FULL TITLE: **Health-related quality of life in acute heart failure: Association between patient-reported symptoms and markers of congestion**

SHORT TITLE: HRQL in acute heart failure

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Total Word Count: **1,911**

Twitter handle: @UoGHeartFailure @BrighamWomens

Short tweet: HRQL in AHF: Association between symptoms and markers of congestion

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.2699

ABSTRACT

Aims: The aim of this study was to examine the association between patient-reported symptoms and the extent of pulmonary congestion in acute heart failure (AHF).

Methods and results: In this prospective, observational study, patient-reported symptoms were assessed at baseline using the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) (range 0-100; 0 worst) in patients hospitalized for AHF. In a subset, patient-reported dyspnea at rest and on exertion was examined (range 0-10; 10 worst) at baseline. In addition, 4-zone lung ultrasound (LUS) was performed at baseline at the time of echocardiography. B-lines were quantified offline, blinded to clinical findings, in a core laboratory. Chest x-ray (CXR) and physical examination findings were collected from the medical records.

Among 322 patients (mean age 72, 60% men, mean LVEF 39%) with AHF, the median KCCQ-TSS score was 33 [interquartile range 18-48]. Worse KCCQ-TSS was associated with worse NYHA class, dyspnea at rest and on exertion, and peripheral edema (p trend <0.001 for all). However, KCCQ-TSS was not associated with the extent of pulmonary congestion, as assessed by the number of B-lines on LUS, or findings on CXR or physical examination (p trend > 0.30 for all). Similarly, KCCQ-TSS was not significantly associated with echocardiographic markers of left ventricular filling pressure, pulmonary pressure or with NT-proBNP.

Conclusions: Among patients hospitalized for AHF, at baseline, KCCQ-TSS was not associated with pulmonary congestion assessed by LUS, CXR or physical examination. These findings suggest that the profound reduction in KCCQ-TSS in patients with AHF may not be solely explained by pulmonary congestion.

Key Words: acute heart failure, quality of life, symptoms, pulmonary congestion, lung ultrasound

BACKGROUND

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is now the most commonly used instrument to measure self-reported health-related quality of life (HRQL) and symptoms in patients with heart failure (HF).[1–3] The KCCQ is sensitive to changes in HRQL and symptoms in patients with HF and could be useful for remote monitoring via telemedicine, potentially identifying development of worsening congestion.[4] We have investigated the association between KCCQ and markers of central and peripheral congestion found on imaging studies (chest x-ray (CXR), ultrasound), physical examination and using laboratory markers in patients with AHF.[5]

AIMS

We investigated the association between the patient-reported symptoms, using the KCCQ-Total Symptom Score (KCCQ-TSS) and markers of congestion, with particular focus on pulmonary congestion, in patients hospitalized for AHF.

METHODS

Study population

This is a secondary analysis of a 2-site, prospective, observational study in adult patients hospitalized due to AHF at two hospitals in Boston (US) and Glasgow (UK). The study population has been previously described.[6] Briefly, patients were enrolled from inpatient units (both sites) and emergency department observation units (Boston) if they were admitted with a diagnosis of AHF (presenting with HF signs and symptoms and requiring intravenous

diuretics irrespective of ejection fraction). Key exclusion criteria were important lung diseases potentially affecting LUS findings (e.g. pulmonary fibrosis), isolated right HF, B-type natriuretic peptide <100 pg/mL in Glasgow and N-terminal pro-B-type natriuretic peptide (NT-proBNP) <1400 pg/mL in Boston, or current dialysis. Patients gave written informed consent before participation. This study complied with the Declaration of Helsinki and was approved by the local institutional review boards.

