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Kansas City Cardiomyopathy Questionnaire Incompletely Captures Symptoms in Patients with Hypertrophic Cardiomyopathy

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Abstract

Objectives: Evaluate whether the Kansas City Cardiomyopathy (KCCQ) adequately quantifies quality of life in patients with Hypertrophic Cardiomyopathy (HCM).

Background: KCCQ was developed as a health-related quality of life (HRQoL) metric for patients with congestive heart failure. It has not been validated in patients with HCM, nor is it designed to capture symptoms specific to HCM.

Methods: This single-center retrospective study from December 2015 to May 2017 included 73 patients (age = 54 (+/- 15), males = 58%). We correlated 21 variables with KCCQ. Participants underwent clinical evaluation, KCCQ, a post-prandial Bruce protocol hemodynamic stress echocardiogram, and NT-ProBNP. Spearman correlations were used for continuous variables, Tukey's t-test for categorical variables, and t-tests for binary variables.

Results: Correlation was significant with stress test metrics, including resting and peak left ventricular outflow tract gradients ($r = -0.25$; $p = 0.034$ and $r = -0.236$; $p = 0.044$, respectively), exercise time ($r=0.576$, $p<0.001$), and VO_2 max ($r=0.58$, $p<.001$). KCCQ was significantly associated with dyspnea (t-test $p<0.001$), chest pain (regression coefficient -9.592, $p=0.003$), Canadian Cardiovascular Society score ($r= -0.401$, $p<0.001$) and New York Heart Association score ($r= -0.630$, $p<0.001$), but not with NT-ProBNP, syncope, presyncope, or palpitations. KCCQ correlated strongly with dyspnea but weakly or not at all with other HCM-specific symptoms and metrics.

Conclusions: While the KCCQ does capture traditional heart failure symptoms, we believe it is ineffective as a HRQoL tool in HCM patients as HCM-specific symptoms are not well quantified. Further, we feel that a new HCM-specific HRQoL should be developed.

Abbreviations

HCM: Hypertrophic cardiomyopathy; KCCQ: Kansas City Cardiomyopathy Questionnaire; HRQoL: Health Related Quality of Life; HSE: Hemodynamic Stress Echocardiography; NT-ProBNP: Serum N-terminal Pro-Brain Natriuretic Peptide; LVOT: Left Ventricular Outflow Tract; METs: Metabolic Equivalents; CCS: Canadian Cardiovascular Society score; NYHA: New York Heart Association score; BMI: Body Mass Index

Introduction

It has long been recognized that health is not simply the lack of illness; in fact, as far back as 1948, the World Health Organization defined health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity [1]". Implicit in this definition is the notion that quality of life contributes to overall state of health. Patient-reported, disease-specific health-related quality of life (HRQoL) questionnaires are increasingly incorporated into clinical trials and clinical care as a means of assessing multiple aspects of patient well-being. Studies of HRQoL metrics have shown that patients' perception of their health-related quality of life is a useful supplement to physiologic assessment in predicting outcomes and providing more accurate assessment of patients' medical needs [2].

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a HRQoL measure that evaluates heart failure health domains, including physical limitations, symptoms, quality of life, social limitations, symptom stability, and self-efficacy. Questions are written such that higher scores correspond to overall better quality of life [3]. This metric has been studied in many cardiomyopathy cohorts including congestive heart failure, heart failure secondary to chronic anemia, ischemic cardiomyopathy, and aortic stenosis, all of which have shown the KCCQ to be a valid, reproducible, reliable test with prognostic capability [4-8].

These studies have demonstrated the clinical utility of KCCQ in guiding management for patients. For example, KCCQ accurately identifies heart failure patients who are most likely to require readmission within 30 days of discharge, so it has been suggested that patients with lower KCCQ scores at discharge should have earlier follow-up than those with higher KCCQ scores [4]. Similarly, KCCQ aids post-myocardial infarction risk stratification [6], providing accurate assessment of risk without the need for more expensive studies. Consequently, the KCCQ has proven to be a useful tool in guiding management decisions, reducing healthcare costs, and gaining understanding of patients' perception of their quality of life.

