < 0.001).

Twenty-two variables were significantly associated with all-cause mortality in univariate analysis (P < 0.05), including the 6MWT (*Table 2*). All these variables were included in a final multivariate Cox regression model, and 17 variables were independent predictors of all-cause mortality. Obstructive lung disease and diabetes mellitus could not be removed in backward regression analysis. Serum potassium, heart rate, per cent of the recommended beta-blocker dose, use of MRA, implantable cardioverter-defibrillator, and sex were not significant predictors for mortality and therefore not shown in *Table 2*.

A history of cancer in the last 5 years, higher age, lower 6MWT, and higher natriuretic peptides were the strongest predictors for death (all P < 0.001) (*Table 2*).

There were 2932 patients who did not do the 6MWT for administrative or physical or other conditions. These patients had significantly worse prognosis than and patients who walked the shortest (Category 3) with crude mortality of 26% (P = 0.007).

The ROC curve analysis of the relation between the 6MWT and all-cause mortality is shown in *Figure 3*. The area

Figure 1 Scatter diagrams of 6 min walk test (6MWT) related to selected variables.

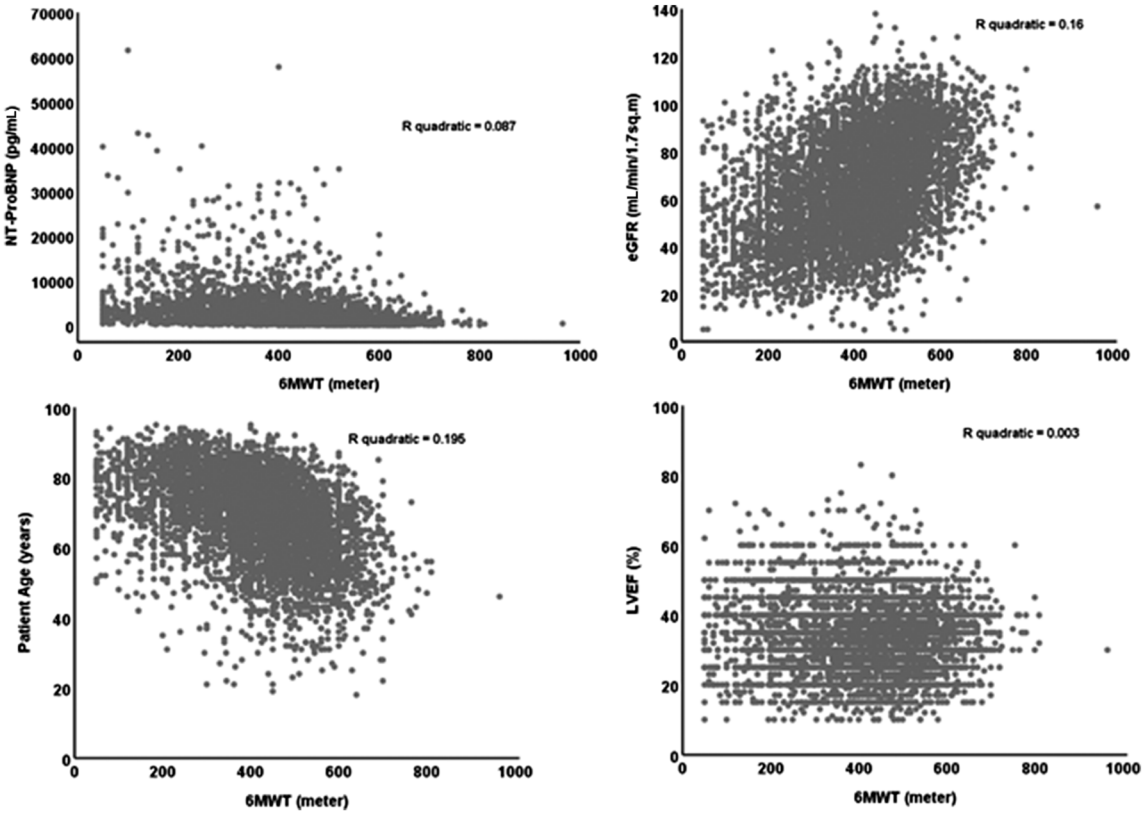
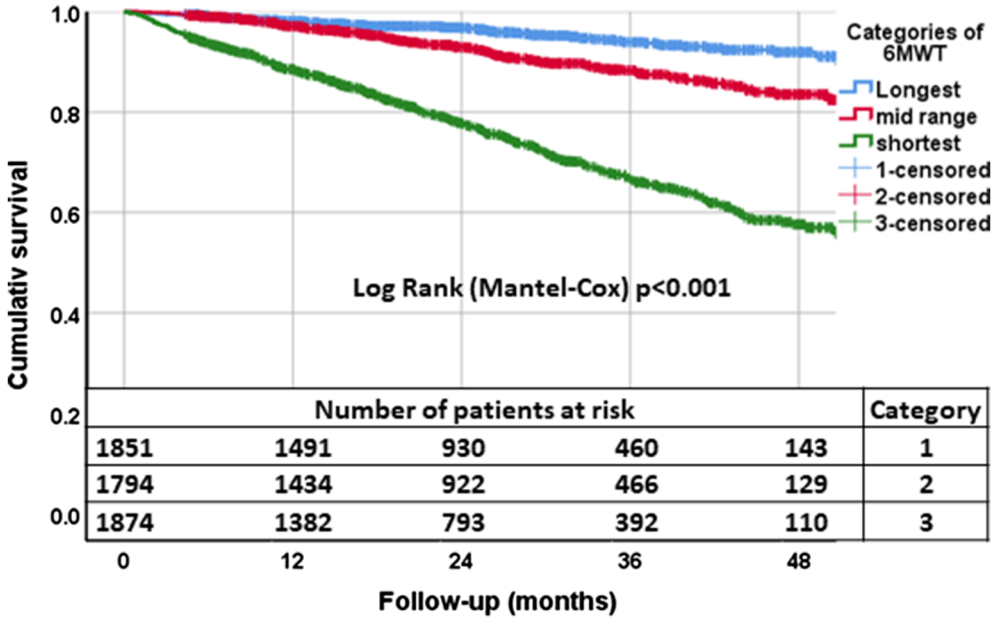


