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ORIGINAL RESEARCH ARTICLE

Patient-reported outcomes in heart failure with preserved vs. reduced ejection fraction: focus on physical independence

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Abstract

Aims The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a widely used patient-reported outcome measure in heart failure (HF). The KCCQ was validated in patients with HF with reduced ejection fraction (HFrEF), leaving knowledge gaps regarding its applicability in HF with preserved ejection fraction (HFpEF). This study addresses the psychometric properties of internal consistency and reliability, construct, and known-group validity of KCCQ in both HFrEF and HFpEF. We aimed to evaluate the psychometric properties of the KCCQ and their prognostic significance in HFpEF and HFrEF, within a large prospective multinational HF cohort.

Methods and results We examined the 23-item KCCQ in the prospective multinational ASIAN-HF study [4470 HFrEF (ejection fraction <40%); 921 HFpEF (ejection fraction ≥50%)]. Internal consistency (using Cronbach's alpha) showed high reliability in HFrEF and HFpeF: functional status score: 0.89 and 0.91 and clinical summary score: 0.89 and 0.90, respectively. Confirmatory factor analysis in HFrEF validated the five original domains of KCCQ (physical function, symptoms, self-efficacy, social limitation, and quality of life); in HFpEF, questions measuring physical function and social limitation had strong correlation ($r = 0.66$) and different domains emerged. We proposed an additional physical independence summary score, especially in HFpEF (comprising the original physical function and social limitation domains), which showed good internal consistency ($\alpha = 0.89$) and has comparable receiver operating characteristic curve 0.766 ± 0.037 with the clinical summary score (receiver operating characteristic curve 0.774 ± 0.037), in predicting 1 year death and/or HF hospitalization.

Conclusions Our results confirmed the robustness of the KCCQ clinical summary score in HF regardless of ejection fraction group. In the assessment of physical capacity in HFpEF, our results suggest strong interaction with social limitation, and we propose a summary score comprising both components be used.

Keywords Quality of life; Heart failure; Patient-reported outcomes; Psychometric properties; Kansas City Cardiomyopathy Questionnaire

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†On behalf of the ASIAN-HF investigators (Supporting Information, Appendix S1).

Introduction

The Kansas City Cardiomyopathy Questionnaire (KCCQ) yields disease-specific patient-reported outcomes (PROs) that evaluate the domains of physical limitation, symptoms, quality of life (QoL), social limitation, and self-efficacy in patients with heart failure (HF). It was developed in 2000 based on 129 HF cases with reduced left ventricular ejection fraction

(HFrEF).[1] It has been used in multiple studies and clinical trials to evaluate health-related QoL, mainly in HFrEF.[2] While clinical endpoints are important, PROs are an important component of patient-centred care. They allow patients to validly, reproducibly, and sensitively quantify their experiences with illness. PROs may also shift before clinical endpoints occur, allowing healthcare professionals to more sensitively track clinical progress.[3] This has translated to an increased focus on PROs as an endpoint in HF clinical trials, including both HFrEF and HF with preserved ejection fraction (HFpEF).[4,5]

However, there is currently a knowledge gap; as the KCCQ was developed for patients with HFrEF, psychometric properties such as internal consistency, validity, and factor analysis of KCCQ have not been adequately evaluated in HFpEF.[6] Patients with HFpEF and HFrEF have differing clinical characteristics and co-morbidity burden.[7–9] It is important to ensure that the assumptions underpinning the use of the KCCQ in HFrEF remain valid in HFpEF. While Joseph *et al.*[10] demonstrated that the KCCQ overall summary score correlated well with the New York Heart Association (NYHA) classification in HFpEF, the individual KCCQ domains of physical function, total symptoms, social limitation, and QoL and their interactions in HFpEF have not been studied. Our study additionally looks at these individual components and identifies the key differences that influence PROs in HFpEF and HFrEF.

Studying the psychometric properties of KCCQ provides evidence of how the measurement properties were assessed and gives clinicians confidence in using this tool for patient care. Reliability and validity are considered the main measurement properties. Reliability refers to the degree to which the measurement is free from measurement error,[11] which is significant when interpreting results. Validity refers to the degree the PRO is an adequate reflection of the intended property measured.[11] If an instrument does not have adequate construct or content validity, then it may not be assessing the property that it purports to.

We aimed to evaluate the psychometric properties of the KCCQ and their prognostic significance in HFpEF and HFrEF, within a large prospective multinational HF cohort.

Methods

Study participants

The ASIAN-HF Registry, as previously described,[7,12] is a contemporary prospective multinational study of patients from 11 regions in Asia, aged 18 years or older, with chronic symptomatic HF (Stage C, with at least one episode of decompensated HF in the past 6 months that resulted in admission to hospital or treatment at an outpatient clinic). Diagnosis of HF was made clinically. HFrEF was defined by left ventricular ejection fraction <40% and HFpEF by left ventricular ejection fraction ≥50%. Further, in the latter, 99.5% of HFpEF patients had structural or functional abnormalities fulfilling the 2016 European Society of Cardiology criteria for diastolic dysfunction (E/e′ ≥ 13, E′ medial/lateral <9 ms), left atrial enlargement, or left ventricular hypertrophy.[12,13] We excluded HF caused by severe valvular heart disease, life-threatening co-morbidity with life expectancy of <1 year, those unable or unwilling to give consent, and those already participating in another clinical trial. Patients with mid-range ejection fraction were not recruited into this study.