Patient-reported outcome measures

HF related symptom burden was assessed using the KCCQ on the day of the ultrasound assessments and physical examination. The KCCQ is a self-reported tool asking patients to reflect on their status over the preceding 2 weeks with scores ranging from 0-100, and higher scores indicating better HRQL.[2] There are 8 domains and several summary scores, including the total symptom score (TSS), clinical summary score (CSS) and overall summary score (OSS). The KCCQ-TSS includes questions that directly relate to dyspnea frequency/burden, including items detailed in *Table 1*; therefore, the focus of this analysis was on the KCCQ-TSS. In a subset of participants, patient-reported dyspnea at rest (at the time of assessment) and on exertion (over the past 2 weeks) was examined using a numeric ranking scale (NRS) ranging from 0-10 (0: no dyspnea; 10: severe dyspnea) at the same time as the KCCQ.[6,7]

Lung ultrasonography

LUS was performed at baseline (within a median of 1 day from admission to the hospital) at the time of echocardiography by trained investigators using conventional echocardiographic equipment as previously described.[6,8] A simplified 4-zone imaging protocol was used for LUS

assessment at both sites, and all images were analyzed offline by a core laboratory.[6] The sum of the maximum number of B-lines from each zone was used to obtain the total number of B-lines for each patient.

Other markers of congestion

CXRs (within 24 hours of ultrasound examinations), physical examination and laboratory tests were performed at baseline and clinical and demographic data were collected by trained investigators from medical records at each site as previously described.[6,8] Functional limitation at baseline was reported using the New York Heart Association (NYHA) classification.

Statistical analyses

Only patients with KCCQ-TSS score and LUS data available at baseline were included in this analysis. Patients were categorized according to tertile of KCCQ-TSS. Continuous variables are described as mean (standard deviation) or median and interquartile range, depending on normality, and categorical variables as counts and percentages. Trends across KCCQ-TSS tertiles were assessed using chi-squared tests of trend (for categorical variables), linear regression (for normally distributed variables), and Cuzick's nonparametric test for trend.[9] Cubic spline models were used to estimate the potentially non-linear associations between KCCQ-TSS and key congestion markers at baseline. The number of knots were selected according to the lowest values of Akaike information criterion (3 to 7 knots considered). The Spearman's rank correlation coefficient was used to assess associations between key KCCQ domains and markers of congestion. In sensitivity analyses, we repeated the above analyses according to tertile of dyspnea scores at rest and exertion by the NRS. A p-value of less than 0.05 was considered

statistically significant. Analyses were performed using Stata 16.1 and 15.1 (StataCorp®, Texas, USA).

RESULTS

Among 322 patients with both KCCQ and LUS performed at baseline, the mean age was 72 (±12) years, 60% were male, and most were White (86%) [*Table 2*]. Common co-morbidities included hypertension (77%), atrial fibrillation/flutter (55%), and diabetes (37%). Most patients had a prior diagnosis of HF (63%), almost half of all patients had previously been hospitalized for HF and 30% had an LVEF ≥50%. Ninety-five percent of study participants were enrolled from cardiology units.

Symptom burden, as assessed by KCCQ-TSS, NYHA class, dyspnea at rest, and dyspnea on exertion, was high in this cohort. The median KCCQ-TSS was 33 [IQR 18-48]. Patients with lower (worse) KCCQ-TSS scores were younger, had higher body mass index, and were more likely to have diabetes and asthma/COPD. Lower KCCQ-TSS scores were associated with greater use of diuretics before admission (p=0.001), and lower albumin level (p=0.002) at baseline. Ejection fraction was similar across KCCQ-TSS tertiles.

Table 3 categorizes markers of congestion by tertile of KCCQ-TSS. Patients in the lowest quartile of KCCQ-TSS (worst total symptom score) had a higher prevalence of peripheral edema at presentation, with 92% in the lowest quartile versus 61% in the highest quartile (p for trend <0.001) (*Figure 1*). Worse total symptom score was also associated with worse dyspnea at rest and on exertion as assessed by the NRS (p<0.001). There were no significant associations identified between KCCQ-TSS tertile and other markers of central congestion, including NT-proBNP (p=0.83) and E/e' (p=0.41). There was no statistically significant association between