Since KCCQ has proven valid in multiple cardiomyopathy cohorts, it has been proposed that KCCQ could also be applied to the Hypertrophic Cardiomyopathy (HCM) population. HCM is the most common monogenetic cardiovascular disease in the world, affecting an estimated one in 200-500 people. HCM is also the most common cause of sudden death in young athletes in the United States. KCCQ has increasingly been incorporated into HCM clinical drug studies, in which sponsors, including the Food and Drug Administration, regularly require patients to complete a KCCQ as a method of monitoring quality of life and subjective experience throughout the course of a study. Some HCM centers also incorporate KCCQ into their clinical practices for these purposes. Despite this, to date there has been little or no validation of the KCCQ as a HRQoL tool in HCM. Published data on use of KCCQ in the HCM population appears to be limited to one small, single-site study of 24 HCM patients, which found only a moderate correlation between KCCQ and percent predicted peak VO_2 max ($r = 0.444$) and New York Heart Association (NYHA) score ($r = -0.623$) [9].

Although there is some clinical overlap between patients with HCM and those in the previously-mentioned cardiomyopathy populations, many symptoms and limitations are exclusive to HCM. In addition to dyspnea, HCM patients frequently experience symptoms related to arrhythmias, chest pain, presyncope, syncope, and the psychological impact of the hereditary nature of HCM. Importantly, providers often

recommend exercise restriction in individuals who are much younger than the general heart failure patient. Moreover, obstructive HCM is a dynamic condition, with symptomatic exacerbation in response to exercise, ambient temperature, specific types of meals, and emotional triggers. Given these limitations and our own anecdotal observations, we hypothesize that the KCCQ does not adequately capture symptoms unique to the HCM population, and as such it alone is insufficient as a HRQoL tool.

Methods

Study population

This retrospective study enrolled subjects from the Oregon Health & Science University (OHSU) HCM Center between December 2015 and May 2017. The study was approved by the OHSU Institutional Review Board, including a waiver of consent. Eligible patients were ≥18 years of age with a diagnosis of HCM (defined as patients with left ventricular wall thickness ≥ 15mm without other known cause of hypertrophy and/or ≥ 13 mm with a known family history of HCM or HCM-causing genetic variant). All eligible patients completed a KCCQ during a clinic visit with an OHSU HCM clinic physician or physician's assistant, underwent a post-prandial Bruce protocol hemodynamic stress exercise echocardiography (HSE) within two weeks of the clinic visit, and had serum N-terminal Pro-Brain Natriuretic Peptide (NT-ProBNP) drawn within 4 weeks of the clinic visit.

HSE

Patients underwent post-prandial Bruce protocol HSE via upright treadmill exercise per standard Bruce protocol. Patients were instructed to continue cardiac medications (beta-blocker, calcium channel blocker and/or disopyramide) as prescribed and to eat a hearty meal two hours prior to the test. The site of left ventricular outflow tract (LVOT) obstruction was localized via pulsed-wave Doppler in 3- and 5-chamber views from the transthoracic apical window. Peak LVOT gradient was estimated with continuous wave Doppler, with care taken to avoid the signal from a mitral regurgitation jet. Multiple attempts were made in order to attain the highest peak LVOT gradient at rest and following provocative measures. Echocardiographic and Doppler data on LVOT obstruction were acquired at rest and immediately following peak exercise. Metabolic equivalents (METs) were converted to VO_2Max via the standard METs = VO_2/3.5 calculation. VO_2Max (predicted) was calculated using the Wasserman calculation [10].

Patient-reported symptoms

Patient-reported symptoms were obtained during the clinic visit. Patients completed the KCCQ short form, which incorporates several domains: physical limitations, symptom frequency, quality of life, and social limitations [11]. The short form provides scores for each domain (0-100) as well an overall summary score, calculated as an average of the four domain scores. For data analysis, we used only the overall summary score. In addition to the KCCQ, Canadian Cardiovascular Society angina (CCS) and NYHA scores were recorded by the provider during the visit, and patients were directly questioned about the presence or absence of syncope, presyncope, dyspnea, palpitations, and chest pain.