A total of 6480 patients (5276 HFrEF and 1204 HFpEF) were recruited. Self-administered KCCQ at the baseline clinic visit was used in this analysis. Non-English-speaking participants used certified versions of the KCCQ translated into their native languages. Patients with incomplete KCCQ questionnaire were excluded. Information from 5391 patients was used in this analysis.

Ethics approvals were obtained from the local institutional review committee of each participating centre, and all participants gave informed consent. The study conformed to the ethical guidelines in the Declaration of Helsinki.

Data collection

Demographic and clinical data were collected at baseline, including clinical signs and symptoms, functional status, date of diagnosis with HF, duration of HF, transthoracic echocardiography, clinical and lifestyle risk factors, medical history, and co-morbidities. PRO was assessed using the 23-question KCCQ and visual analogue scale (VAS). Patients were followed up for 2 years for the outcomes of death and cause-specific admission to hospital. Causes of death or admission to hospital were adjudicated by a central event adjudication committee using pre-specified criteria.

Instruments

The KCCQ is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status and the impact of HF symptoms on physical, social function, and QoL within a 2 week recall period. It takes an average of 4–6 min to complete. The KCCQ is scored from 0 to 100, with higher scores representing better health status. Self-administered KCCQ at the baseline visit was used in the current analysis. Non-English-speaking participants used certified versions of the KCCQ, which had been translated into their native languages.[14]

The KCCQ tool quantifies five distinct domains and two summary scores. The domains include physical function (Question 1), total symptoms (Questions 2–9), self-efficacy and knowledge (Questions 10 and 11), social limitation

(Question 15), and QoL (Questions 12–14). Two summary scores are computed: the functional status score combining the physical limitation and symptom domains (excluding symptom stability Question 2), and a clinical summary score combining the functional status score with QoL and social limitation domains.

The generic instrument used to measure health status was the VAS for health perception. At the two ends of the scale are two descriptors representing extremes of health states (i.e. worst possible health and perfect health). The patient rates his satisfaction by making a vertical mark on the 100 mm line. The measurement in millimetres is converted to the same number of points ranging from 0 to 100 points. The VAS is a generic health-related PROs, which has been used in previous HF studies before the KCCQ became widely available.[15,16]

The NYHA classification is the most widely used system in clinical practice and research studies. This physician-reported system focuses on physician interpretation of a HF patient's quantification of symptom severity and description of extent of functional impairment.[17]

Data analysis

Kansas City Cardiomyopathy Questionnaire and the VAS were tabulated as per recommended methods.[1] Data were analysed using StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. to examine construct validity, reliability, and confirmatory factory analysis[18] in HFrEF and HFpEF.

Internal consistency reliability (the extent to which the questions grouped together are appropriate to measure the same property) was assessed for each KCCQ domain using Cronbach's alpha.[19] Construct validity of KCCQ scales (the ability to measure the intended property in reference to acknowledged standards) was assessed relating KCCQ scales to the VAS and the physician-reported NYHA classification. A correlation value of 0.6 or higher, 0.4–0.5, and 0.2–0.3 was considered a strong, moderate, and weak correlation, respectively.[20] Structural equation modelling was used to analyse the relationship between measured variables (questions in KCCQ) and latent constructs (domains in KCCQ). Examples of constructs were the five domains identified by the KCCQ in HFrEF. For this paper, the term domain and construct were used interchangeably. Specifically, we assessed if the domains specified by KCCQ in HFrEF were applicable to HFpEF and sought to validate the summary scores in HFpEF. Using factor analysis, we determined the optimal number of factors using Kaiser's rule (i.e. eigenvalue >1). To identify items contributing to factors, we used the criterion of factor loading more than 0.4 as cut-off.[21] Latent factor covariances and model fit were also considered. The statistical approach for KCCQ validation is summarized in *Table 1*.

All statistical analyses were conducted at a significance level of 0.05, and all tests were two tailed whenever appropriate.

Results

The cohort comprised 5391 patients (82.9% HFrEF) from different parts of Asia. Their baseline characteristics are presented in *Table 2*. The median age of patients with HFpEF was 69 vs. 60 years in HFrEF. Patients with HFpEF (vs. HFrEF) were more likely to have co-morbid atrial fibrillation and hypertension and to be of Chinese ethnicity. In contrast, patients with HFrEF were approximately two times more likely to have coronary artery disease and have higher event rates of HF hospitalization and/or death. Approximately 30% of patients were in NYHA Class III/IV in both groups.

Reliability

Overall, internal consistency reliability was high: scale reliability of functional status score for HFrEF and HFpEF was good at 0.89 for both and the clinical summary score at 0.91 and 0.90, respectively.

In both HFrEF and HFpEF, the self-efficacy domain was less fitting to the overall KCCQ scale, compared with the other domains. This was demonstrated by an increased alpha when the self-efficacy domain was removed (0.92–0.95 and 0.93–0.95 in HFrEF and HFpEF, respectively) and lower item-to-scale and item-to-rest correlation in both HFrEF and HFpEF (*Table 3*).

Detailed item-to-test analyses were performed to look at how well individual questions correlated with the other questions in each of the original KCCQ five domains (see Supporting Information, *Table S3*). All the items in KCCQ had a correlation coefficient of >0.50 except for Question 2 (relating to symptom stability in the last 2 weeks) in the total symptoms domain, with a low correlation coefficient of 0.351 and 0.395 for HFrEF and HFpEF, respectively. Our findings supported the omission of Question 2 in the computation of the functional status score.

Construct validity

The total symptoms domain, functional status score, and the clinical summary score had moderate correlation (>0.4) with NYHA class (*Table 4*) for both HF cohorts. For VAS, only the clinical summary score had better correlation while the functional status had weak correlation for both HF cohorts.

