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ORIGINAL ARTICLE

Translation of the Frailty Paradigm from Older Adults to Children with Cardiac Disease

Chaitanya Panchangam[1,4] · David A. White[2,3] · Suma Goudar[2,3] · Brian Birnbaum[2,3] · Lindsey Malloy-Walton[2,3] · Jami Gross-Toalson[2] · Kimberly J. Reid[2] · Girish Shirali[2,3] · Anitha Parthiban[2,3]

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Abstract

Children and adolescents with cardiac disease (CCD) have significant morbidity and lower quality of life. However, there are no broadly applicable tools similar to the frailty score as described in the elderly, to define functional phenotype in terms of physical capability and psychosocial wellbeing in CCD. The purpose of this study is to investigate the domains of the frailty in CCD. We prospectively recruited CCD (8–17.5 years old, 70% single ventricle, 27% heart failure, 12% pulmonary hypertension; NYHA classes I, II and III) and age and gender matched healthy controls (total $n=56$; CCD $n=34$, controls $n=22$; age 12.6 ± 2.6 years; 39.3% female). We measured the five domains of frailty: slowness, weakness, exhaustion, body composition and physical activity using developmentally appropriate methods. Age and gender-based population norms were used to obtain Z scores and percentiles for each measurement. Two-tailed t-tests were used to compare the two groups. The CCD group performed significantly worse in all five domains of frailty compared to healthy controls. Slowness: 6-min walk test with Z score -3.9 ± 1.3 vs -1.4 ± 1.3, $p<0.001$; weakness: handgrip strength percentile 18.9 ± 20.9 vs 57.9 ± 26.0, $p<0.001$; exhaustion: multidimensional fatigue scale percentile 63.7 ± 13.5 vs 83.3 ± 14.4, $p<0.001$; body composition: height percentile 43.4 ± 29.5 vs 71.4 ± 25.2, $p<0.001$, weight percentile 46.0 ± 36.0 vs 70.9 ± 24.3, $p=0.006$, BMI percentile 48.4 ± 35.5 vs 66.9 ± 24.2, $p=0.04$, triceps skinfold thickness 41.0 ± 24.0 vs 54.4 ± 22.1, $p=0.04$; physical activity: pediatric activity questionnaire score 2 ± 0.6 vs 2.7 ± 0.6, $p<0.001$. The domains of frailty can be quantified in children using developmentally appropriate methods. CCD differ significantly from controls in all five domains, supporting the concept of quantifying the domains of frailty. Larger longitudinal studies are needed to study frailty in CCD and examine if it predicts adverse health outcomes.

Clinical Trial Registration: The ClinicalTrials.gov identification number is NCT02999438. https://clinicaltrials.gov/ct2/show/NCT02999438.

Keywords Frailty · Children with heart disease · Fontan · Heart failure · Pulmonary hypertension · Congenital heart disease · Cardiomyopathy · Quality and outcomes

Abbreviations

CCD	Children and adolescents with cardiac disease
NYHA	New York Heart Association
BMI	Body mass index
PedsQL™ Multidimensional Fatigue scale	Pediatric Quality of Life Inventory Multidimensional Fatigue scale
PAQ-C, PAQ-A	Pediatric activity questionnaire for children and adolescents

✉ Chaitanya Panchangam
panchangams@health.missouri.edu

[1] Department of Child Health, University of Missouri Health Care, Columbia, MO, USA

[2] The Ward Family Heart Center, Children's Mercy Hospital, Kansas City, MO, USA

[3] UMKC School of Medicine, Kansas City, MO, USA

[4] University of Missouri-Columbia, 500 N Keene St, Suite 207, Columbia, MO 65201, USA

MAQ-C, MAQ-A	Modifiable activity questionnaire for children and adolescents
6MWT	6-Min walk test