KCCQ-TSS by tertile (*Table 2*) or KCCQ-TSS as a continuous variable (*Figure 2*) and either the total number of B-lines , or tertiles of B-lines ($p>0.75$ for all). There was no significant interaction between B-lines and asthma/COPD, B-lines and age, or B-lines and LVEF. Similarly, there were no statistically significant differences by tertile of TSS and CXR markers of pulmonary congestion or findings on auscultation. These results were similar in patients without prior HF diagnosis and in patients without prior HF hospitalization. In addition, the associations with congestion markers were similar for the KCCQ-CSS and OSS, as well as related domains (Supplemental Table S1). Likewise, when analyzed across tertiles of dyspnea scores at rest and, separately, on exertion using the NRS, we found no significant association between patient-reported dyspnea scores and objective measures of pulmonary congestion (LUS, CXR or physical examination; $p>0.10$ for all) in this cohort.

CONCLUSION

In this analysis of over 300 well-characterized patients hospitalized for AHF, KCCQ-TSS had only a limited association with markers of central congestion (*Figure 3*). In particular, there was no association between KCCQ-TSS and the number of B-lines and other markers of pulmonary congestion, or with the biomarker most commonly associated with congestion in HF, NT-proBNP. However, KCCQ-TSS was associated with NYHA class, patient-reported dyspnea and peripheral edema.

Although the KCCQ was initially developed in two cohorts of HFrEF patients: one of 70 stable ambulatory patients and one of 59 hospitalized patients with AHF, we did not find any correlation with objective measures of pulmonary congestion in this AHF cohort, despite specific questions around dyspnea and orthopnea in this instrument.[2] This suggests that the KCCQ-TSS

may reflect subjective dyspnea burden but not necessarily the degree of pulmonary congestion in this population. Patient-reported dyspnea in HF is likely multifactorial and may in part be attributable to comorbidities (e.g. obesity, asthma/COPD) and mechanisms not solely explained by pulmonary congestion. Younger patients may experience dyspnea at a lower level of pulmonary congestion due to higher levels of physical activity at baseline. Although there was no significant difference in HF duration across KCCQ-TSS tertiles in this cohort, it is possible that patients with longstanding HF may have developed pulmonary vascular remodeling with resulting higher thresholds for the development of pulmonary edema despite elevated intravascular pressure and associated dyspnea. Another potential explanation for our findings could be that LUS itself is a poor marker of pulmonary congestion. However, we and others have previously demonstrated strong associations between B-line count and conventional markers of congestion such as CXR, clinical examination findings, invasive hemodynamics and natriuretic peptides in HF, which would speak against this.[6,10]

Patients admitted to an intensive care unit at screening or who were unable to provide informed consent were not eligible for participation in this study. Our results may therefore not be generalizable to these patient cohorts.

Our findings are important from both a research and a clinical perspective. Patient-reported symptoms are becoming more important in clinical practice and in trials, with a move towards remote or telemedicine practice following the coronavirus disease 2019 (COVID-19) pandemic. Our findings suggest that patient-reported symptoms may not reflect worse pulmonary congestion and should not be used in isolation for such a purpose.

Sources of Funding

Dr. Platz has received research support from the National Heart, Lung and Blood Institute (grant number K23HL123533).

Drs. Campbell and McMurray have received research support from the British Heart Foundation (grant number PG/13/17/30050).

Disclosures

M.M.Y.L.'s employer, Glasgow University, has received grant support from Boehringer Ingelheim.

S.D.S. has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, Puretech Health.

J.J.V.M.'s employer, Glasgow University, has received payments from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, KBP Biosciences, Novartis, Pfizer, and Theracos for his work on clinical trials, consulting and other activities and he has received personal payments from Abbott, Hikma, Ionis, Sun Pharmaceuticals and Servier.

E.P.'s employer has received support from Novartis for consulting work, and she has consulted for scPharmaceuticals outside of the submitted work. She has received research support from NHLBI and NIDDK.

All other authors report that they have no relationships relevant to the contents of this paper to disclose.