Table 1 Statistical approach for validation of KCCQ

Property assessed	Component assessed	Reference measure	Statistical test
Internal consistency/reliability	Individual questions contributing to KCCQ domains (physical function, total symptoms, self-efficacy and knowledge, and quality of life)	—	Cronbach's alpha
Construct validity	KCCQ domains (physical function, total symptoms, self-efficacy and knowledge, social limitation, and quality of life)	Visual analogue scale and NYHA class	Correlation
Known-group validity	KCCQ domains (physical function, total symptoms, self-efficacy and knowledge, social limitation, and quality of life)	NYHA class, heart failure admissions, and mortality	*t*-test and one-way ANOVA with Bonferroni correction
Confirmatory factor analysis	Factors analysed with individual questions in KCCQ	—	Principal component factor analysis with oblique rotation and structural equation modelling

KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association.

Known-group validity

The KCCQ domains of physical function, total symptoms, QoL, and the clinical summary score showed a stepwise decline with increasing severity of NYHA class for both HFrEF and HFpEF, before and after adjustment for gender, region, body mass index, symptoms such as lower limb oedema, paroxysmal nocturnal dyspnoea, dyspnoea at rest and exertion, angina, chronic obstructive pulmonary disease, and mortality at 1 year ($P < 0.001$ for both) (Supporting Information, *Table S1*).

There were also significantly lower scores across all domains in patients with 1 year adverse outcomes of HF admissions and/or death compared with event-free HFrEF patients after adjustment. However, there were no significant differences between physical function and symptoms scores of patients with 1 year mortality or HF hospitalizations in HFpEF. The receiver operating characteristic (ROC) curve of the clinical summary score for predicting death or HF at 1 year was 0.721 ± 0.011 for HFrEF and 0.774 ± 0.037 for HFpEF. All domains were comparable with the KCCQ clinical summary score in predicting 1 year outcomes except lower ROC curve for QoL in HFrEF ($P = 0.002$). Details of the association of KCCQ scores with HF readmission, mortality, and composite endpoints are presented in Supporting Information, *Table S2*. The adjusted Kaplan–Meier curve of the clinical summary score for time to the composite endpoint of first HF readmission or death is presented in *Figure 1A*, demonstrating known-group validity whereby earlier events and a higher proportion of events occurred in patients with lower scores at baseline.

Confirmatory factor analysis

Using confirmatory factor analysis with cut-off of eigenvalue >1, we identified six latent constructs/domains for HFrEF and five latent constructs/domains for HFpEF. The six domains identified in patients with HFrEF were (i) physical function pertaining to basic activities of daily living such as bathing and dressing (Questions 1A–1C), (ii) higher-order physical activity such as doing yard work (Questions 1D–1F), (iii) symptom frequency and burden, pertaining to fatigue and shortness of breath (Questions 2 and 5–9), (iv) symptom frequency and burden pertaining to leg swelling (Questions 3 and 4), (v) QoL and social limitation (Questions 12–15), and (vi) self-efficacy (Questions 10 and 11). This corresponded to the KCCQ original domains where (i) and (ii) were combined together to form the domain of physical function, (iii) and (iv) formed total symptoms, (v) was further divided to QoL and social limitation, and (vi) was self-efficacy. The scree plots, which show the number of factors (with eigenvalue >1) to retain from the factor analysis, can

