ESC European Society of Cardiology
European Journal of Preventive Cardiology (2024) **31**, 2036–2043
https://doi.org/10.1093/eurjpc/zwae291

FULL RESEARCH PAPER
Heart failure and cardiomyopathies

Prognostic value of Borg scale following 6-min walk test in hospitalized older patients with heart failure

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Received 8 April 2024; revised 3 July 2024; accepted 3 September 2024; online publish-ahead-of-print 5 September 2024

See the editorial comment for this article 'Beyond the walk: the prognostic value of dyspnoea in heart failure', by G. Halasz and R. Mistrulli, https://doi.org/10.1093/eurjpc/zwae358.

Aims The 6-min walk test (6MWT) is a widely accepted tool for evaluating exercise tolerance and physical capacity, and the 6-min walk distance (6MWD) is an established prognostic factor in patients with heart failure (HF). However, the prognostic implications of post-6MWT dyspnoea remain unknown. We aimed to investigate the prognostic value of Borg scores after the 6MWT in patients with HF.

Methods and results Patients hospitalized for HF who underwent the 6MWT before discharge were included. Post-test dyspnoea was assessed using the Borg scale. Patients were stratified into low and high Borg score groups based on the median Borg score. The primary outcome was 2-year mortality. Among 1185 patients analysed, the median Borg score was 12. The 6MWD was significantly shorter in the high Borg score group than in the low Borg score group. The 2-year mortality rate was 20.2%. In the Kaplan–Meier analysis, the high Borg score group demonstrated an association with 2-year mortality, which remained significant even after adjustment for conventional risk factors, including the 6MWD. Furthermore, the Borg scale provided significant net reclassification improvement to the conventional risk model incorporating 6MWD.

Conclusion In hospitalized patients with HF, post-6MWT Borg scores were associated with 2-year mortality independent of the 6MWD, providing incremental prognostic value to the 6MWD. Even if patients are able to walk long distances for 6 min, it is essential to closely observe dyspnoea immediately thereafter.

Lay summary Our study investigated the significance of breathlessness after a walking test in patients with heart failure and found that this provides important information about their prognosis. The key findings are as follows:

- Patients with heart failure who felt more breathless after the 6-min walk test (6MWT) were at a higher risk of mortality within 2 years.
- The level of breathlessness after the 6MWT provided additional information about prognosis beyond just how far patients could walk during the test.

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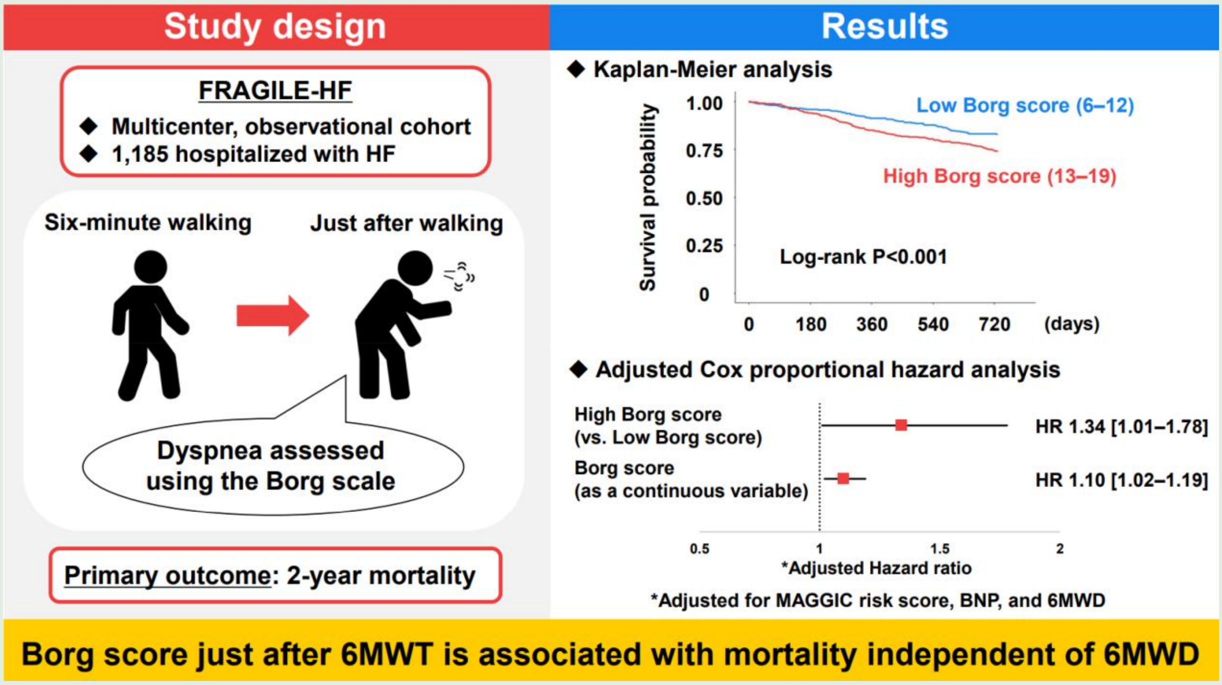
Graphical Abstract