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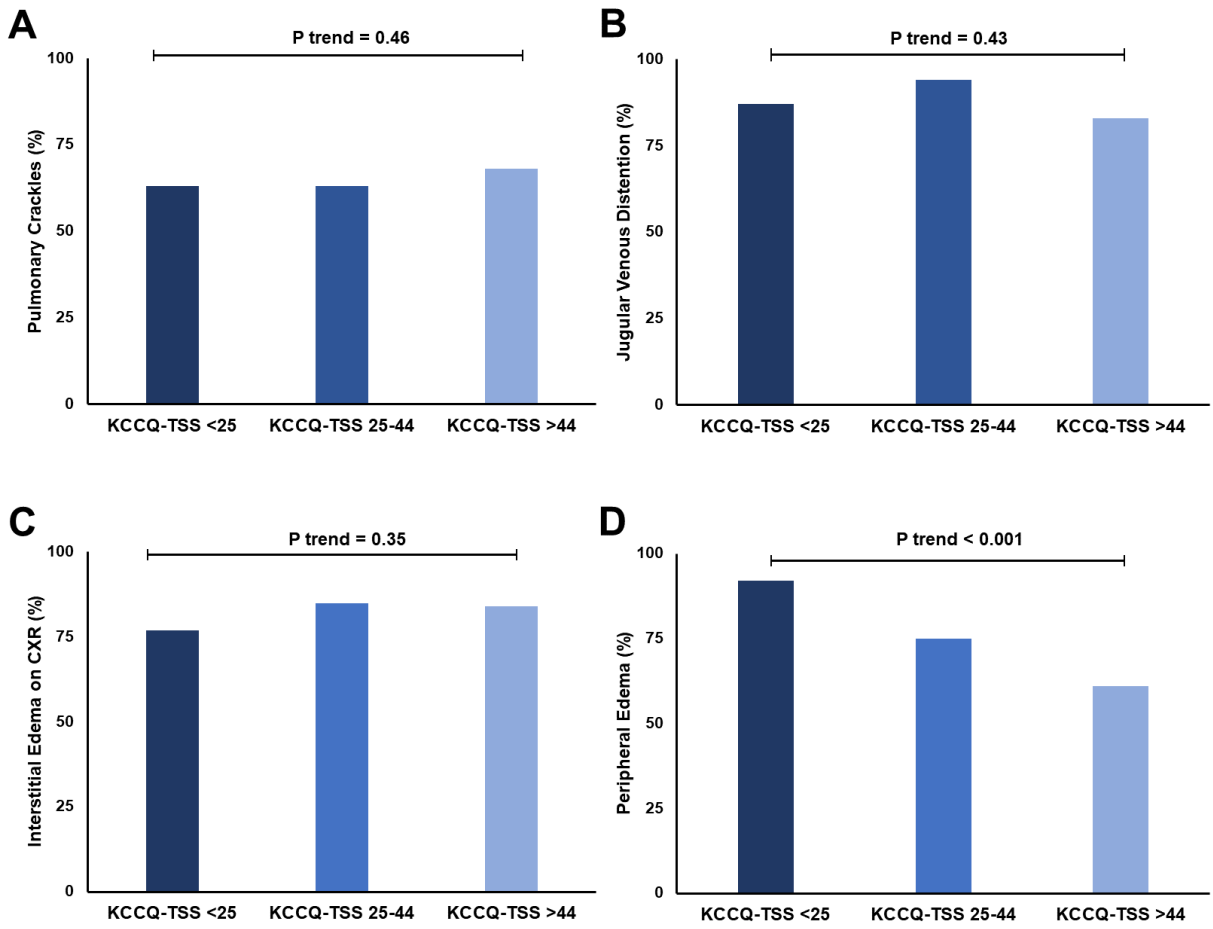
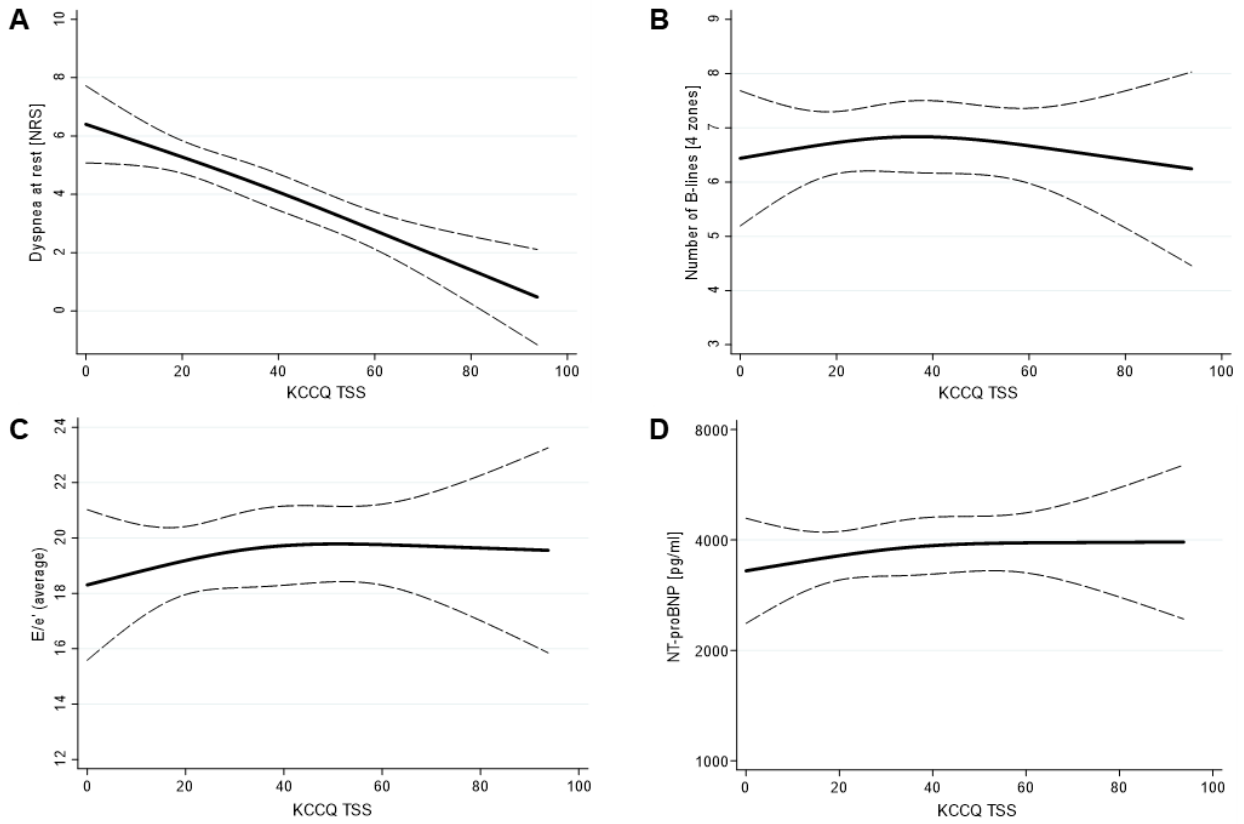
Figure 1. Relationship between KCCQ-TSS in tertiles and physical examination and chest x-ray findings