Introduction

The frailty phenotype was described by the Cardiovascular Health Study Collaborative Research Group in older adults as a complex syndrome resulting from cumulative declines across multiple physiologic systems and leading to decreased resistance to stressors [1]. Fried et al. quantified frailty as a score based upon measurements in five domains: (1) slowness, (2) weakness, (3) self-reported exhaustion, (4) shrinkage (body composition) and (5) low physical activity. In the elderly, the frailty score has been validated as an objective assessment of overall health in chronic disease states; higher frailty scores have been associated with adverse health outcomes [1] and mortality [2], including peri-procedural mortality [3, 4]. Recent studies have suggested that frailty as a physiological phenotype may exist beyond the geriatric population. A multi-institutional study in young adult survivors of childhood cancer demonstrated that the prevalence of frailty in this population is 7.8%; with higher frailty scores associated with an increased risk of morbidity and mortality [5]. A recent multicenter study compared frailty measures in children with compensated chronic liver disease to those with end-stage liver disease and found this tool to be useful in identifying the sickest individuals [6]. However, frailty has not been studied in children and adolescents with cardiac disease (CCD).

Advances in management have significantly improved the long-term survival of CCD such as heart failure, pulmonary hypertension and single ventricle disease with Fontan physiology; however, these patients continue to experience significant morbidities, including exercise intolerance [7, 8], neurocognitive delays [9], frequent hospitalizations [10] and lower quality of life [11–13]. Although serial tests such as cardiac imaging, exercise testing, and laboratory markers are frequently used as surrogate measures to monitor disease progression, there currently exists no clinical measure that can quantify the overall health status of the CCD patient and predict the risk for adverse health outcomes.

The aim of this prospective study was to evaluate the five domains of frailty in CCD and compare them to age and sex matched healthy controls. We hypothesized that: (1) the domains of frailty as described by Fried et al. can be adapted for measurement in children and adolescents using developmentally appropriate methods; and (2) CCD would perform worse than age and gender matched healthy controls across these domains.

Methods

Study Design and Recruitment

We prospectively recruited children and adolescents aged 8–17.5 years with and without CCD for this age and gender matched, case–control study. We included participants in the CCD group ($n = 34$) if they had one or more of three cardiac conditions: Single ventricle physiology with Fontan surgery, heart failure, or pulmonary arterial hypertension requiring pharmacotherapy. All patients with heart failure were classified as AHA stage B or C and were asymptomatic at the time of enrollment. We excluded participants who were wheelchair bound, tracheostomy and/or ventilator-dependent, or had significant physical limitations that could affect their ability to complete testing. Participants who were NYHA class IV, heart failure post heart transplantation within the past 1 year or Fontan surgery within the past 6 months were also excluded. Control participants ($n = 22$), with no known chronic medical conditions, were age and sex matched to the participants in the CCD group. We excluded controls who took any prescription medications in the past 30 days. Participants were recruited by posting flyers in the cardiology clinic at our hospital and through the hospital's internal electronic newsletter. Detailed inclusion and exclusion criteria are shown in Table 1. The study protocol was approved by the Children's Mercy Hospital Institutional Review Board-16060468. Written informed consent and assent was obtained from parents and children prior to participation in any research-related data collection.

Frailty Domain Measurements

Considering the assessments used to measure the frailty domains in the Cardiovascular Health Study were developed for a geriatric sample, we modified the methodology for a sample of children and adolescents. Table 2 lists the frailty domains as described in the Cardiovascular Health Study [1] and the developmentally appropriate measurements that we obtained for each domain in our study population. Multiple measures were obtained for the domains of shrinkage/body composition and physical activity in order to determine which method was the easiest to collect (for dissemination of the frailty paradigm in clinical settings) while accurately capturing the domain's construct.

In the original Frailty paper by Fried and colleagues, slowness was measured with a 15 ft. walk test on all participants. The researchers used population data to define slowness as the slowest 20% of the population [1]. Unlike the adult population, the 15 ft. walk test does not have

Table 1 Inclusion and exclusion criteria for the CCD group

Inclusion criteria
Males and females aged 8–17.5 years old
One or more of the three following cardiac diagnoses
(1) Fontan physiology with Fontan palliative surgery completion at least 6 months prior to study enrollment
(2) Heart failure (Ross/New York Heart Association classifications I–III)
(3) Pulmonary arterial hypertension, confirmed by cardiac catheterization and requiring use of at least one pulmonary vasodilator medication or supplementary oxygen
Exclusion criteria
Heart transplantation within the past 1 year
Known severe neurological or respiratory diseases, eating disorders or physical limitations which may impact their ability to perform study procedures
Tracheostomy and ventilator dependency
Unstable angina or myocardial infarction in the last 4 weeks
Inability to perform six continuous minutes of walking, handgrip dynamometry, or complete questionnaire measures as described in the "Methods" section
NYHA class IV
Primary cardiologist deems that the study is not appropriate for the subject