Table 2 Baseline characteristics of patients

Demographics	All (n = 5391)	HFrEF (n = 4470)	HFpEF (n = 921)	P-value
Asian region				
East Asia	2130 (39.5%)	1600 (35.8%)	530 (57.2%)	Ref
South Asia	1511 (28.0%)	1300 (29.1%)	211 (22.7%)	<0.001
Southeast Asia	1756 (32.5%)	1570 (32.1%)	186 (20.1%)	<0.001
Age	62.1 (53.1–70.8)	60.5 (52.0–69.0)	69.3 (60.0–77.6)	<0.001
Ethnicity				
Chinese	1646 (30.5%)	1201 (26.9%)	445 (48.0%)	Ref
Indian	1689 (31.3%)	1444 (32.3%)	245 (26.4%)	<0.001
Malay	757 (14.0%)	677 (15.2%)	80 (8.6%)	<0.001
Japanese/Korean	948 (17.6%)	801 (17.9%)	147 (15.8%)	<0.001
Other	354 (6.6%)	344 (7.7%)	10 (1.1%)	<0.001
Male	3924 (72.7%)	3453 (77.2%)	471 (50.8%)	<0.001
Body mass index				
<18.5	311 (6.24%)	290 (6.8%)	21 (3.0%)	Ref
18.5–22.9	1533 (30.7%)	1371 (32.0%)	162 (23.0%)	0.042
23–27.4	1885 (37.8%)	1638 (38.2%)	247 (35.1%)	0.002
27.5 and up	1258 (25.2%)	984 (22.9%)	284 (38.9%)	<0.001
Weight	65.0 (57.0–75.0)	65.0 (57.0–70)	67.2 (58–77.8)	0.006
NYHA class				
I	577 (11.8%)	465 (11.3%)	112 (14.9%)	Ref
II	2593 (53.2%)	2154 (52.2%)	439 (58.5%)	0.155
III	1407 (28.9%)	1231 (29.8%)	176 (23.5%)	<0.001
IV	298 (6.1%)	275 (6.7%)	23 (3.1%)	<0.001
Ejection fraction (%)	30 (24.0–37.0)	28.0 (22.0–33.8)	60.0 (55.0–56.6)	<0.001
Atrial fibrillation	1055 (19.6%)	797 (17.9%)	258 (27.8%)	<0.001
Implantable cardiac defibrillator device therapy	732 (13.6%)	656 (14.7%)	76 (8.2%)	<0.001
Hospitalization for HF in last 6 months	2011 (62.7%)	1734 (62.2%)	277 (65.9%)	0.231
Hypertension	2855 (53.0%)	2221 (49.8%)	634 (68.5%)	<0.001
Diabetes mellitus	2098 (39.0%)	1700 (38.1%)	398 (43.0%)	0.005
Prior stroke	326 (6.1%)	258 (5.8%)	68 (7.3%)	0.070
Peripheral arterial disease	153 (2.8%)	135 (3.0%)	18 (1.9%)	0.071
Chronic obstructive lung disease	458 (8.5%)	371 (8.3%)	87 (9.4%)	0.283
Coronary artery disease	2464 (45.8%)	2189 (49.1%)	275 (29.7%)	<0.001
Depression	65 (1.2%)	48 (1.1%)	17 (1.8%)	0.054
Dementia	39 (0.7%)	28 (0.6%)	11 (1.2%)	0.067
Peptic ulcer disease	186 (3.4%)	130 (2.9%)	56 (6.0%)	<0.001
Moderate to severe liver disease	159 (2.9%)	142 (3.2%)	17 (1.8%)	0.028
Cancer	190 (3.5%)	140 (3.1%)	50 (5.4%)	0.001
History of smoking	2178 (40.5%)	1969 (44.1%)	209 (22.6%)	<0.001
History of alcohol overuse	1402 (26.0%)	1259 (28.2%)	143 (15.5%)	<0.001
Beta-blocker therapy	3489 (74.5%)	3044 (76.2%)	445 (64.2%)	<0.001
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker therapy	3419 (73.0%)	2984 (74.7%)	435 (62.7%)	<0.001
Mineralocorticoid receptor antagonist therapy	2521 (53.8%)	2356 (59.0%)	165 (23.8%)	<0.001
Digoxin therapy	1211 (25.8%)	1151 (28.8%)	60 (8.6%)	<0.001
Heart failure hospitalization	658 (13.7%)	605 (15.2%)	53 (6.2%)	<0.001
Death	886 (18.4%)	819 (20.6%)	67 (7.9%)	<0.001
Composite outcome of heart failure hospitalizations and/or death	1350 (28.0%)	1241 (31.2%)	109 (12.9%)	<0.001

HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.

be found in Supporting Information, *Figure S1A* and *S1B* for HFrEF and HFpEF, respectively.

The five domains identified in HFpEF included three that were similar to HFrEF and two that were different. The domains that remained the same are (i) physical function pertaining to basic activities of daily living such as bathing and dressing (Questions 1A–1C), (ii) symptom frequency and burden pertaining to leg swelling (Questions 2–4), and (iii) self-efficacy (Questions 10 and 11). The two domains that were different in HFpEF were rearrangements of the remaining questions into (iv) higher-order physical activity, for example, yardwork and groceries, and social limitation, for example, recreational activities and hobbies, visiting out of home, and intimate relationships (Questions 1D–1F and 15A–15D), and (v) QoL related to shortness of breath and fatigue (Questions 5–9 and 12–14).

Structured equation modelling was performed on the earlier items and domains for HFrEF and HFpEF, and the results are shown in *Figure 2A* and *2B*, respectively. There was strong correlation (>0.6) between physical function, symptoms,

Table 3 Summary of KCCQ scores and Cronbach's alpha

Domains/summary scores	Heart failure with reduced ejection fraction				Heart failure with preserved ejection fraction			
	Median [IQR]	Item-to-test correlation	Item-to-rest correlation	Cronbach's alpha	Median [IQR]	Item-to-test correlation	Item-to-rest correlation	Cronbach's alpha
Physical function	71 [50–90]	0.856	0.804	0.904	80 [58–95]	0.890	0.849	0.918
Total symptoms	75 [52–91]	0.831	0.771	0.907	80 [58–94]	0.816	0.754	0.925
Self-efficacy	75 [50–85]	0.334	0.175	0.954[a]	75 [50–87]	0.411	0.269	0.959[a]
Social limitation	67 [33 91]	0.871	0.808	0.905	83 [58–100]	0.886	0.832	0.920
Quality of life (QoL)	58 [33–75]	0.779	0.705	0.912	67 [50–83]	0.802	0.737	0.926
Functional status	72 [53–88]	0.926	0.917	0.896	67 [46–83]	0.954	0.939	0.912
Clinical summary	67 [46–83]	0.983	0.977	0.891	72 [56–85]	0.985	0.980	0.909
Physical independence[b]	77 [56–91]	0.938	0.905	0.899	76 [62–89]	0.921	0.895	0.916
Overall				0.920				0.933