Legend:

Proportion of patients with physical exam (a, b, d) or chest x-ray findings (c) indicating congestion by KCCQ-TSS in tertiles; KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptoms Score;

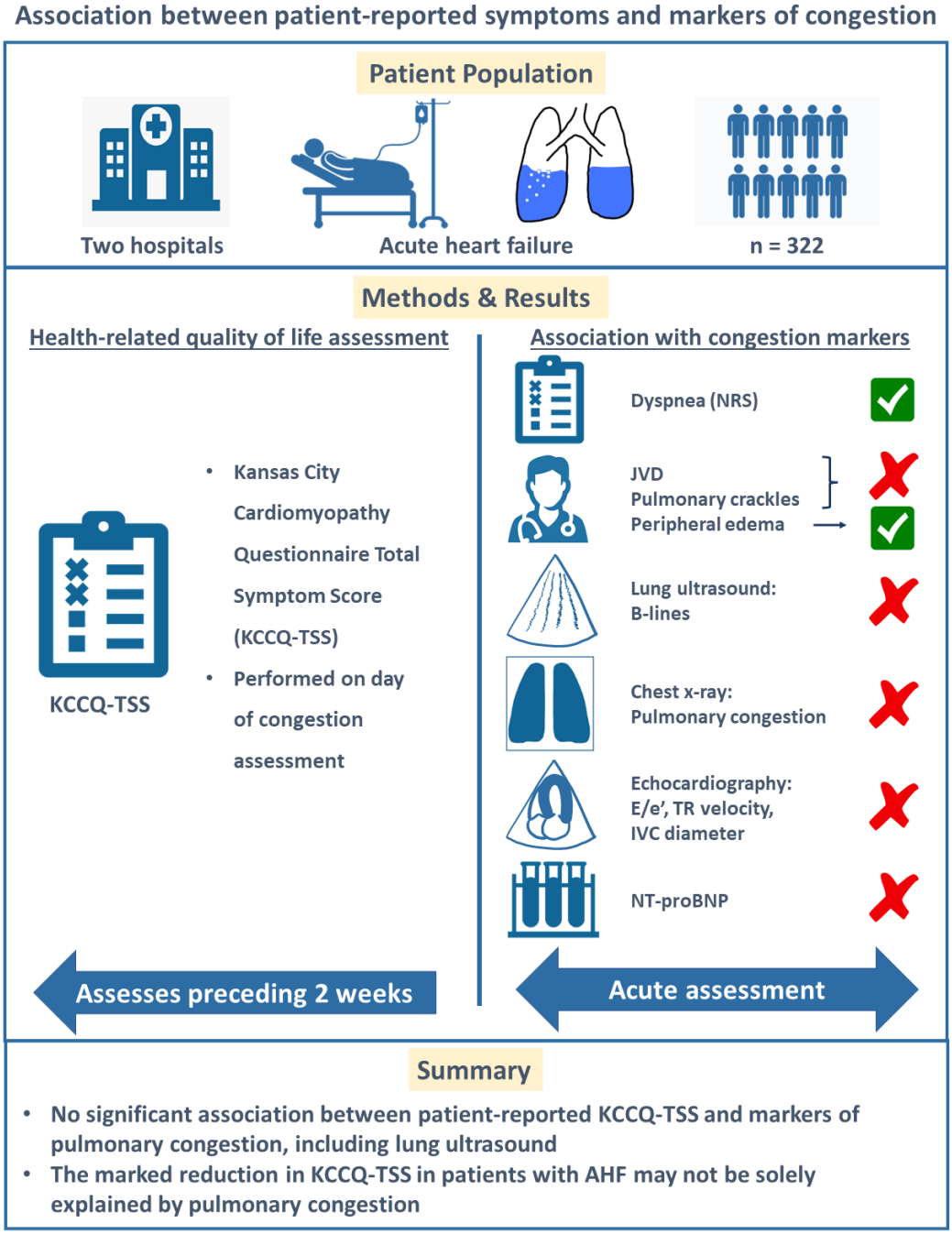
Figure 2. Relationship between KCCQ-TSS and key congestion markers in cubic spline models



Legend:

Restricted cubic spline analysis illustrating the relationship between a) Dyspnea at rest by Numeric Ranking Scale (NRS) (n=175, p<0.001), b) Number of B-lines on lung ultrasound (n=322, p=0.93), c) E/e' (average) (n=263, p=0.51), d) NT-proBNP (n=300, p=0.45) with KCCQ-TSS at baseline. None of the 4 associations were significantly non-linear.