Figure 2 Kaplan–Meier survival plots of patients with heart failure from the first visit at specialized outpatient heart failure hospital clinics in relation to tertile categories of the 6 min walk test.



under the curve (AUC) was 0.74 (P < 0.001; 95% CI 0.72–0.76). The optimal cut-point for prediction for survival was 380 m, with the highest sum for the sensitivity of 0.71 and specificity of 0.67.

Discussion

The present large-scale study found the 6MWT to be a strong, independent predictor of mortality in chronic HF outpatients. The prognostic value of the 6MWT was independent of natriuretic peptide levels and NYHA functional class and consistent for patients with HF of both ischaemic and non-ischaemic aetiologies.

The analysis was based upon data from the first registered visit of HF patients referred for optimization of HF treatment at 40 Norwegian specialized HF outpatient clinics. Following the first visit, most patients underwent further up-titration of HF treatment, ensuring optimized contemporary HF treatment at the end of the follow-up period. Although the HF treatment was not optimized at the time of the 6MWT, a high percentage of patients were treated with beta-blockers and an ACEi/ARB. Patients with the worst 6MWT performance were more frequently treated with beta-blockers and an MRA, and they had a higher dosage of beta-blockers and lower dosage of ACEi/ARB than had the best performers in the 6MWT at the first visit (P < 0.01). This finding is consistent with poor 6MWT performers being older and more frequently suffering from atrial fibrillation and HFpEF.

Natriuretic peptides are strong prognostic predictors in HF patients.[19–23] The present study found a strong prognostic value of the 6MWT independent of other major prognostic markers including the natriuretic peptides. Notably, history of cancer within the last 5 years before the 6MWT was found to be an additional strong independent predictor of mortality. To our knowledge, this is the first time this association has been made in HF population assessed by the 6MWT.