NT-ProBNP

A blood sample for NT-ProBNP analysis was drawn within 4 weeks of the clinic visit. Serum NT-proBNP was measured using the Elecsys 2010 System (Roche Diagnostics, Indianapolis, IN), which uses two polyclonal antibodies that bind to the amino terminal part of NT-proBNP. Daily 2-point quality control calibration is performed and logged electronically. Samples were collected in heparinized tubes by an authorized phlebotomist in the outpatient laboratory. Samples are stored at -20ºC prior to batch processing.

Statistical methods

Study authors had full access to all data in the study and take responsibility for its integrity and data analysis. All data points were classified as continuous, ordered categorical, or binary variables. The associations between continuous and ordered categorical variables were assessed using Spearman correlation. Partial correlation coefficients were also estimated adjusting for age, gender and body mass index. T-tests were used for binary clinical factors, and 95% two-sided confidence intervals were constructed for all correlations. For categorical variables (NYHA, CCS) and clinical symptoms by dyspnea status, one factor ANOVA with Tukey's post hoc T-tests were computed.

Sample size was selected based on the required number of subjects to construct 95% two-sided confidence intervals for Spearman correlations of width 0.5 that excluded a clinically meaningful correlation of at least 0.7 or -0.7. A sample size of 60 was determined necessary for this precision in estimation. Seventy-three patients were deemed eligible (age = 54 +/-15 years, males = 58%) and included in the study. Twenty-one variables were correlated with KCCQ and summarized in Table 1: age, gender, body mass index (BMI), $V0_2$Max (predicted), $V0_2$Max (actual), resting and exercise peak LVOT gradients, total exercise time on stress test, NT-ProBNP value, NYHA and CCS class, and the individual patient-reported symptoms of syncope, presyncope, dyspnea, chest pain, and palpitations.

To assess the association of dyspnea and other clinical symptoms with KCCQ, a linear regression model was fit with KCCQ as the dependent outcome and NYHA class, CCS score, dyspnea, syncope, presyncope, chest pain, palpitations, age, gender, and body mass index as independent variables. This model evaluated whether clinical symptoms were independently significantly associated with KCCQ score after adjusting for other clinical characteristics. Subgroup analyses within cohorts of subjects defined as those with and without dyspnea

Table 1: Patient Demographics.

	n=73
Male (%)	42 (57.5)
Mean age (years, SD*)	54.07 (±14.94)
Mean KCCQ† score (SD)	50.08 (±12.94)
Mean VO_2Max (mL/kg/mn, SD)	29.97 (±13.06)
Median LVOT resting gradients (mmHg, IQR‡)	18.5 (7.52, 48.0)
Median LVOT peak gradients (mmHg, IQR)	54.5 (19.0, 122.0)
Median NT-ProBNP (pg/mL, IQR)	454.0 (169.0, 122.0)
Mean total exercise time (seconds, SD)	453.56 (±198.04)
NYHA§ 1 (%)	30 (41.1)
NYHA 2 (%)	21 (28.8)
NYHA 3 (%)	22 (30.1)
CCS‖ 1 (%)	58 (79.5)
CCS 2 (%)	8 (11.0)
CCS 3 (%)	6 (8.2)
CCS 4 (%)	1 (1.4)
Patient-reported syncope (%)	15 (20.5)
Patient-reported presyncope (%)	30 (41.1)
Patient-reported dyspnea (%)	40 (54.8)
Patient-reported chest pain (%)	26 (35.6)
Patient-reported palpitations (%)	39 (53.4)

*SD: Standard Deviation
† KCCQ: Kansas City Cardiomyopathy Questionnaire
‡ IQR: Interquartile Range
§ NYHA: New York Heart Association classification
‖ CCS: Canadian Cardiovascular Society functional classification of angina

were performed to generate hypotheses about potential interactions of dyspnea with other clinical symptoms in the relationship with KCCQ.