Table 2 Frailty domains and measures

Frailty domain	Measures used for adults[a]	Measures used for pediatrics
(1) Slowness	15 ft. walk test	6-min walk test
(2) Weakness	Handgrip strength	Handgrip strength
(3) Exhaustion	CES depression scale	PedsQL Multidimensional Fatigue scale
(4) Shrinkage/body composition	Weight loss (over time)	Triceps skinfold thickness, height, weight, BMI, MUAC
(5) Diminished physical activity	Energy expenditure estimated with physical activity recall questionnaire	Accelerometer, PAQ-C and PAQ-A, MAQ

CES Centers for Epidemiological Studies, *PedsQL* pediatric quality of life inventory, *BMI* body mass index, *MUAC* mid-upper arm circumference, *PAQ* physical activity questionnaire for children (C) or adolescents (A), *MAQ* modifiable activity questionnaire

[a]Fried et al. [1]

published normative values in children and adolescents. Hence, it would be difficult to compare the results of this test between an 8 year old and a 15 year old who have markedly different stride lengths. Similar to other studies measuring frailty in youth [6], we elected to use the 6-min walk test as our measure of slowness, as it has published age and sex-based reference values for the pediatric population [14]. We provided participants with a measuring wheel with handle adjusted for their height. We asked them to walk back and forth along a 30-m path in a low traffic hallway for six continuous minutes. They were permitted to self-regulate their walking speed without jogging or running and were allowed to stop at any time to rest or lean against a wall, but not allowed to sit unless they requested that the test be terminated. We used standard 6MWT reference values for children and adolescents [14] to generate *Z* scores.

We measured weakness using a handheld dynamometer to quantify grip strength. After sizing the dynamometer to the size of the participant's hand, we asked participants to stand with the dynamometer in their dominant hand with their arm bent at 90° and squeeze it as hard as they could for 3 s. We recorded the highest of three consecutive readings. We used age and sex-adjusted normative values [15] to generate percentiles.

We assessed exhaustion using the PedsQL™ Multidimensional Fatigue scale which is an 18-item questionnaire designed to measure child and parent perception of fatigue. The multidimensional fatigue scale is comprised of three subscales of six items each: (1) general fatigue; (2) sleep/rest fatigue; and (3) cognitive fatigue. This scale has been validated in children and adolescents with diverse medical conditions [16–21].

We assessed body composition by measuring height, weight, body mass index (BMI), mid-upper arm circumference, and triceps skinfold thickness. These measurements were converted to percentiles based on reference values by age and sex [22–24].

We assessed physical activity with self-reported physical activity questionnaires—the pediatric activity questionnaire (PAQ-C or A, for children or adolescents, respectively) and the modifiable activity questionnaire (MAQ-A, for children and adolescents). In addition, we objectively quantified physical activity using a waist worn accelerometer. The self-administered PAQ-C and PAQ-A provides a 7-day physical activity recall [25, 26]. We scored each questionnaire item and calculated a composite score ranging from 1 to 5 with higher scores indicating higher levels of activity [27]. The MAQ-A is an interviewer-administered questionnaire that asks participants to report household and recreational forms of physical activity over the past year. We used this information to calculate the average number of hours per week (hr/wk) of physical activity over the past year [28, 29]. We objectively measured physical activity with an ActiGraph wGT3X-BT accelerometer (ActiGraph LLC, Pensacola, FL) worn on an elastic belt over the non-dominant hip for seven consecutive days. Three days with ≥ 10 h/day of wear time was required for inclusion. The device was programmed to store data at 1-min epochs. Mean accelerations per minute were analyzed using the ActiLife 6 Single software and classified using the Evenson cut-points for moderate-to-vigorous intensity physical activity, MVPA [30]. MVPA in min/day were compared to estimates of physical activity from the PAQ-C or A and the MAQ-A to determine which subjective measure of physical activity was most accurate.