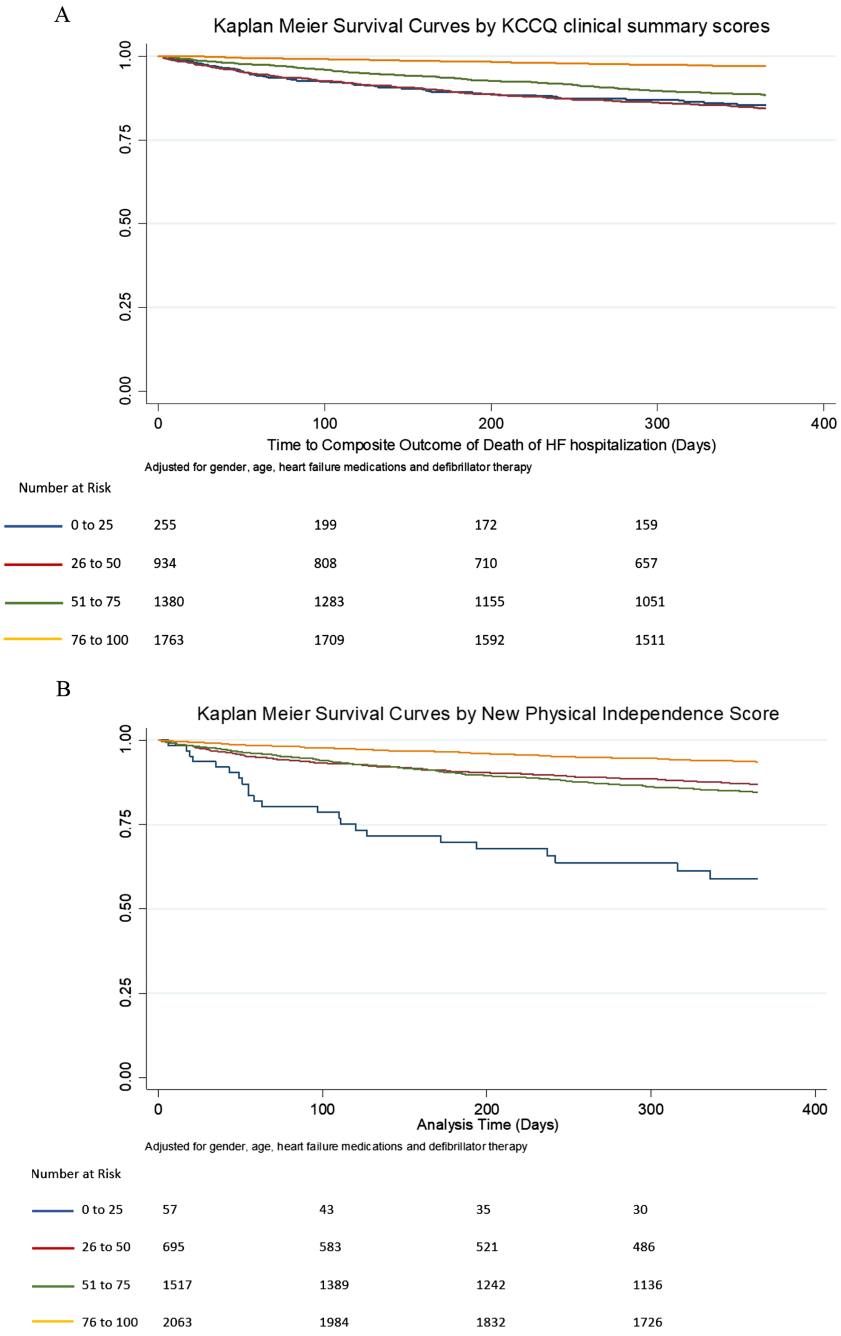
IQR, inter-quartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire.
[a]An increase in Cronbach's alpha, compared with overall, suggests decreased reliability for that domain; that is, reliability of the scale increases when the domain is removed.
[b]New summary score.

Table 4 Known-group validity correlation with visual analogue scale and NYHA class

	Correlation of individual domains and NYHA class		Correlation of individual domains and visual analogue scale	
	Patients with HFrEF	Patients with HFpEF	Patients with HFrEF	Patients with HFpEF
Physical function	−0.39	−0.40	0.34	0.39
Total symptoms	−0.43	−0.44	0.25	0.33
Quality of life	−0.34	−0.34	0.37	0.40
Social limitation	−0.39	−0.40	0.36	0.41
Self-efficacy	−0.08	−0.23	0.14	0.17
Functional status score	−0.46	−0.46	0.38	0.39
Clinical summary score	−0.46	−0.47	0.42	0.44
New physical independence score	−0.43	−0.45	0.38	0.41

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, inter-quartile range; NYHA, New York Heart Association.

Figure 1 (A) Kaplan–Meier curve of heart failure (HF) patients stratified by Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary scores at baseline, adjusted for age, gender, HF medications, and defibrillator therapy. (B) Kaplan–Meier curve of HF patients stratified by KCCQ clinical summary scores at baseline, adjusted for age, gender, HF medications, and defibrillator therapy.



QoL, and social limitation domains in both HFrEF and HFpEF, supporting the overall clinical summary score as a valid tool for PRO assessment.

The strong association between higher-order physical activity and social limitation in HFpEF was not captured by the original physical function domain and the functional status score. There was no significant difference in physical function and symptom scores between HFpEF patients with and without HF hospitalization or mortality (Supporting Information, *Table S2*). We therefore proposed the new physical independence summary score, which comprised both the physical function and social limitation domains from the original KCCQ