Results

HSE data

The average KCCQ score was 50.08 and average calculated $V0_2Max$ was 29.97 mL/kg/min. Interquartile range of resting LVOT gradient was 18.50 mmHg [7.52, 48.00] increasing to 54.50 mmHg [19.00, 122.00] at peak exercise, and average total exercise time was 453.56 seconds (Table 1). As per Figure 1, KCCQ showed weak but statistically significant negative correlation with resting and peak LVOT gradients ($r = -0.25$; $p = 0.034$ and $r = -0.236$; $p = 0.044$, respectively). There were also positive correlations between KCCQ and both exercise time ($r=0.576$, $p<0.001$) and VO_2max ($r=0.546$, $p<.001$). After adjusting for age, gender, and BMI, exercise time and VO_2max remained statistically significant (exercise $r = 0.483$, $p < 0.001$; VO_2max $r= 0.429$, $p < 0.001$), but LVOT resting and peak gradients did not (resting $r = -0.168$, $p = 0.168$; peak $r = -0.171$, $p = 0.157$) (Figure 1).

There is a weak negative correlation between both resting and provoked left ventricular outflow tract gradient and the overall KCCQ score. There is a moderate correlation between exercise capacity as measured by exercise time or calculated peak oxygen consumption and the overall KCCQ score.

Patient-reported and physician-classified symptoms

Most patients (n=56, 76.7%) reported one or more symptoms, most commonly dyspnea (54.8%) followed by palpitations (53.4%), presyncope (41.1%), chest pain (35.6%), and syncope (20.5%). We categorized patient symptoms into four categories based on reported symptoms: no reported symptoms, any symptoms except dyspnea, only dyspnea, and dyspnea plus at least one other symptom. Comparing average KCCQ between these subgroups (Fig 2), we found that patients with dyspnea plus other symptoms had significantly lower mean KCCQ compared to subjects with no reported symptoms (mean difference in scores -18.912, Tukey's T-test $p<0.001$). Patients with dyspnea only had lower KCCQ scores (mean difference in scores -11.765) than subjects with no symptoms, as did patients reporting only non-dyspnea symptoms (mean difference -4.140), but these comparisons were not statistically significant (Figure 2).

Patients with dyspnea plus other symptoms had significantly lower mean KCCQ compared to subjects with no reported symptoms. Patients with dyspnea only had lower KCCQ scores than subjects with no symptoms, as did patients reporting only non-dyspnea symptoms, but these comparisons did not reach statistical significance.

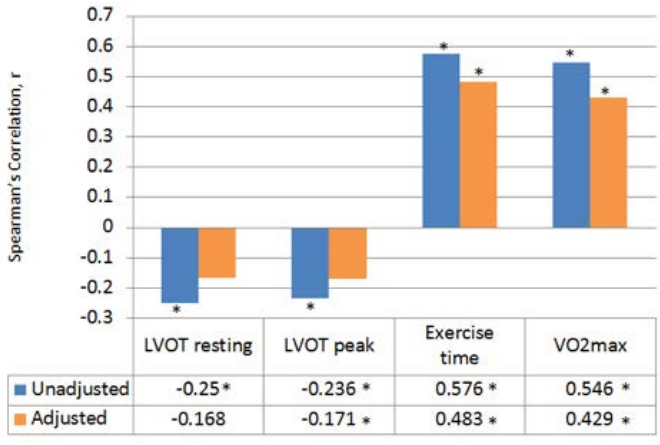

Figure 1: Correlation between KCCQ Score and Stress Test Data. LVOT: Left ventricular outflow tract; Adjusted: adjusted for age, gender, and body mass index; *: statistically significant, $p<0.05$