Demographics and Medical Record Review

We obtained demographic data from all participants to include age, gender, residence, race, household income, school performance, missed school days and medical history including ER visits and hospitalizations in the past year. The detailed list of variables is listed in Table 3.

Statistical Analysis

We report descriptive statistics as means ± standard deviation for continuous variables and frequency with percentage for categorical variables. We assessed differences between cases and control groups using independent *t*-tests and ANOVA for continuous variables; and χ^2 or Fisher's exact test for categorical variables, as appropriate based on cell size. Pearson correlation was calculated among five domains of frailty measures. Cronbach's α was calculated

Table 3 Demographic and medical history variables

Demographic variables (CCD and control groups)	Additional medical history (CCD group only)
Subject variables	Subject variables
Race and ethnicity	Cardiac diagnosis
Grades in school (above/below/average)	Heart failure classification
Failed/repeated grades	
Individual education plan or 504 plan	
Presence of primary care physician	
Other specialty care physicians and health care specialists	
Number of medications	
Past 12 months	
School days missed due to illness	
Emergency room visits	
Hospitalizations	
Intensive care unit admissions	
Days in intensive care unit	
Parent/family variables	
Residence (rural/urban/suburban)	
Primary caregiver of child	
Marital status of caregiver	
Individuals who live in the household	
Education of caregiver	
Employment of caregiver	
Annual household income	
Home status (rent/own)	
Insurance status	

to measure reliability of measures within a domain. Post-hoc comparison was done between the NYHA classes of CCD and controls and adjusted by Tukey test.

General linear modeling was used to compare sedentary, light, moderate, vigorous, and MVPA between youth with and without CCD. Pearson correlation was used to find relationships between MVPA (min/day) to PAQ score and MAQ h/day. Results are presented as median min/day ± standard error.

All statistical tests were two-sided and conducted at the $\alpha = 0.05$ level. Statistical analysis was done using The SAS software v 9.4 (Copyright, SAS Institute, Inc. SAS and all other SAS Institute, Inc. product or service names are registered trademarks or trademarks of SAS Institute, Inc., Cary, NC, USA) and R (R Core Team (2015). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

Results

We recruited 56 participants—34 CCD and 22 controls. The demographic and clinical characteristics of the participants are presented in Table 4. Of the 34 CCD participants, there were 24 that were status post Fontan palliation, 9 with heart failure (including 3 patients with failing Fontan physiology, which was defined as having plastic bronchitis or protein-losing enteropathy) and 4 with pulmonary hypertension. Sixteen of the CCD group were NYHA class I, 15 were NYHA class II and 3 were NYHA class III, while all the controls were in NYHA class I. The CCD group were mostly from lower or middle-income

Table 4 Comparison of demographic and descriptive data between CCD and controls

	CCD ($n=34$) *n* (%)	Controls ($n=22$) *n* (%)	*p*-value
Age (years)	12.3 ± 2.8	11.9 ± 2.3	0.58
Sex			
Males	21 (62)	13 (59)	0.84
Females	13 (38)	9 (41)	
Race			
White	27 (80)	21 (96)	0.09
Non-white	7 (20)	1 (4)	
Household annual income			
< $60,000	12 (35)	4 (18)	< 0.01*
$60,000–$150,000	18 (53)	7 (32)	
> $150,000	1 (3)	11 (50.0)	
No answer	3 (9)	0 (0.0)	
NYHA class			
I	16 (47)		
II	15 (44)		
III	3 (9)		
Parent-reported academic performance			
Above average	6 (18)	14 (64)	< 0.01*
Average	22 (65)	8 (36)	
Below average	6 (18)	0 (0)	
IEP or Plan 504			
No	12 (35)	21 (96)	< 0.01*
Yes	14 (41)	1 (4)	
Unknown	8 (24)	0 (0)	
School days missed in the past year due to illness			
0–5	20 (59)	21 (95.5)	0.025*
6–10	8 (23)	1 (4.5)	
11–15	1 (3)	0 (0.0)	
> 15	5 (15)	0 (0.0)	

Significant differences are denoted with *

NYHA New York Heart Association, *IEP* school-based individualized education plan

families, while the controls were mostly from middle or higher income families. The CCD group were more likely to have school absenteeism from illnesses, with average or below average school performance reported by the parent, and more frequently needing IEP or Plan 504 at school.