Figure 3. Graphical Abstract



Legend:

KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptoms Score; NRS: Numeric ranking scale; JVD: Jugular venous distention; TR: Tricuspid regurgitation; IVC: Inferior vena cava; AHF: Acute heart failure

Table 1. KCCQ questions related to total symptom score

Over the past 2 weeks, how many times did you have ***swelling in your feet, ankles or legs*** when you woke up in the morning?
Over the past 2 weeks, how much has ***swelling in your feet, ankles or legs*** bothered you?
Over the past 2 weeks, on average, how many times has ***fatigue*** limited your ability to do what you want?
Over the past 2 weeks, how much has your ***fatigue*** bothered you?
Over the past 2 weeks, on average, how many times has ***shortness of breath*** limited your ability to do what you wanted?
Over the past 2 weeks, how much has your ***shortness of breath*** bothered you?
Over the past 2 weeks, on average, how many times have you been ***forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath***?

Table 2. Baseline characteristics by KCCQ-TSS tertile

			Tertile of KCCQ-TSS			
		Total	**TSS <25**	**TSS 25-44**	**TSS >44**	**p-value (trend)**
	N	**N=322**	**N=110**	**N=110**	**N=102**	
Age	322	72.4±13	70.5±12	72.4±13	74.4±13	0.031
Female	322	130 (40)	51 (46)	43 (39)	36 (35)	0.10
Caucasian	322	277 (86)	90 (82)	95 (86)	92 (90)	0.08
BMI (kg/m^2)	318	28.8±7.9	30.3±9.6	28.6±7.2	27.3±6.2	0.006
Heart rate (bpm)	320	83.0±21	85.8±21	80.6±21	82.6±22	0.26
SBP (mmHg)	320	128.6±27.	127.4±27	126.6±27	132.1±28	0.22
LVEF (%)	322	39±16	39±15	39±16	40±16	0.68
Medical history						
Previous HF diagnosis	322	203 (63)	69 (63)	74 (67)	60 (59)	0.58
Previous HF hospitalization	322	144 (45)	50 (46)	56 (51)	38 (37)	0.25
Hypertension	322	249 (77)	85 (77)	88 (80)	76 (75)	0.65
Diabetes mellitus	322	119 (37)	52 (47)	39 (36)	28 (28)	0.003
Atrial fibrillation/flutter	322	176 (55)	56 (51)	65 (59)	55 (54)	0.64
Asthma/COPD	322	91 (28)	41 (37)	32 (29)	18 (18)	0.001
Myocardial infarction	322	113 (35)	42 (38)	35 (32)	36 (35)	0.65
ICD	322	39 (12)	10 (9)	16 (15)	13 (13)	0.41
Home medications						
Beta-blocker	322	232 (72)	73 (66)	86 (78)	73 (72)	0.38
ACEi/ARB/ARNI	322	158 (49)	54 (49)	47 (43)	57 (56)	0.34
Aldosterone blocker	322	43 (13)	18 (16)	11 (10)	14 (14)	0.56
Diuretics	322	206 (64)	81 (74)	72 (66)	53 (52)	0.001
Digoxin	322	27 (8.4)	12 (11)	8 (7)	7 (7.0)	0.29
Calcium channel blocker	322	71 (22)	26 (24)	21 (19)	24 (24)	0.97
Baseline laboratory results						
Sodium (mmol/L)	322	137±5	137±5	138±4	137±4	0.57
Hemoglobin [g/dl]	322	11.8±2.1	11.7±2.2	11.7±2.1	11.9±2.2	0.46
BUN [mg/dl]	322	25 [18-41]	24 [17-41]	26 [19-45]	24 [19-34]	0.68
Creatinine [mg/dl]	322	1.2 [0.9-1.8]	1.2 [0.8-1.8]	1.3 [1.0-1.9]	1.2 [1.0-1.8]	0.98
Albumin [g/dl]	294	3.5±0.5	3.4±0.4	3.5±0.5	3.6±0.5	0.002

Data are presented as mean±SD or median [IQR] for continuous measures, and n (%) for categorical measures. ACEi= angiotensin-converting enzyme inhibitor; ARB= angiotensin receptor blocker; ARNI= angiotensin receptor neprilysin inhibitor; BMI= body mass index; BUN= blood urea nitrogen; COPD= chronic obstructive pulmonary disease; HF= heart failure; ICD= implantable cardioverter defibrillator; KCCQ-TSS= Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF= left ventricular ejection fraction; NYHA= New York Heart Association; SBP= systolic blood pressure.