Keywords Borg scale • Dyspnoea • Heart failure • Prognosis • Six-minute walk test

Introduction

Heart failure (HF), a clinical syndrome characterized by impaired exercise tolerance and related symptoms such as dyspnoea on exertion, is associated with high readmission and mortality rates.[1,2]

The 6-min walk test (6MWT) is an inexpensive, reproducible, and well-validated tool for assessing exercise tolerance or physical capacity in patients with HF, as recommended by recent guidelines.[3,4] Moreover, the 6MWT is useful for risk stratification of patients with HF, because multiple studies have demonstrated that a shorter 6-min walk distance (6MWD) is strongly associated with higher mortality.[5–10] Consequently, the 6MWD has been used as a key endpoint in many clinical trials.[11–13] However, these prior studies have overlooked the information on post-test symptoms.

The Borg scale is a simple tool for rating perceived exertion.[14] According to the American Thoracic Society (ATS) guidelines on the 6MWT, dyspnoea at the end of the 6MWT should be assessed using the Borg scale.[15] Although the association between the 6MWD and prognosis in patients with HF is robust, no studies have examined the association between post-6MWT Borg scores and prognosis in this population.

Therefore, we aimed to investigate (i) whether the Borg scale score after the 6MWT is associated with prognosis independent of the 6MWD and (ii) whether it provides additional prognostic value to that of the 6MWD in patients with HF.

Methods

Study design and population

The present study was a *post hoc* subanalysis of the FRAGILE-HF cohort study (UMIN000023929). The FRAGILE-HF study design and primary results have been previously reported in detail.[16–18] In brief, the FRAGILE-HF was a multicentre, prospective, observational cohort study conducted from September 2016 to March 2018 at 15 centres in Japan. This registry enrolled 1332 consecutive hospitalized older patients (age ≥65 years) with HF who could ambulate at discharge. Only the first hospitalization during the study period was registered. Heart failure decompensation was diagnosed based on the Framingham criteria.[19] The exclusion criteria were previous heart transplantation or presence of a left ventricular assist device, chronic peritoneal dialysis or haemodialysis, and acute myocarditis. Patients with missing data on brain natriuretic peptide (BNP) or N-terminal proBNP levels and those with a BNP level <100 pg/mL or N-terminal proBNP level <300 pg/mL on admission were also excluded. Physical examinations, echocardiograms, and blood tests were conducted while patients were in a clinically stable state before discharge. Cognitive function was assessed using the Mini-Cog, and a Mini-Cog score of ≤2 was considered to indicate cognitive dysfunction.[20]

In the present study, we included participants of the FRAGILE-HF study who had completed the 6MWT before discharge. Patients with missing data regarding Borg scores or 6MWD were excluded.

The FRAGILE-HF study was conducted in compliance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects after obtaining approval from the Ethics Committee or Institutional Review Board of each participating centre. The requirement for obtaining written informed consent was waived because the study met the conditions of the Japanese ethical guidelines for epidemiological studies.

Six-minute walk test and dyspnoea assessment

The 6MWT was conducted by skilled physical therapists and/or HF specialists before discharge after clinical HF stabilization. The test was performed in an unobstructed hallway according to the ATS guidelines.[15] Patients were instructed to walk as fast as possible between two points 30 m apart, and the distance walked within a 6-min duration was documented. Patients were permitted to use an assistive device as needed. According to the ATS guidelines, assessment of oxygen saturation is optional; therefore, in the FRAGILE-HF study, oxygen saturation was not measured. Details of the 6MWT evaluation, which followed the ATS guidelines, are provided in the Supplementary material online, *Table S1*.

Post-test dyspnoea was assessed using the Borg scale immediately after test completion.[14] We used the Borg scale scores ranging from 6 to 20, with higher scores indicating more severe dyspnoea (see Supplementary material online, *Table S2*).[14] Patients were divided into high and low Borg score groups based on the median Borg scale.