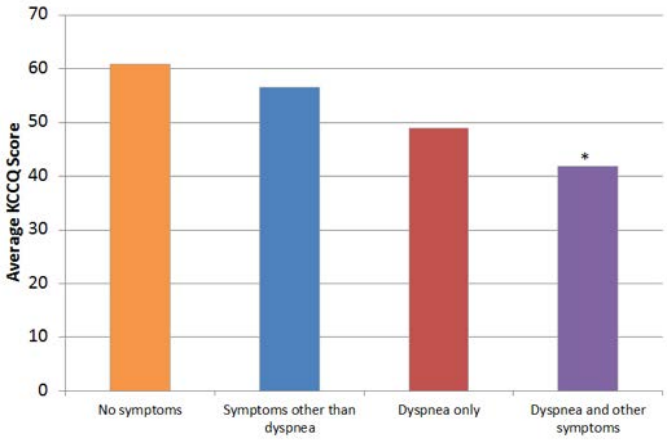

Figure 2: Average KCCQ Score by Patient-Reported Symptoms, Stratified by Presence/Absence of Dyspnea

*: Statistically significant as compared by Tukey's t-test to no symptoms, $p<0.05$

We compared patients both with and without dyspnea, syncope, presyncope, chest pain and/or palpitations (Fig 3). Patients with each symptom had significantly lower scores than patients without the symptom (t-test dyspnea $p =0.002$, syncope $p = 0.026$, presyncope $p<0.001$, chest pain $p<0.001$, and palpitations $p = 0.060$). However, in the subgroup of patients without dyspnea but with another symptom, the absence of dyspnea rendered any association non-significant (syncope $p=0.054$, presyncope $p=0.346$, chest pain $p= 0.219$, palpitations $p=0.271$). In the subgroup of patients reporting dyspnea in addition to another symptom, only chest pain was found to have a significant impact on the KCCQ score (t-test $p = 0.018$) (Figure 3).

We further analyzed the relationship between dyspnea and KCCQ score through a linear regression model (S1 Table) regressing KCCQ on clinical characteristics. This model demonstrated a significant association of KCCQ with chest pain (regression coefficient -9.592, $p=0.003$) after adjusting for other clinical symptoms, NYHA class, CCS score, age, gender, and BMI. An exploratory subgroup analysis of total KCCQ score in patients reporting dyspnea with chest pain was also significant (-12.653, $p = 0.018$), but in the subgroup analysis of patients without dyspnea, the KCCQ did not correlate with chest pain (-4.009, $p = 0.320$). In this model, KCCQ showed no significant correlation with syncope, presyncope, and palpitations, regardless of presence/absence of dyspnea.

A majority of our cohort (58.9%) had NYHA ≥2 but most (79.5%) had CCS score of 1. Both NYHA and CCS scores correlate negatively with KCCQ ($r= -0.630$, $p<0.001$ and $r= -0.401$, $p<0.001$ respectively). Patients with NYHA scores of 2 did significantly worse than those with NYHA 1 ($p=0.002$), and likewise for NYHA 3 versus NYHA 1 ($p<0.001$). There was no statistically significant difference in KCCQ scores for patients with CCS 1 versus 2 or 3.

Laboratory result

NT-ProBNP did not correlate significantly with KCCQ with and without adjustment for age, gender and BMI (unadjusted $r= -0.107$, $p = 0.368$; adjusted $r= -0.074$, $p = 0.545$).

Discussion

Many factors have been shown to impact quality of life for patients with HCM, including atrial fibrillation [12], sleep apnea [13], the presence of an implantable cardiac defibrillator [14], temperature extremes [15], mood and anxiety disorders [16], childhood diagnosis [1], and the hereditary nature of the disease [18]. Although the KCCQ has been shown to be robust in evaluating quality of life in many cardiomyopathy cohorts [4-8], it has not been thoroughly evaluated in