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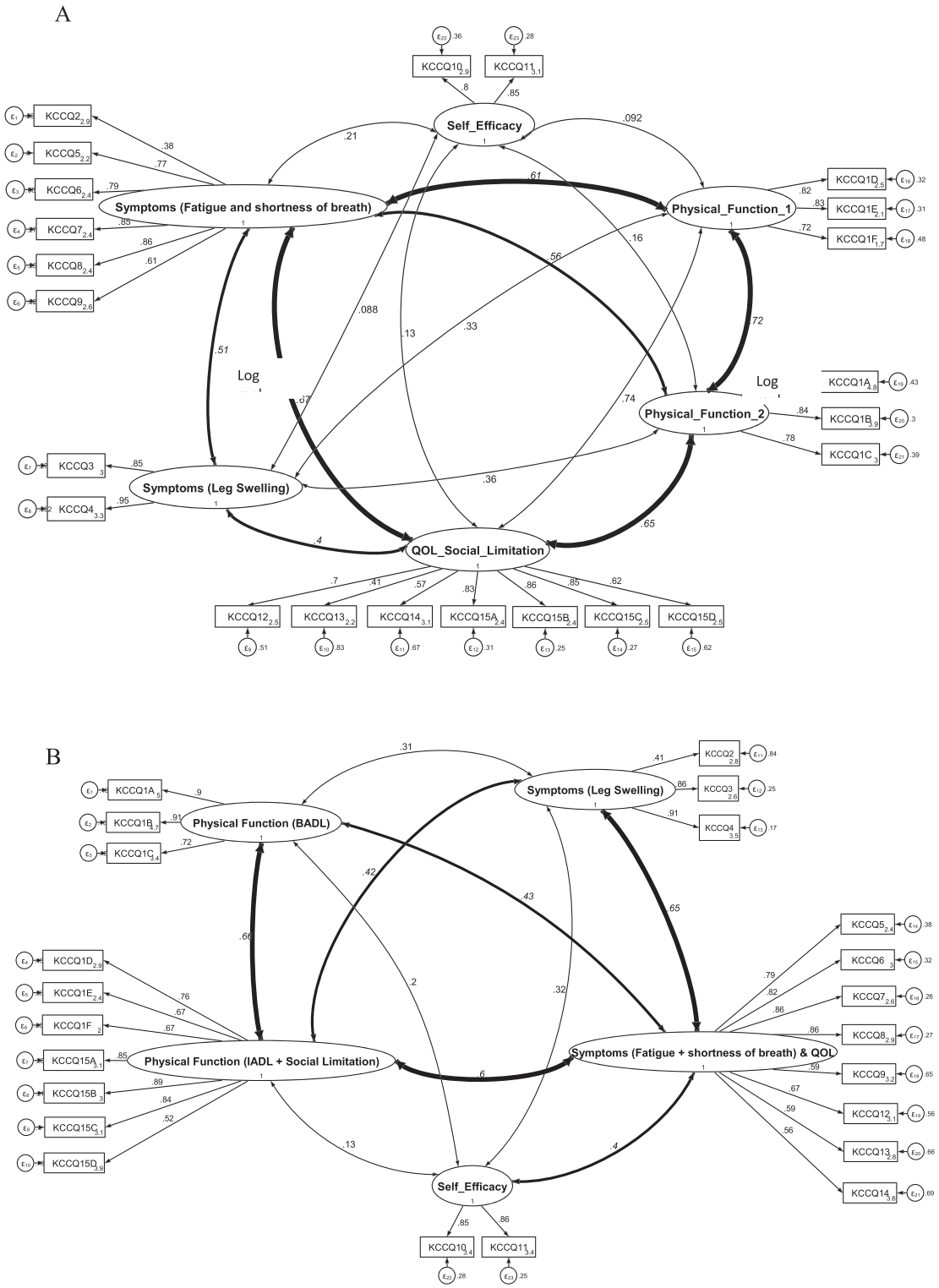
Figure 2 (A) Confirmatory factor analysis and sequential equation modelling of Kansas City Cardiomyopathy Questionnaire (KCCQ) questions in heart failure with reduced ejection fraction. The values show the strength of association between question to domain and between the different domains. The thickness of the arrows represents the strength of association between the various domains. (B) Confirmatory factor analysis and sequential equation modelling of KCCQ questions in heart failure with preserved ejection fraction. The values show the strength of association between question to domain and between the different domains. The thickness of the arrows represents the strength of association between the various domains. BADL, basic activities of daily living; IADL, instrumental activities of daily living; QOL, quality of life.



to better quantify physical capacity, especially in HFpEF. Patients with events have significantly lower physical independence summary score compared with event-free persons.

Physical independence summary score

Our proposed physical independence summary score, composing of Questions 1A–1F and 15A–15D (the physical function and social limitation domains) showed excellent internal consistency in both patients with HFrEF and HFpEF, with scale reliability coefficients of 0.89 and 0.91, respectively. It is also comparable with the clinical summary score in predicting 1 year outcomes with ROC curve of 0.723 ± 0.011 and 0.766 ± 0.037 in HFrEF and HFpEF, respectively. Known-group validity is also demonstrated where patients with lower physical independence score had higher proportion of events, similar to the overall clinical summary sore (*Figure 1B*). Compared with physical function, the patients with mortality or HF hospitalization had lower scores compared with those who were event free in HFpEF.

Table 5 summarizes individual questions, currently used summary scores, and the new proposed summary score in both ejection fraction groups, before and after adjusting for gender, country region, NYHA functional class, symptoms, and mortality at 1 year (factors known to impact health-related QoL in prior HF trials). The physical independence score, like the overall clinical summary score, was significantly different in HFrEF and HFpEF.