Outcomes

The primary outcome was all-cause mortality within 2 years after discharge, a pre-determined outcome of the FRAGILE-HF study. The secondary outcome was a composite of HF readmission or all-cause death within 2 years. Patients were routinely followed up after discharge at intervals of at least 3 months or as required by their medical condition. In patients who did not attend scheduled outpatient follow-ups, prognostic data were acquired through telephone interviews, and relevant medical records were obtained from other departments responsible for the patient's care or through their family.

Statistical analyses

Continuous data with normal distribution are expressed as mean values with standard deviations while those with skewed distribution as median values with interquartile ranges (IQRs). Categorical data are summarized as frequencies with percentages. Variables were log-transformed as needed for subsequent analyses. Between-group differences were assessed using Student's *t*-test or Mann–Whitney's *U* test for continuous variables and the χ^2 or Fisher's exact test for categorical variables.

To evaluate the association between Borg scores and the primary outcome, Kaplan–Meier survival curves were plotted and survival rates were compared between the groups using the log-rank test. The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) risk score,[21] log-transformed BNP values, and 6MWD were used as adjustment variables in the adjusted Cox proportional hazard model. The MAGGIC risk score included the patients' age, sex, left ventricular ejection fraction (LVEF), body mass index, creatinine levels, New York Heart Association class, smoking status, comorbidities (diabetes and chronic obstructive pulmonary disease), history of HF, and medication use (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers). This risk score has been validated to differentiate outcomes related to mortality within Japanese populations with HF, even after adding BNP levels.[22] In addition, we conducted a subgroup analysis according to the LVEF values, with a cut-off value of 40%.

To determine whether Borg scores improved the performance of the conventional risk model for predicting mortality in patients with HF, continuous net reclassification improvement was calculated.

To address missing data, multiple imputation using chained equation methods was performed. All variables listed in *Table 1* underwent the imputation process, and 20 imputed data sets were generated using the mice package in R.

A two-tailed $P < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3–900051–07-0, URL http://www.R-project.org).

Results

Patient characteristics

A total of 1332 hospitalized patients were registered in the FRAGILE-HF study. After excluding those with missing data on 6MWD or Borg scores, 1185 patients were included in the current analysis.

The median age of the study population was 81 (IQR, 74–86) years and 57.5% were male. The distribution of post-6MWT Borg scores is illustrated in *Figure 1*. The median Borg score was 12 (IQR, 11–13; range, 6–19), with 575 patients in the high Borg score group (Borg scale score >12) and 610 patients in the low Borg score group (Borg scale score ≤12).

Patient baseline characteristics are shown in *Table 1*. Compared with the low Borg score group, the high Borg score group comprised older patients, had a higher proportion of New York Heart Association class III/IV and chronic obstructive pulmonary disease, higher LVEF values, and shorter 6MWD.

The correlation between Borg scores and 6MWD or BNP was statistically significant but weak [vs. 6MWD: $r = -0.17$; 95% confidence interval (CI), −0.23 to −0.12; $P < 0.001$; vs. BNP: $r = 0.09$; 95% CI, 0.03–0.15; $P = 0.003$).

Outcomes

In the included study patients, prognostic information was available for 1165 (98.7%). During the 2-year follow-up period after discharge, 235 (20.2%) deaths were observed: 139 (24.5%) in the high Borg score group and 96 (16.1%) in the low Borg score group. In the Kaplan–Meier analysis, the high Borg score group had significantly lower survival rates (log-rank $P < 0.001$; *Figure 2*). In the unadjusted Cox proportional hazard analysis, the high Borg score was significantly associated with 2-year mortality [hazard ratio (HR), 1.61; 95% CI, 1.24–2.09; $P < 0.001$; *Table 2*]. This association remained significant even after adjustment for the MAGGIC risk score, log-transformed BNP values, and 6MWD (adjusted HR, 1.34; 95% CI, 1.01–1.78; $P = 0.041$; *Table 2*), and when the Borg score was considered a continuous variable (unadjusted model: HR, 1.17; 95% CI, 1.09–1.25; $P < 0.001$; adjusted model: HR, 1.10; 95% CI, 1.02–1.19; $P = 0.012$; *Table 2*). No significant interaction was observed between the presence/absence of cognitive dysfunction and the high/low Borg score groups with regard to the prognostic impact (P for interaction = 0.119; Supplementary material online, *Figure S1*).