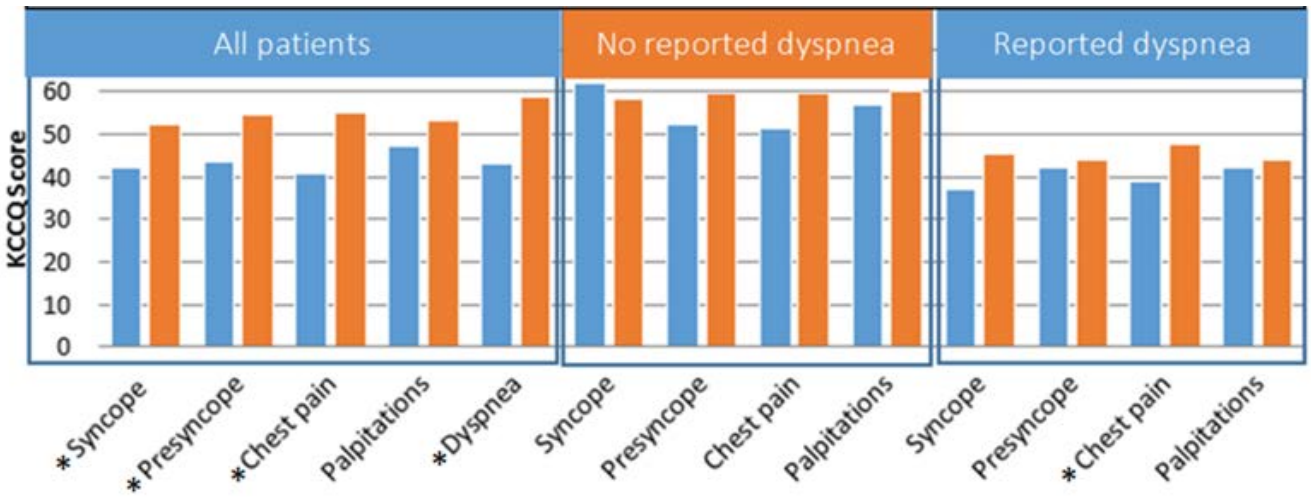

Figure 3: Mean KCCQ Scores by Patient-Reported Symptom.

Patients with each symptom had significantly lower scores than patients without the symptom (left panel). The group of patients without dyspnea but with another symptom, the absence of dyspnea rendered any association with overall KCCQ score non-significant (middle panel). Patients who reported dyspnea in addition to other HCM-symptoms had overall lower KCCQ scores (right panel).

the HCM population and is not specifically designed to capture any of the above factors. Through our clinical and research experience using the KCCQ with our HCM patients, we became concerned that the KCCQ alone was an insufficient tool to capture the breadth of aspects that affect the quality of life of patients with HCM.

Our study, the largest of its kind, confirms that KCCQ's strength is in capturing the impact of dyspnea on quality of life. The correlation between dyspnea and total KCCQ score was robust, even when correcting for confounding variables, and is not surprising given that KCCQ directly questions patients about shortness of breath. When analyzing all patient-reported symptoms, KCCQ also correlated significantly with syncope, presyncope, and chest pain. Both NYHA and CCS classes also correlate with total KCCQ score and support the idea that KCCQ captures aspects of heart failure and chest pain in the HCM population. Subgroup analysis, categorized according to the presence or absence of dyspnea, shows that dyspnea is the primary driver of the overall correlation. Importantly, in patients who did not report dyspnea, there was no correlation between chest pain, syncope, presyncope, or palpitations and the total KCCQ score. Additionally, while there may be correlations between the various symptoms and the KCCQ score, the absolute values obtained in our HCM cohort differ from those observed in other forms of heart failure when evaluated by NYHA class as originally described in the literature [11].

Patients undergoing exercise stress testing demonstrated that longer exercise times and better VO_2max correlated with better KCCQ scores. Increased resting and peak LVOT gradients negatively correlated, albeit weakly, with total KCCQ score; however, this correlation did not remain after adjusting for age, gender, and BMI. The unadjusted correlations may be related again to dyspnea and chest pain: patients with increased gradients frequently report chest pain and/or dyspnea and typically do not perform as well on exercise testing as their HCM peers without these symptoms [19]. Interestingly, there was no correlation between KCCQ and NT-ProBNP values. This is surprising, given that NT-ProBNP has been demonstrated to predict exercise capacity in HCM patients [20] and exercise capacity correlated with KCCQ.