Discussion

Our study addressed the gap in knowledge pertaining to these psychometric properties of KCCQ in HFpEF and demonstrated good overall internal consistency and reliability, construct, and known-group validity of the KCCQ as a PRO instrument in HFpEF. HFpEF is a disease of the elderly and multimorbid[8]; as such, while survival is an important outcome, it is also important to monitor how well these patient groups are coping and their QoL. As they are reported directly by the patient, without interpretation by the clinician or other caregiver, PROs directly indicate 'patient suffering' in chronic diseases and provide information that supplements 'hard' clinical outcomes such as mortality and HF readmissions.[5]

Our confirmatory factor analysis revealed subtle differences between HFrEF and HFpEF: while our analysis demonstrated fidelity of the measured questions to the five original KCCQ domains in HFrEF, two other different domains emerged, suggesting a difference in patients' experience with symptoms in HFpEF. The new domain of higher-order activity and social limitation, composing of Questions 1D–1F and 15A–15D, suggested a close relationship between the ability to leave the house (such as yardwork and chasing the bus) and social limitation (e.g. recreation and hobbies). The second domain that differed was relationship of QoL to other measured questions. In HFrEF, QoL and the social limitation belonged to the same domain; in HFpEF, QoL was categorized with symptom burden of fatigue and shortness of breath while social limitation was categorized with higher-order physical activity. This suggests that fatigue and shortness of breath are key influences of QoL in patients with HFpEF, consistent with the findings in the Swedish HF registry.[22] Conversely, social limitation and QoL are more correlated in HFrEF.

Our findings indicating higher-order activity and social limitation being more interrelated in HFpEF were consistent with recent reports from the comparison study between PARAGON-HF and PARADIGM-HF trials for HFpEF and HFrEF, resepectively.[23] Although the KCCQ overall clinical summary scores were comparable in PARAGON-HF and PARADIGM-HF, significant differences remained in higher-order physical activity and social interaction such as climbing flight of stairs without stopping, jogging/hurrying, and intimate and sexual relationships, even after multivariable adjustment.[23] This additional domain is not captured by the physical function or the functional status score. The KCCQ functional status score includes physical function and total symptoms but not social limitation domain; physical function has a stronger relationship with social limitation ($r = 0.66$), compared with symptoms ($r \approx 0.4$) in HFpEF. This significantly contrasts with HFrEF, where strong correlation between physical function and symptoms (correlation coefficient >0.6) makes the KCCQ functional score a reasonable assessment tool. Our proposed new summary score, the physical independence score, combining the physical function and social limitation domain, would address this limitation in HFpEF and may be considered in addition to the physical function domain and clinical summary score. We found that the physical independence score improved internal consistency and showed moderate correlation with both patient-assessed VAS and physician-assessed NYHA status. These concepts and new summary scores should be validated in other HFpEF cohorts.

Furthermore, despite having non-significantly different scores under the total symptoms domain, patients with HFpEF fared significantly worse with symptoms pertaining to leg swelling but were significantly better in symptoms pertaining to shortness of breath and fatigue when compared with patients with HFrEF, highlighting subtle differences. Our results are also congruent with previous reports on the association of KCCQ clinical summary score and clinical outcomes in patients with HF including those with HFpEF.[10,24]

This study is limited in that, unlike some previous reports, it does not contain repeat data to assess for recall and intra-class correlation and repeat KCCQ on follow-up to assess the responsiveness of this scale.[24] Our study cohort included Asian patients, albeit from 11 different regions across

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Table 5 KCCQ questions, all domains, summary scores, and new proposed summary scores for HFrEF and HFpEF