Table 3. Congestion markers by KCCQ-TSS tertile assessed at baseline

			Tertile of KCCQ-TSS			
		Total	**<25**	**25-44**	**>44**	**p-value (trend)**
	N	**N=322**	**N=110**	**N=110**	**N=102**	
LUS						
B-line number	322	6 [3-10]	6 [3-10]	6 [3-10]	6 [3-10]	0.82
B-line tertiles	322					0.77
0-4		112 (35)	42 (38)	36 (33)	34 (33)	
5-9		120 (37)	37 (34)	42 (38)	41 (40)	
≥10		90 (28)	31 (28)	32 (29)	27 (27)	
CXR*						
Vascular congestion	150	108 (72)	34 (72)	40 (76)	34 (68)	0.63
Interstitial edema	151	124 (82)	36 (77)	46 (85)	42 (84)	0.35
Alveolar edema	151	20 (13)	8 (17)	6 (11)	6 (12)	0.48
Clinical exam						
SpO2 (%)	319	96 [95-98]	96 [95-98]	96 [95-98]	97 [95-98]	0.28
Supplemental oxygen	317	86 (27)	26 (24)	30 (28)	30 (29)	0.36
Jugular venous distension >4cm §	295	260 (88)	88 (87)	92 (94)	80 (83)	0.43
S3 on heart auscultation	320	49 (15)	19 (17)	15 (14)	15 (15)	0.60
Pulmonary crackles	322	207 (64)	69 (63)	69 (63)	69 (68)	0.46
Peripheral edema	322	245 (76)	101 (92)	82 (75)	62 (61)	<0.001
Echocardiography						
E/e' (average)	263	19±8	19±9	19±8	20±8	0.41
TR velocity [m/s]	292	2.9 (0.6)	2.9 (0.6)	2.9 (0.6)	2.9 (0.6)	0.52
IVC diameter [cm]	275	2.3 [1.9-2.6]	2.3 [2.0-2.7]	2.2 [1.8-2.6]	2.2 [1.8-2.5]	0.06
Laboratory						
NT-proBNP [pg/ml]	300	3622 [1764-7678]	3982 [1717-7585]	3317 [1835-7384]	3622 [1702-8338]	0.83
KCCQ scores						
KCCQ-TSS	322	33 [18-48]	12 [5-18]	33 [29-40]	58 [49-73]	--
KCCQ-CSS	322	36 [21-50]	16 [9-26]	36 [28-43]	57 [47-74]	<0.001
KCCQ-OSS	322	34 [19-48]	16 [8-27]	34 [26-44]	55 [42-68]	<0.001
NYHA Class	322					<0.001
I/II		97 (30)	15 (14)	32 (29)	50 (49)	
III		166 (52)	68 (62)	59 (54)	39 (38)	
IV		59 (18)	27 (25)	19 (17)	13 (13)	
Numeric rating scale						
Dyspnea at rest (median score)	175	4 [1-7]	6 [4-8]	5 [1-7]	2 [0-5]	<0.001
Dyspnea on exertion (median score)	171	8 [6-9]	9 [8-10]	8 [7-10]	6 [5-9]	<0.001

* Only patients with CXR within 24 hours of LUS included;
§ Measured from angle of Louis;

Data are presented as mean±SD or median [IQR] for continuous measures, and n (%) for categorical measures. CXR= chest x-ray; IVC= inferior vena cava; KCCQ-TSS= Kansas City Cardiomyopathy Questionnaire Total Symptom Score; CSS= Clinical Summary Score; OSS= Overall Summary Score; LUS= lung ultrasound; NT-proBNP= N-terminal pro-B-type natriuretic peptide; NYHA= New York Heart Association class; S3= third heart sound; SpO_2= oxygen saturation; TR= tricuspid regurgitation.