Slowness

The 6MWT *Z* scores were significantly lower for the CCD group as compared with controls (*Z* score − 3.9 ± 1.3 vs − 1.4 ± 1.3, $p < 0.001$, Table 5). Interestingly, the mean *Z* score for controls was also lower than expected at − 1.4 ± 1.3. In the CCD group, 23 of the 34 (68%) participants had 6MWT *Z* scores below − 3; 10 (29% of the CCD) had 6MWT *Z* score below − 5. In comparison, 5 (23%) of the controls had *Z* score below − 2.

Weakness

The CCD group had significantly lower handgrip strength as compared to controls (Table 5). 21 (62%) of the CCD group had handgrip strength below the 25th percentile. In comparison, nearly 64% of the controls had handgrip strength above the 50th percentile.

Exhaustion

The maximum score on the PedsQL Multidimensional Fatigue scale is 100, with higher scores indicating less perceived fatigue. The CCD group had significantly lower scores on both the child (58.1 ± 22.4 vs 83.3 ± 14.4 for controls) and parent proxy (63.1 ± 19.5 vs 93.1 ± 5.4 for controls) versions of this scale. Table 5 shows the comparison between the child multidimensional fatigue scale between CCD and controls. Within the CCD group, 62% scored less than 70 on the child form, while only 3 of the controls (14%) scored less than 70.

Body Composition

The CCD group had statistically significant differences in height, weight, BMI and triceps skinfold thickness as compared with the controls with lower values in CCD. The mean values for height percentile were 43.4 ± 29.5 for CCD as compared to 71.4 ± 25.2 for controls, $p < 0.01$; weight percentile 46.0 ± 36.0 for CCD and 70.9 ± 24.3 for controls, $p < 0.01$, BMI percentile 48.4 ± 35.5 for CCD and 66.9 ± 24.2 for controls, $p = 0.04$ and triceps skinfold thickness percentile 41.0 ± 24.0 for CCD and 54.4 ± 22.1 for controls, $p = 0.04$. There was no significant difference in mid-upper arm circumference between the two groups with mean percentile values of 40.1 ± 25.8 for CCD and 49.8 ± 27.7 for controls, $p = 0.19$. Triceps skinfold thickness was accepted as the most appropriate measure for the body composition domain due of the ease of collection and the fact that unlike other anthropometric measurements, it is less affected by other factors such as genetic/chromosomal anomalies (Table 5).

Physical Activity

The CCD group were significantly less physically active than the controls, with lower scores for the PAQ (2.0 ± 0.6 for CCD and 2.7 ± 0.6 for controls, $p < 0.01$ with lower score representing less physical activity) and lower past year hr/wk of activity from the MAQ (7.6 ± 6.3 hr/wk for CCD and 11.3 ± 6.1 hr/wk for controls, $p = 0.03$). The data from the accelerometer supported the PAQ and MAQ outcomes by demonstrating that the CCD group had less min/day of moderate intensity physical activity (CCD: 18.8 ± 3.4 min/day; Control: 36.1 ± 4.1 min/day, $p < 0.01$), less vigorous intensity physical activity (CCD: 4.4 ± 1.2 min/day; Control: 9.9 ± 1.5 min/day; $p < 0.01$) and MVPA (CCD: 22.2 ± 3.4 min/day; Control: 46 ± 5.2 min/day, $p < 0.01$). Interestingly, there were no between group differences for sedentary time (CCD: 701.8 ± 15.1 min/day; Control: 702 ± 18.4; $p = 0.07$) or light intensity physical activity (CCD: 357.9 ± 12.6 min/day; Control: 335 ± 15.5;

Table 5 Comparison of frailty domains and measures between CCD and controls

Frailty domain	Accepted measure	CCD ($n = 34$)	Controls ($n = 22$)	*p*-value
(1) Slowness	6MWT (*Z* score)	− 3.9 ± 1.3	− 1.4 ± 1.3	< 0.01*
(2) Weakness	Dominant handgrip strength (percentile)	18.9 ± 20.9	57.9 ± 26.0	< 0.01*
(3) Exhaustion	PedsQL-Child Multidimensional Fatigue scale (score)	58.1 ± 22.4	83.3 ± 14.4	< 0.01*
(4) Shrinkage/body composition	Triceps skinfold thickness (percentile)	41.0 ± 24.0	54.4 ± 22.1	0.04*
(5) Diminished physical activity	PAQ-C/A (score)	2.0 ± 0.6	2.7 ± 0.6	< 0.01*