Regarding the secondary outcome, 528 (45.4%) events were observed: 284 (50.1%) in the high Borg score group and 244 (40.9%) in the low Borg score group. Kaplan–Meier analysis demonstrated that the high Borg score group had a significant higher incidence of the secondary outcome compared with the low Borg score group (log-rank $P = 0.001$; *Figure 2*). Cox proportional hazard analysis revealed that higher Borg score was significantly associated with the secondary outcome independent of the 6MWD (categorical variables: adjusted HR, 1.20; 95% CI, 1.01–1.43; $P = 0.039$; continuous variables: adjusted HR, 1.06; 95% CI, 1.01–1.11; $P = 0.022$; Supplementary material online, *Table S3*).

In the analysis of the incremental prognostic information for all-cause mortality provided by Borg scores, the Borg scale, when considered as both a continuous and a categorical variable, offered significant additional prognostic value to the 6MWD (*Table 3*). Moreover, although the 6MWD showed a significant incremental prognostic value when added to the conventional risk model comprising MAGGIC risk score + log-transformed BNP model, the Borg scale provided further additive prognostic value to the MAGGIC risk score + log-transformed BNP + 6MWD model (*Table 3*).

We also performed a sensitivity analysis excluding 125 patients with a history of chronic obstructive pulmonary disease and found that

Table 1 Baseline characteristics based on Borg scale scores

	All $n = 1185$	Low Borg score group $n = 610$	High Borg score group $n = 575$	P value	Missing data, n (%)
Age (years)	81 [74–86]	80 [72–85]	81 [76–86]	<0.001	0 (0)
Male sex, n (%)	681 (57.5)	363 (59.5)	318 (55.3)	0.158	0 (0)
NYHA class III/IV on admission, n (%)	152 (12.8)	48 (7.9)	104 (18.1)	<0.001	0 (0)
Body mass index (kg/m^2)	21.4 (3.8)	21.3 (3.8)	21.6 (3.9)	0.223	3 (0.3)
SBP (mmHg)	114 (17)	113 (16)	114 (18)	0.455	0 (0)
DBP (mmHg)	62 (11)	62 (11)	62 (11)	0.593	0 (0)
Heart rate (b.p.m.)	71 (14)	71 (14)	72 (15)	0.193	0 (0)
Left ventricular ejection fraction (%)	45.7 (16.8)	44.6 (16.6)	46.9 (17.0)	0.020	12 (1)
Prior history of heart failure				0.495	2 (0.2)
<1.5 years	173 (14.6)	83 (13.6)	90 (15.7)		
>1.5 years	474 (40.0)	241 (39.5)	233 (40.5)		
None	536 (45.2)	284 (46.6)	252 (43.8)		
Comorbidities, n (%)					
Atrial fibrillation	528 (44.6)	264 (43.3)	264 (45.9)	0.381	0 (0)
Coronary artery disease	413 (34.9)	209 (34.3)	204 (35.5)	0.670	0 (0)
Chronic obstructive pulmonary disease	125 (10.6)	48 (7.9)	77 (13.4)	0.002	0 (0)
Diabetes mellitus	422 (35.6)	224 (36.7)	198 (34.4)	0.430	0 (0)
Hypertension	842 (71.1)	439 (72.0)	403 (70.1)	0.482	0 (0)
Laboratory data					
Haemoglobin (g/dL)	11.8 (2.0)	12.0 (2.0)	11.7 (2.0)	0.012	2 (0.2)
Haematocrit, %	36.3 (5.8)	36.7 (5.8)	35.9 (5.9)	0.014	2 (0.2)
Albumin (g/dL)	3.5 (0.5)	3.5 (0.5)	3.4 (0.5)	0.057	37 (3.1)
Creatinine (mg/dL)	1.38 (0.8)	1.34 (0.6)	1.42 (0.9)	0.125	2 (0.2)
Blood urea nitrogen (mg/dL)	26 [20–36]	25 [19–35]	27 [20–37]	0.115	2 (0.2)
Sodium (mEq/L)	139.0 (3.8)	139.1 (3.7)	138.8 (4.0)	0.143	2 (0.2)
Potassium (mEq/L)	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)	0.757	2 (0.2)
Brain natriuretic peptide (pg/mL)	277 [135–501]	259 [124–481]	286 [150–528]	0.095	139 (11.7)
Medication at baseline, n (%)					
ACE-Is or ARBs	811 (68.4)	442 (72.5)	369 (64.2)	0.002	0 (0)
β-Blockers	881 (74.4)	468 (76.7)	413 (71.8)	0.062	0 (0)
Mineralocorticoid receptor antagonists	593 (50.0)	312 (51.1)	281 (48.9)	0.450	0 (0)
Loop diuretics	1036 (87.4)	540 (88.5)	496 (86.4)	0.255	0 (0)
Physical function					
Six-minute walk distance (m)	242 [151–345]	271 [198–365]	215 [120–328]	<0.001	0 (0)
MAGGIC risk score	26 [23–30]	26 [22–30]	26 [23–30]	0.669	26 (2.2)
Cognitive dysfunction, n (%)	429 (36.4)	217 (35.6)	212 (37.1)	0.628	5 (0.4)
Length of hospital stay (days)	17 [13–24]	17 [13–23]	18 [14–26]	0.002	0 (0)