In the present study, a 6MWT of <380 m demonstrated the strongest association with mortality. The AUC for the 6MWT was 0.74 and compares well with that of other studies.[7,11,13] However, despite a higher proportion of patients with a worse NYHA functional class, the distance walked in the present study was longer compared with that of previous reports (325 m).[7,13] The reason for this difference is not clear.

The present study is the largest study addressing the prognostic value of the 6MWT. It included HF patients of different aetiologies with a large range of heart function and a high prescription rate of evidence-based treatments at the 6MWT time and during follow-up. The findings may therefore be considered valid in most HF outpatients prescribed contemporary HF therapy.

Our findings underscore the clinical importance and support the use of 6MWT in the assessment of patients with chronic HF.[13,24]

Table 2 Univariate and multivariate Cox regression analysis of time to death

	Univariate regression				Multivariate regression[a]			
	95% CI for HR				95% CI for HR			
	HR	Lower	Upper	*P*-value	HR	Lower	Upper	*P*-value
Cancer last 5 years	3.994	3.263	4.889	<0.001	3.179	2.574	3.926	<0.001
Age (years)	1.073	1.064	1.081	<0.001	1.036	1.025	1.047	<0.001
6MWT per 10 m	0.947	0.942	0.952	<0.001	0.979	0.972	0.986	<0.001
*N*tiles of peptides				<0.001				<0.001
*N*tiles of peptides (1)	2.147	1.683	2.739	<0.001	1.257	0.975	1.620	0.079
*N*tiles of peptides (2)	4.835	3.872	6.037	<0.001	1.861	1.450	2.389	<0.001
Daily diuretic dose	1.004	1.003	1.004	<0.001	1.002	1.001	1.003	<0.001
NYHA				<0.001				0.001
NYHA (II)	2.788	1.880	4.113	<0.001	1.461	0.979	2.180	0.064
NYHA (III)	6.595	4.463	9.747	<0.001	1.971	1.303	2.981	0.001
NYHA (IV)	6.878	3.411	13.969	<0.001	1.865	0.885	3.933	0.101
LVEF				<0.001				<0.001
LVEF (HFmrEF)	0.788	0.644	0.965		0.860	0.696	1.064	0.165
LVEF (HFpEF)	1.927	1.560	2.382		1.422	1.128	1.793	0.003
BMI	0.942	0.928	0.958	<0.001	0.968	0.951	0.986	0.001
Non-smoker				<0.001				0.002
Ex-smoker	1.355	1.143	1.607	<0.001	1.339	1.119	1.601	0.001
Current smoker	1.014	0.798	1.288	0.911	1.423	1.099	1.843	0.007
Uric acid	1.003	1.002	1.004	<0.001	1.001	1.000	1.002	0.002
S-sodium	0.946	0.925	0.967	<0.001	0.965	0.943	0.988	0.003
eGFR	0.968	0.965	0.971	<0.001	0.993	0.988	0.998	0.003
Ischaemic HF	1.222	1.055	1.416	<0.001	1.217	1.038	1.426	0.015
PM	1.655	1.354	2.024	<0.001	1.289	1.046	1.588	0.017
Anaemia	2.443	2.100	2.843	<0.001	1.215	1.032	1.432	0.020
COPD or asthma	1.547	1.305	1.834	<0.001	1.183	0.988	1.418	0.068
Diabetes mellitus	1.326	1.157	1.604	<0.001	1.166	0.977	1.393	0.089
CRT implanted	1.539	1.173	2.018	0.002				0.478
Systolic BP	0.993	0.989	0.997	<0.001				0.314
ACEi/ARB dose (%)	0.992	0.990	0.994	<0.001				0.646
Stroke	1.512	1.217	1.878	<0.001				0.485
QRS width	1.005	1.003	1.007	<0.001				0.984

6MWT, 6 min walk test; ACEi/ARB dose (%), per cent of the recommended dose of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure mid-range ejection fraction; HFpEF, heart failure preserved ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PM, pacemaker stimulation in the ventricle.
[a]The variables in the table are sorted according to the size of the Wald number (highest to lowest).