Significant differences are denoted with *

6MWT 6-min walk test, *PedsQL* pediatric quality of life inventory, *PAQ* physical activity questionnaire for Children (C) or Adolescents (A)

$p = 0.867$). Using the objectively measured MVPA as a reference we found the PAQ was a better subjective measure of habitual physical activity than the MAQ (PAQ: $R^2 = 0.48$, $p = 0.006$; MAQ: $R^2 = 0.015$, $p = 0.933$, Table 5). One participant from the CCD group was excluded from the accelerometer data analysis due to inadequate wear time.

NYHA Class and Frailty Domains

Due to the uneven sample sizes within the CCD group for each NYHA class, those classified as NYHA class II or III were combined into a single group. Of the 34 participants in the CCD group, 16 (47%) were in NYHA class I, while 18 participants (53%) were in NYHA class II or III. Figure 1a–e compares each frailty domain between the CCD group dichotomized by NYHA class and controls. Both CCD groups (NYHA class I and NYHA class II/III) scored

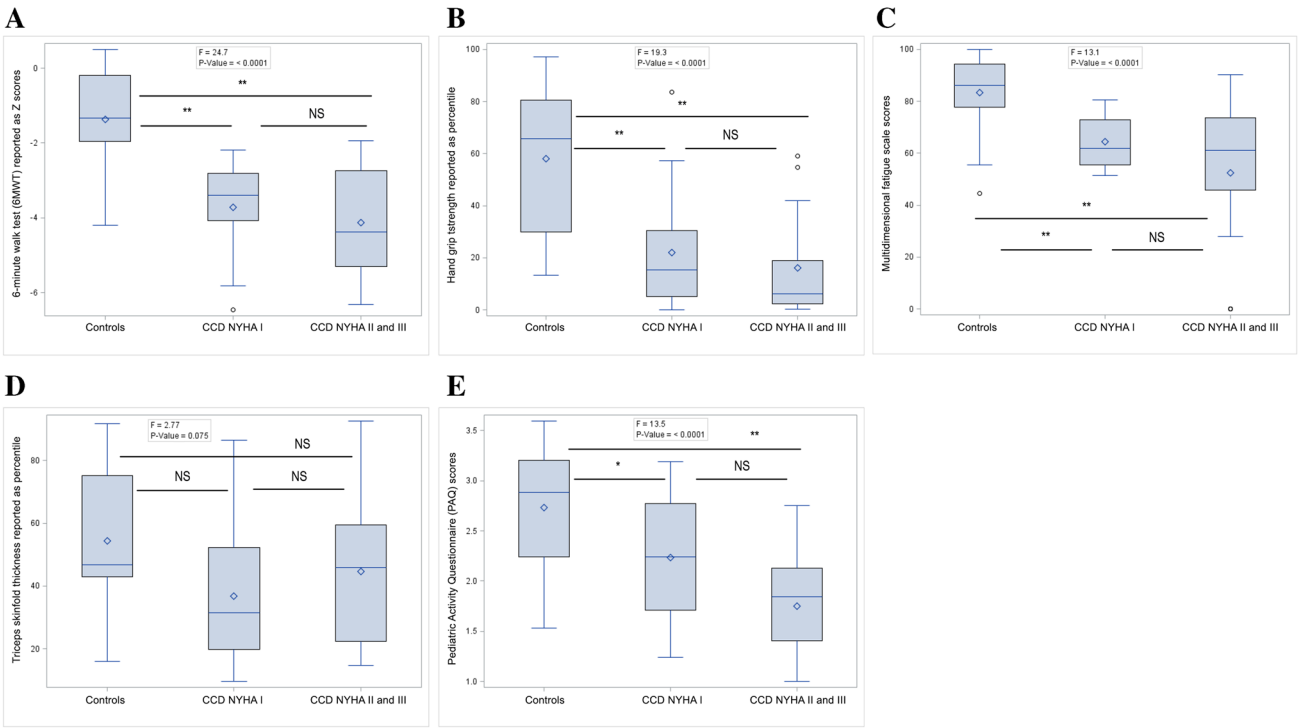

Fig. 1 Frailty domains by group with CCD group categorized by NYHA class. (A): Slowness - 6 minute walk test (6MWT) z-score; (B): Weakness - Hand grip strength percentile; (C): Exhaustion - Multidimensional Fatigue scale score; (D): Shrinkage/Body composition - Triceps skinfold thickness percentile; (E): Diminished physical activity - Pediatric activity questionnaire (PAQ) score. NYHA – New York Heart Association heart failure classification. NS = Not significant, * = $p < 0.05$, ** = $p < 0.01$

Table 6 Correlations between frailty domains

	6MWT	Handgrip strength	PedsQL Multidimensional Fatigue scale	Triceps skinfold thickness
6MWT				
Handgrip strength	$r = 0.7$, $p < 0.01$*			
PedsQL Multidimensional Fatigue scale	$r = 0.46$, $p = 0.01$*	$r = 0.39$, $p < 0.01$*		
Triceps skinfold thickness	$r = 0.27$, $p = 0.04$*	$r = 0.39$, $p < 0.01$*	$r = 0.07$, $p = 0.61$	
PAQ-C/A	$r = 0.49$, $p < 0.01$*	$r = 0.45$, $p < 0.01$*	$r = 0.32$, $p = 0.02$*	$r = -0.05$, $p = 0.74$

Significant differences are denoted with *

6MWT 6-min walk test, *PAQ* physical activity questionnaire for Children (C) or Adolescents (A)

significantly lower than controls for: 6MWT, handgrip strength, PedsQL Multidimensional Fatigue scale, and PAQ, but not triceps skinfold thickness. Within the CCD group, there were no significant differences between NYHA class groups for any frailty domain.

Correlation Between the Frailty Measures Within and Between Domains