Continuous variables are presented as median [interquartile range] or mean (standard deviation). Categorical variables are presented as number (percentage).
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; NYHA, New York Heart Association; SBP, systolic blood pressure.

higher Borg score was significantly associated with higher incidence of the primary outcome (log-rank $P < 0.001$) and the secondary outcome (log-rank $P = 0.002$).

Subgroup analysis by left ventricular ejection fraction values

The Kaplan–Meier analysis revealed that the high Borg score group was significantly associated with 2-year mortality both in patients with an LVEF <40% ($n = 474$) and in those with an LVEF ≥40% ($n = 678$) (*Figure 3*). We observed no significant interaction between LVEF <40%/≥40% and Borg scores regarding the prognostic impact after adjustment for MAGGIC risk score, log-transformed BNP values, and 6MWD (as categorical variables: P for interaction = 0.421; as continuous variables: P for interaction = 0.633).

Discussion

The key findings of the present study were as follows: (i) post-6MWT Borg scores were associated with increased 2-year mortality and a combined outcome independent of the 6MWD, and (ii) post-6MWT Borg scores provided incremental prognostic value to the 6MWD. The current study is the first to demonstrate an additive prognostic value of Borg scores achieved after the 6MWT to the 6MWD in patients with HF.

Prognostic implication of the Borg scale and 6-min walk distance in heart failure

While cardiopulmonary exercise testing is considered the gold standard for evaluating exercise tolerance and physical capacity, the 6MWT has gained broader usage in clinical practice due to its simplicity and comparable prognostic value.[23] The prognostic implication of the 6MWT has been reported in many studies on HF, with generally consistent findings regarding the association between 6MWD and prognosis: the shorter the 6MWD, the poorer the prognosis, both in HF with reduced and preserved LVEF.[7,10,24] A meta-analysis revealed that a decrease of 50 m in the 6MWD was associated with 18 and 43% increase in mortality and readmission rates, respectively.[5] Furthermore, the 6MWD provided incremental prognostic value to conventional risk factors for HF.[8] Therefore, some researchers have argued that the 6MWD should be included as the 'sixth vital sign'.[25,26] Our findings are consistent with those of the above studies; nonetheless, these previous studies only assessed the walking distance without considering the symptoms observed after testing, although these can be easily evaluated and their assessment is recommended in the official statement.[15]

The Borg scale was developed to assess perceived exertion and breathlessness during physical activity[27,28] and is one of the most widely used tools in patients with HF.[29] The clinical implication of Borg scale scores in patients with HF has been reported in prior studies. In a randomized controlled trial including 42 patients with HF who performed cardiopulmonary exercise testing, exercise guided by Borg scores between 11 and 13 was useful to keep the participants' heart rate within the range of the anaerobic threshold and respiratory compensation point.[30] However, few studies have evaluated the prognostic impact of Borg scores in patients with HF. Only one clinical study of 273 patients with advanced HF (INTERMACS profile of 4–7 and LVEF ≤35%) showed that the peak Borg score during cardiopulmonary exercise testing was a significant predictor of death, durable mechanical circulatory support implantation, or cardiac transplantation at 1 year.[31] Additionally, evidence on the prognostic implication of the Borg scale obtained following the 6MWT is scarce, with only one study demonstrating the prognostic value of this score, with high post-6MWT Borg scores associated with high 5-year mortality in patients with