In summary, our study demonstrates that KCCQ adequately captures the impact of dyspnea and, to a lesser degree, chest pain on the quality of life as measured by KCCQ in HCM patients. The KCCQ also correlated, though less vigorously, with total exercise time, VO_2max, and resting and peak gradients. The KCCQ does not adequately address other important HCM-related symptoms (syncope, presyncope, and palpitations) that impact the quality of life in patients with HCM, and as such is inadequate for assessing HCM-related quality of life. An HCM-specific HRQoL questionnaire needs to be developed in order to do so. This is of particular importance in an era when new drug, device and procedural options are becoming available for HCM patients, coupled with the Food and Drug Administration's recent mandate to include patient-reported outcomes in studies.

Our study is limited by the usual pitfalls of a single-center retrospective chart review; generalizability may be limited and our study could be replicated elsewhere to verify reproducibility of results. Additionally, we assessed only the KCCQ overall summary score but did not do sub-analysis of individual domain scores. It is possible that analyzing these subgroups could provide valuable insights into which specific measures within the KCCQ provide the most accurate/valuable assessments of quality of life in HCM patients. As mentioned above, there are many metrics not studied here (age at diagnosis, the hereditary nature of HCM, etc.) that are known to impact quality of life in HCM patients. A more accurate measure of quality of life in HCM patient would ideally analyze aspects of the wide range of variables seen in this population.

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Supplementary Material

Supplementary Table 1: Linear regression model regressing KCCQ on clinical characteristics.

	All subjects	Without dyspnea	With dyspnea
	(1)	(2)	(3)
NYHA II vs I	-3.001 (3.053) p = 0.330	-5.963 (2.659) p = 0.035	2.090 (6.278) p = 0.742
NYHA III vs I	-5.482 (3.537) p = 0.127	-19.697 (6.374) p = 0.006	0.963 (6.179) p = 0.878
CCS 2 vs 1	-0.811 (4.021) p = 0.841		-2.415 (5.307) p = 0.653
CCS 3 vs 1	2.615 (4.678) p = 0.579		0.321 (6.101) p = 0.959
CCS 4 vs 1	-13.514 (9.817) p = 0.174		-14.736 (12.329) p = 0.243
Dyspnea	-6.124 (3.445) p = 0.081		
Syncope	-5.359 (2.974) p = 0.077	2.545 (4.077) p = 0.539	-7.771 (4.665) p = 0.108
Presyncope	0.918 (2.908) p = 0.754	-6.173 (4.039) p = 0.141	2.533 (4.325) p = 0.564
Chest pain	-9.592 (3.051) p = 0.003	-4.009 (3.942) p = 0.320	-12.653 (4.987) p = 0.018
Palpitations	1.693 (2.494) p = 0.500	1.453 (2.435) p = 0.557	5.166 (4.864) p = 0.298
Age	-0.098 (0.077) p = 0.210	-0.107 (0.072) p = 0.154	-0.095 (0.144) p = 0.517
gender=male	-0.053 (2.264)	-0.001 (2.636)	-1.295 (3.874)
	p = 0.982	p = 1.000	p = 0.741
Body Mass Index	-0.486 (0.148) p = 0.002	-0.212 (0.185) p = 0.263	-0.662 (0.223) p = 0.007
Intercept	79.488 (6.773) p < 0.001	72.569 (7.051) p < 0.001	74.214 (13.056) p < 0.001
Observations	73	33	40
R^2	0.611	0.538	0.460
Adjusted R^2	0.525	0.358	0.220

Coefficients (standard error of coefficients) with p-values are reported. Note in subjects without dyspnea there was not sufficient numbers of subjects in the CCS classes to include in the model.

Coefficients (standard error of coefficients) with p-values are reported. Note in subjects without dyspnea there was not sufficient numbers of subjects in the CCS classes to include in the model.

There is a significant association of KCCQ with chest pain after adjusting for other clinical symptoms, NYHA class, CCS score, age, gender, and BMI. An exploratory subgroup analysis of total KCCQ score in patients reporting dyspnea with chest pain was also significant, but in the subgroup analysis of patients without dyspnea, the KCCQ did not correlate with chest. In this model, KCCQ showed no significant correlation with syncope, presyncope, and palpitations, regardless of presence/absence of dyspnea.