The Cronbach's α value between various anthropometric measures was 0.9, suggesting strong correlation. The Cronbach's α value for child filled and parent proxy versions of the PedsQL Multidimensional Fatigue scale was 0.80, while that for the PAQ and MAQ was 0.7. Table 6 lists the correlation (Pearson's correlation coefficient) between the different domains of frailty. There were positive correlations between most of the frailty domains with Pearson correlation coefficients ranging from 0.27 to 0.7. Body composition measured with triceps skinfold thickness did not significantly correlate with exhaustion measured with PedsQL Multidimensional Fatigue scale or physical activity measured with PAQ-C/A, but it did correlate with handgrip strength and 6MWT. The significant correlations indicate that the domains complement each other, but are not identical, avoiding too much overlap and redundancy.

Discussion

To our knowledge, this is the first study that attempts to examine the phenotype of frailty in CCD. We found that it is feasible to assess and measure the domains of frailty in children, by adapting the original measures described in geriatric population to those that are developmentally appropriate for the pediatric population. Furthermore, we found that the CCD participants performed significantly worse than age and gender matched healthy controls in all five domains of frailty.

We chose three specific forms of CCD—Fontan physiology, heart failure, and pulmonary hypertension because these conditions are associated with significant morbidity, mortality and a lifelong burden on health and economics [31–33]. With improvements in medical management, the survival of CCD has improved considerably [34, 35] and the focus is now shifting towards optimizing their quality of life [7–9, 11, 12]. At present, there is no clear consensus on parameters that can help to identify patients at highest risk of adverse health outcomes such as hospitalization or mortality. The current standard of medical care consists of periodic ambulatory clinic visits with testing including echocardiography, exercise testing, and monitoring for arrhythmia. While these tests provide useful information about cardiac function, they neither correlate with overall debility; nor do they adequately predict risk of future adverse events [36–39]. Knowing that debilitating morbidities are not limited to only specific cardiac conditions, the intention of this study was to develop a broad based, generalizable clinical measure of infirmity for children and adolescents with cardiac disease. CCD have similar potential to score poorly within each domain of frailty regardless of diagnoses, therefore we chose a heterogeneous sample of different cardiac diagnoses with known higher physical and psychosocial burden of disease.