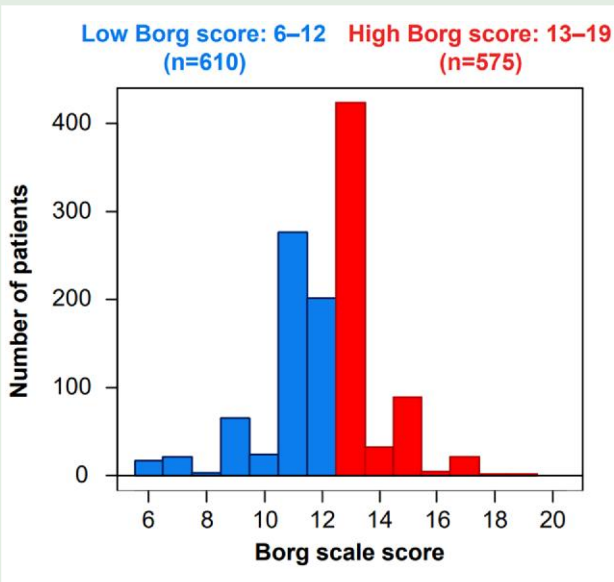


Figure 1 Distribution of Borg scores. The median score was 12 (interquartile range, 11–13; range, 6–19).

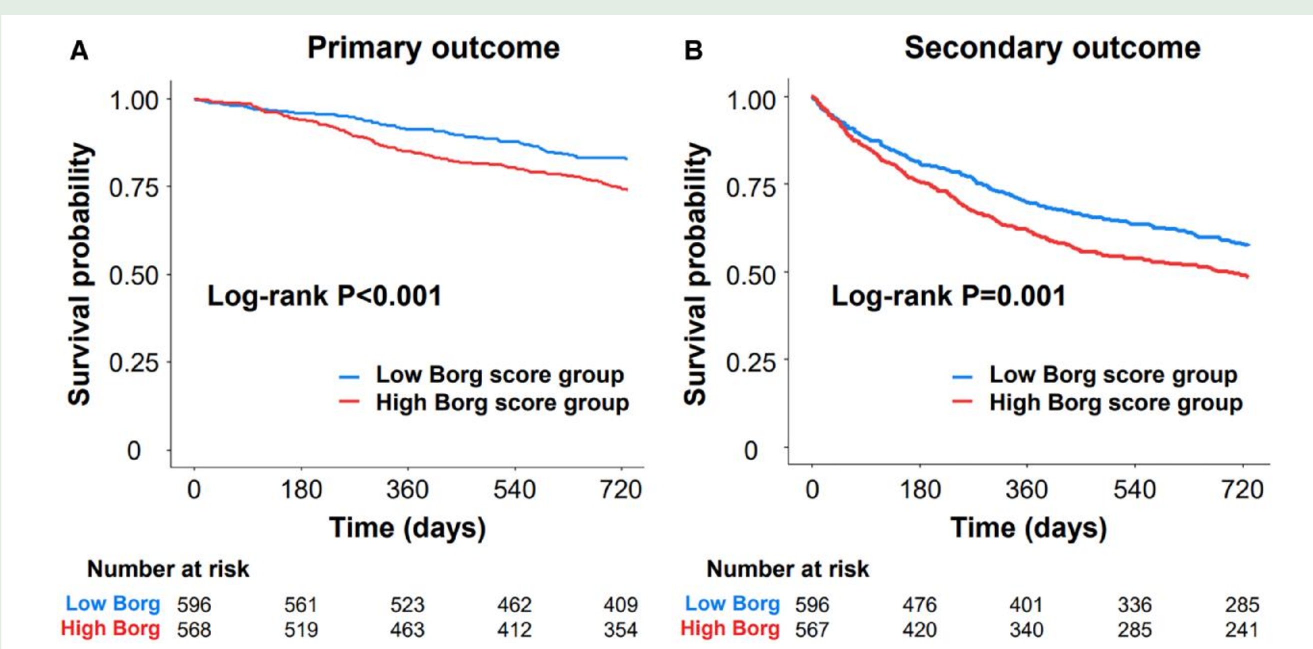


Figure 2 Kaplan–Meier curves for the primary and secondary outcomes. The high Borg score group showed a significant association with 2-year all-cause death (*A*) and a composite of heart failure readmission or all-cause death (*B*).

Table 2 Cox proportional hazard analysis for 2-year mortality

	Unadjusted model			Adjusted Model 1[a]			Adjusted Model 2[b]		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Borg scale score (as a continuous variable)	1.17	1.09–1.25	<0.001	1.15	1.07–1.23	<0.001	1.11	1.03–1.19	0.004
High Borg score group (vs. low Borg score group)	1.61	1.24–2.09	<0.001	1.55	1.20–2.02	<0.001	1.38	1.06–1.80	0.018

[a]Adjusted for MAGGIC risk score and log-transformed BNP.
[b]Adjusted for MAGGIC risk score, log-transformed BNP, and 6WMD.