	Unadjusted[a]			Adjusted[b,c]		
	HFrEF	HFpEF	*P*-value	HFrEF	HFpEF	*P*-value
Basic activities of daily living						
Dressing yourself	75.8 ± 15.7	76.3 ± 15.4	0.363	76.1 ± 0.1	76.8 ± 0.2	0.074
Showering/having a bath	73.7 ± 18.7	75.5 ± 16.4	<0.001	73.3 ± 0.1	76.3 ± 0.3	0.008
Walking 100 yards on level ground	64.8 ± 21.7	68.8 ± 20.1	<0.001	65.2 ± 0.1	68.4 ± 0.3	0.123
Independence and social interaction						
Doing gardening/housework	62.0 ± 24.6	67.9 ± 23.1	<0.001	61.3 ± 0.1	65.3 ± 0.3	0.011
Climb a flight of stairs without stopping	55.1 ± 25.6	62.1 ± 26.0	<0.001	54.2 ± 0.1	60.3 ± 0.4	<0.001
Hurrying or jogging (as if to catch a bus)	52.5 ± 30.6	66.7 ± 33.0	<0.001	51.0 ± 0.1	62.9 ± 0.3	<0.001
Hobbies, recreational activities	60.5 ± 25.2	70.3 ± 22.9	<0.001	58.8 ± 0.1	67.1 ± 0.3	<0.001
Working or doing household chores	60.1 ± 25.3	71.0 ± 23.9	<0.001	58.5 ± 0.1	67.0 ± 0.4	<0.001
Visiting family or friends out of your home	61.9 ± 24.8	71.6 ± 23.1	<0.001	60.5 ± 0.1	68.4 ± 0.4	<0.001
Intimate relationships with loved ones	71.0 ± 29.0	84.6 ± 21.6	<0.001	69.5 ± 0.1	83.3 ± 0.3	<0.001
Symptom/quality of life						
Symptom stability	50.4 ± 17.5	48.8 ± 17.6	0.012	51.0 ± 0.1	50.6 ± 0.2	0.515
Leg swelling frequency	52.2 ± 17.4	49.2 ± 18.7	<0.001	52.6 ± 0.1	48.5 ± 0.4	<0.001
Leg swelling bothering	62.3 ± 19.1	61.7 ± 19.8	0.350	62.7 ± 0.1	60.2 ± 0.4	0.003
Fatigue limitation	57.3 ± 26.3	62.5 ± 25.5	<0.001	57.0 ± 0.1	60.2 ± 0.4	0.042
Fatigue bothering	48.2 ± 20.0	54.7 ± 18.3	<0.001	48.2 ± 0.1	51.9 ± 0.3	0.005
Shortness of breath limitation	60.5 ± 25.6	64.1 ± 24.7	<0.001	59.9 ± 0.2	61.1 ± 0.4	0.376
Shortness of breath bothering	49.3 ± 20.9	54.7 ± 18.7	<0.001	49.2 ± 0.1	51.4 ± 0.4	0.931
Sleep upright/3 pillows	49.4 ± 18.6	52.9 ± 16.3	<0.001	49.8 ± 0.1	52.3 ± 0.3	0.820
Heart failure limit enjoyment	55.8 ± 22.7	63.3 ± 20.4	<0.001	55.6 ± 0.1	60.5 ± 0.4	0.003
Feeling about current heart failure state	46.6 ± 20.9	55.1 ± 19.5	<0.001	46.4 ± 0.1	52.2 ± 0.2	<0.001
Discouraged or depressed by heart failure	62.2 ± 20.2	67.5 ± 19.0	<0.001	62.3 ± 0.1	67.7 ± 0.2	<0.001
Original KCCQ domain and summary scores						
Physical function	67.2 ± 25.8	73.5 ± 25.0	<0.001	68.3 ± 0.2	73.6 ± 0.4	0.004
Total symptoms score	69.6 ± 25.5	73.9 ± 24.2	<0.001	70.3 ± 0.2	72.6 ± 0.6	0.758
Self-efficacy	64.8 ± 27.2	67.8 ± 24.8	0.003	65.5 ± 0.1	67.6 ± 0.2	0.001
Social limitation	61.4 ± 32.2	74.0 ± 30.2	<0.001	62.2 ± 0.2	74.0 ± 0.5	<0.001
Quality of Life	65.0 ± 25.4	66.0 ± 23.8	<0.001	56.7 ± 0.2	64.8 ± 0.4	<0.001
Functional status score	68.4 ± 23.1	73.7 ± 22.0	<0.001	69.3 ± 0.2	73.1 ± 0.5	0.061
Clinical summary score	63.5 ± 23.2	71.8 ± 22.3	<0.001	64.3 ± 0.2	71.3 ± 0.5	<0.001
New proposed score						
Physical independence score[d]	69.6 ± 19.3	73.9 ± 18.4	<0.001	70.7 ± 0.1	75.8 ± 0.3	<0.001

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, inter-quartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association.
[a]Variables are mean ± standard deviation.
[b]Values are mean ± standard error.
[c]Each KCCQ domain/activity was adjusted for common independent correlates shown to be associated with worse health-related quality of life in trials (gender, region, body mass index, NYHA functional class, lower extremity oedema, paroxysmal nocturnal dyspnoea, dyspnoea at rest, dyspnoea on exertion, angina, and chronic obstructive pulmonary disease) and mortality at 1 year.
[d]New summary score.

Asia, which may limit the generalizability to non-Asian ethnicities/regions.

Nonetheless, our study substantiated previous literature[10] and extended beyond validating the KCCQ as a health status measure in HFpEF. The new physical independence score may also be a more suitable summary score to quantify functional capability in HFpEF and should be used as an adjunct to the KCCQ overall summary score and physical function domain. HFpEF and HFrEF are two distinct illnesses; adapting the KCCQ score according to their disease properties will allow us to assess PROs more accurately in these two different patient cohorts. Additionally, our study showed correlation of KCCQ in HFpEF, not only with the physician-reported NYHA classification but also with patient-reported VAS, a patient's self-quantification of experience living with the illness, which is a new finding. This is the first psychometric validation of KCCQ in HFpEF outside of clinical trial setting, reflecting PRO collection in the real world. It also has a robust sample size including 4470 and 921 patients with HFrEF and HFpEF, respectively. The confirmatory factor analysis and sequential equation modelling, unique to our study, add useful information to clinicians using KCCQ.[25,26]

Conclusions

The KCCQ clinical summary score is a valid PRO to assess disease-specific QoL in patients with HFpEF, similar to patients with HFrEF. Our results suggested subtle differences in domains between HFpEF and HFrEF, where physical independence and social interaction may be more interrelated

in HFpEF. Our proposed physical independence score is an alternative, valid summary score to better reflect functional capacity in HFpEF.

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Conflict of interest

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Author contributions

C.S.P.L. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically reviewed and contributed to the intellectual content of the manuscript. W.H., T.-H.K.T., W.T.T., and C.S.P.L. were involved with the conception of the study. Initial data preparation was performed by W.T.T. W.H. performed the statistical analyses, supported by T.-H.K.T. and W.T.T., and drafted the manuscript. C.S.P.L., U.K., C.A.L., W.S., S.Y.L., and I.A. provided the clinical expertise. T.-H.T.K. and C.A.L. provided expertise on healthcare systems/policy and health services research. C.S.P.L. and A.M.R. adjudicated all mortality and causes of death. All authors have read and approved the final version of the manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Known group validity by NYHA Class.
Table S2. Known group validity by Heart Failure Readmissions, Mortality and Composite Endpoints at 1 year.
Table S3. Correlation of KCCQ items and scales.
Figure S1. (A) Screen plot of eigenvalues in HFrEF (B) Screen plot of eigenvalues in HFpEF.
Appendix S1. List of ASIAN-HF investigators.

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