Limitations

Some potential limitations may apply to the present analysis. Although the 6MWT has been found to be reproducible,[6] the 6MWT is limited by inherent imprecisions. The 6MWT protocol specifies the extent of the motivation allowed to be applied during the test. However, factors such as the experience of the patient and the cheering of bystanders will influence the results of the tests. The walking pace during the test is at the discretion of each patient. Hence, there is no objective measure on how much of the maximal exercise capacity is utilized during the test. These challenges may in particular influence the interpretation of repeated 6MWT during follow-up.

Several co-morbidities are overrepresented in the group that walked shortest with the worst outcome for example anaemia, recent cancer, and COPD/asthma. Although multivariate analysis adjusts for these co-morbidities, they still may influence our findings. In the new instructions for NNHFR data registration, it is now required to report if the 6MWT performance is limited by non-cardiac causes. In this study, only data on all-cause death were available. We therefore cannot specify the relationship between 6MWT performance and other HF-related outcomes.

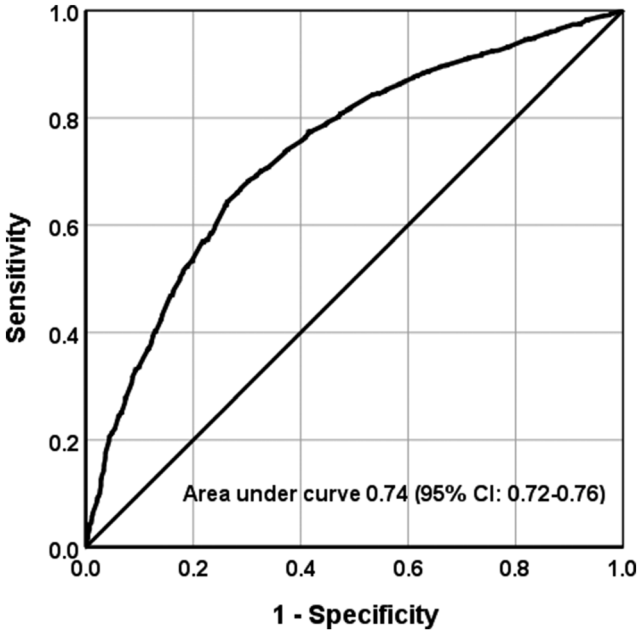
The number of patients with HFpEF is relatively low in this study because many patients in this category have hypertension as the main cause of HF and are taken care of by their local doctor in Norway. The NNHFR encourages health workers to refer more patients with an EF above 40% to hospital outpatient departments for HF in accordance with the Guidelines.[3] We assume it is unlikely that an increase in the number of patients with HFpEF would change the main conclusion of this study.

The NNHFR did not require participating centres to provide information on why the 6MWT was not performed at the time of the data collection for the current study. To address this question, all centres in the NNHFR are now required to report the reason for not performing the 6MWT. These future data will provide valuable information on both the reasons that the 6MWT was not performed and the potential influence of these data on clinical outcomes.

The participating NNHFR centres were instructed to follow the ESC Guidelines for HF and perform the 6MWT as described.[6] These directions were not changed during the lifetime of the registry. However, we do not have precise information on how the 6MWT was performed at each centre, and investigators may have interpreted the 6MWT protocol differently at the 40 hospital outpatient clinics in Norway. This may limit the interpretation of the 6MWT between centres.

Finally, the present analysis was based upon data acquired at the first visit to the outpatient HF clinic prior to the optimization of HF therapy. Prior studies have found that change in the distance walked after 1 month and 1 year did not predict changes in endpoints.[7,25] It is therefore unlikely that postponement of the test would change the validity of the prognostic value of the 6MWT.

Figure 3 Receiver operating characteristic curve showing the value of the 6 min walk test (6MWT) for predicting all-cause mortality at a median 24 months of follow-up in outpatients with chronic heart failure. Optimal cut-point 380 m showing sensitivity of 0.71 and specificity of 0.67.



Conclusions

The 6MWT is a strong independent predictor of all-cause mortality in outpatients with HF. The finding was independent of other strong risk markers. The result supports the use of the 6MWT in the prognostic assessment of patients with HF irrespective of aetiology or LVEF.

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Conflict of interest

All the authors have nothing to declare with respect to the content of this research.

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