Table 3 Comparison of prognostic models for predicting 2-year mortality

Model	NRI	95% CI	*P* value
6MWD		Reference	
6MWD + Borg scale (categorical variables)	0.266	0.124–0.407	<0.001
6MWD + Borg scale (continuous variables)	0.235	0.095–0.375	<0.001
MAGGIC + log BNP		Reference	
MAGGIC + log BNP + 6MWD	0.297	0.146–0.447	<0.001
MAGGIC + log BNP + 6MWD		Reference	
MAGGIC + log BNP + 6MWD + Borg scale (categorical variables)	0.250	0.099–0.401	0.001
MAGGIC + log BNP + 6MWD + Borg scale (continuous variables)	0.201	0.051–0.350	0.008

6MWD, 6-min walk distance; BNP, brain natriuretic peptide; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; NRI, net reclassification improvement.

HF.[32] Importantly, this study included only 172 patients with 60 registered deaths and did not clarify whether the Borg scale provided an incremental prognostic value to the 6MWD. The current study included 1185 patients with 235 registered deaths and clearly demonstrated the incremental prognostic utility of post-6MWT Borg scale scores on the 6MWD.

Clinical implications

The 6MWT is a well-validated, simple, and useful tool for evaluating exercise tolerance and physical capacity, and the 6MWD is a strong prognostic factor in patients with HF. When conducting the 6MWT, healthcare providers should pay attention not only to the walking distance but also to the symptoms after testing to better stratify patients for future risk of mortality. Even if patients can walk long distance in a 6-min period, careful follow-up may be warranted when they have severe perceived exertion and dyspnoea after walking.[33] Nevertheless, further studies should validate our findings in patients with HF.

Limitations

The current study has several limitations that should be acknowledged. First, notably, though the Borg scale provides quantitative results, the assessment is essentially subjective. Thus, various factors, including physical, psychological, or environmental, may affect the results. Specially, the impact of pulmonary diseases on the Borg scale cannot be completely excluded. Second, intra-observer reliability of the Borg scale was not assessed in the current study. In addition, it should be noted that we used the Borg scale ranging from 6 to 20, even though the ATS statement recommends using the modified Borg scale ranging from 0 to 10.[15] However, the original Borg scale ranging from 6 to 20 is optimal for predicting and prescribing exercise intensity in medical rehabilitation,[14] and indeed, the 2020 European Society of Cardiology Guidelines on sports cardiology and exercise in patients with cardiovascular disease[34] and the Japanese Circulation Society/Japanese Association of Cardiac Rehabilitation 2021 Guidelines on Rehabilitation in Patients With Cardiovascular Disease[35] recommend using the Borg scale ranging from 6 to 20 for subjective exercise intensity. Nevertheless, cardiopulmonary exercise testing remains the gold standard method to holistically evaluate exercise capacity, and our study results need to be validated in future studies using cardiopulmonary exercise testing. Third, the assessment using the 6MWT and Borg scale was conducted during the stable period before discharge; however, the precise timing of the test (such as the specific post-admission day) was not clearly defined. Fourth, baseline data between the high Borg scale and the low Borg scale groups differed. For instance, LVEF was higher in the high Borg scale group than that in the low Borg scale group. This might reflect a higher prevalence of HF with preserved LVEF, likely due to the higher proportion of older adults and females in this group. Although a multivariable Cox analysis was performed, it may not have fully addressed such baseline imbalances. Fifth, to enhance the generalizability of our findings, it might be better to perform 6MWT during the stable periods during outpatient visits after discharge. However, the median hospital stay in our study was around 17 days, notably longer than the 4–5 days observed in Western countries.[36] Consequently, the timing of our data collection could be similar to the timing followed in the Western countries, which is during the initial outpatient visit. Finally, notably, our study included only older Japanese patients, which limited the generalizability of our findings in other patient groups, including young or Western populations. Importantly, the median age was 81 years, and the mean body mass index was 21.4, which differed markedly from the corresponding values in the populations with HF in Western countries. Therefore, caution is required in interpreting this study results, and further research targeting Western populations or younger patient cohorts is needed in the future.

Conclusions

In hospitalized patients with HF, high Borg scores after the 6MWT were significantly associated with 2-year mortality independent of the 6MWD, providing incremental prognostic value to the 6MWD. Further studies are required to validate our findings. Healthcare providers should consider post-test symptoms to enhance risk stratification

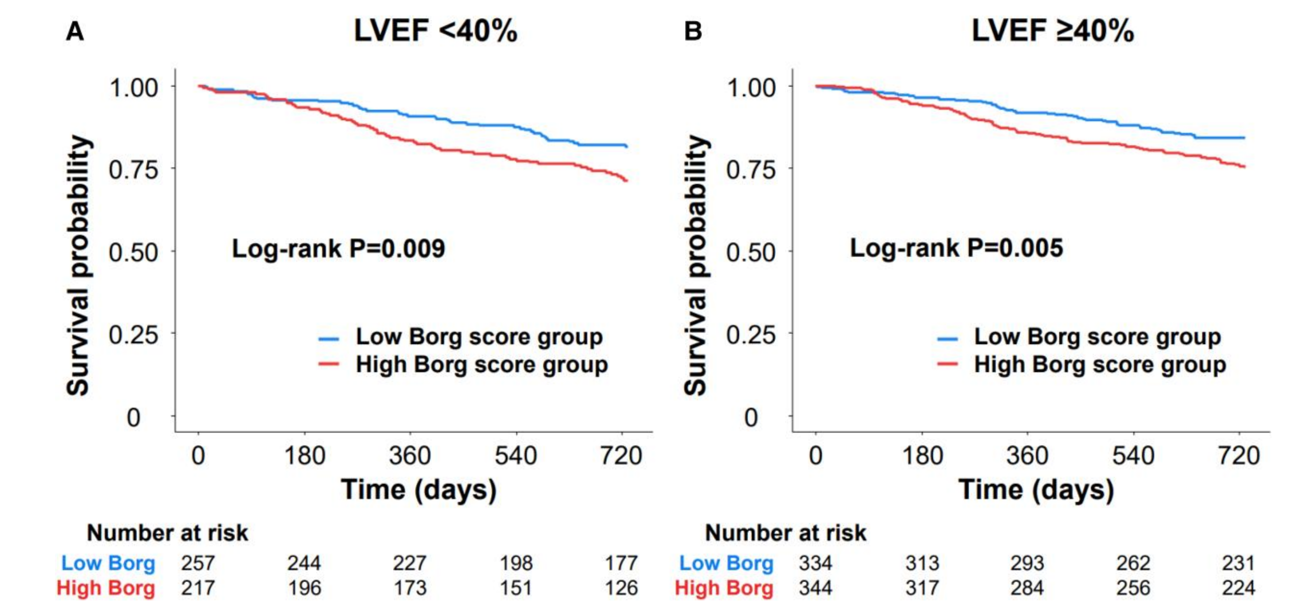


Figure 3 Kaplan–Meier curves for 2-year mortality according to LVEF. The high Borg score group was significantly associated with 2-year mortality both in patients with a left ventricular ejection fraction <40% (*A*) and in those with a left ventricular ejection fraction ≥40% (*B*). LVEF, left ventricular ejection fraction.

and follow-up, especially in patients experiencing severe exertion and dyspnoea despite walking longer distances.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

H.S., D.M., and Y.M. contributed to the conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, and writing of the original manuscript draft. Y.M. contributed to funding acquisition and supervision. All authors revised the manuscript, approved it, and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

Funding

FRAGILE-HF was supported by Novartis Pharma Research Grants and a Japan Heart Foundation Research Grant. This work was also supported by JSPS KAKENHI (22K16152).

Conflict of interest: N.K. is affiliated with a department funded by Philips Japan, Inter Reha Co., Ltd, KYOCERA Corporation, AMI Inc., and Fukuda Denshi Co. Ltd based on collaborative research agreements and received honorarium from Novartis Japan, Otsuka Pharmaceutical Co., Ltd, and Eli Lilly Japan K.K. K.K. received funding outside the submitted work from Eiken Chemical Co., Ltd, and SoftBank Corporation, Ltd. T.K. was affiliated with a department sponsored by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi. Y.M. received an honorarium from Otsuka Pharmaceutical Co., Novartis Pharma K.K., Bayer Inc., and AstraZeneca and a collaborative research grant from Pfizer Japan Inc., Otsuka Pharmaceutical Co., EN Otsuka Pharmaceutical Co., Ltd, and Nippon Boehringer Ingelheim Co., Ltd. The other authors declare no conflicts of interest.

Data availability

The data supporting the findings of this study are available from the corresponding author (Y.M.) upon reasonable request.

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