The frailty score as originally described by Fried et al. [1] was a population-based score in the elderly that were not hospitalized or end stage, and helped identify individuals at the highest risk of mortality. A high frailty score was associated in this study with increased risk of mortality and adverse outcomes. Since the original publication, the frailty score has been extensively studied in adults and has been found to be associated with adverse outcomes in a heterogeneous array of medical conditions such as liver [40] and renal disease [41], post-operative patients [4, 42, 43] and in heart failure [44]. If such a score could be designed and validated in the CCD population, it could be immensely helpful in identifying the patients that are most at risk for deterioration, so that more aggressive medical and supportive therapy could be targeted towards them. The concept could be extended to other chronic disease states in children as well. The frailty score has the advantage of being internationally recognized [45] and widely tested by clinicians in adult literature. We thus sought to adapt the domains of frailty to the pediatric population by using age appropriate techniques that have been well studied over the years and have normal age and gender specific reference values available [14, 15, 22–24].

Lurz et al. recently published their experience in assessing frailty in children with liver disease [6]. In this multicenter study, they recruited 36 children with compensated liver disease and 35 with end-stage liver disease. They found worse frailty scores in those children with end-stage liver disease when compared to controls with compensated chronic liver disease; a frailty score of >5 had the best sensitivity and specificity in identifying children with end-stage liver disease. Similar to our study, the investigators used standard, developmentally appropriate and validated tools to assess the frailty domains, such as grip strength by hand dynamometer, 6MWT, triceps skinfold thickness, PedsQL 4.0 Multidimensional Fatigue scale and the modified PAQ. In our study, we used multiple measures for some of the domains as we have previously described; this is because it is yet unclear which measures could be of most value in generating a future pediatric frailty score. For example, considering subjective reports of physical activity may be skewed

by perception and memory recall, we compared two different validated physical activity questionnaires to physical activity measured objectively via accelerometer. Similar to the study by Voss et al. [46], we found the PAQ for children or adolescents was an accurate subjective measure of physical activity in this population.

Lurz et al. assigned frailty scores for each component based on arbitrary *Z* score cutoffs, with the maximum possible score being 10 (most frail). We chose not to create a score because the current study design did not include longitudinal follow-up for outcome data. At this initial stage, we compared our study participants to normal controls to establish feasibility and clinical relevance.

We found several similarities between our CCD group and the elderly frail population. Both reported higher levels of exhaustion and lower levels of physical activity. One of the key drivers of the frail state in the elderly is chronic undernutrition and loss of lean body mass leading to negative nitrogen balance. Our CCD cohort had lower anthropometric measures and triceps fold thickness compared to controls, though mid arm circumference was similar. A recent study done in patients with Fontan physiology showed that lower height percentiles were associated with worse functional outcomes [47]. However, since congenital heart disease could be associated with genetic short stature, assessment of height may be a confounding variable. Measurement of triceps skinfold thickness should be considered in assessing CCD as it is less affected by other factors such as genetic or chromosomal anomalies. It seems unlikely that children with cardiac disease would lose weight unless severely ill and incapacitated. Therefore, overall somatic growth, or a serial decrease in percentile measurements may be more relevant than weight loss in this population.

In our study, we noted a significant difference in physical performance even between controls and CCD that were functioning at NYHA class I. Given the chronic nature of underlying heart disease and slow progression, it is conceivable that CCD have adapted to it and are unaware of the true extent of their diminished reserves. A study in adults with congenital heart disease (mean age 33 ± 13 years) demonstrated markedly impaired peak oxygen consumption even in participants in NYHA class I as compared to healthy controls [48]. The authors concluded that NYHA class underestimated the true degree of exercise limitation. Lurz et al. noted that the frailty scores in children with chronic liver disease did not correlate with physicians' subjective assessments or commonly used objective scores to assess extent of liver disease [6]. Hence, NYHA classification and physicians' subjective assessments may have limitations that the frailty score, as an objectively measured score may be able to overcome. We did not find a difference within the CCD group for the different NYHA classes; this is likely because the study was underpowered to detect differences within subgroups.

Finally, recent studies have examined the reversibility of frailty as a detrimental physiologic state. Pin Ng et al. looked at the effect of nutritional, physical rehabilitation and cognitive training in frail adults and found that these interventions could improve the frailty score over 12 months; however, there was no difference in secondary outcomes such as hospitalizations or mortality, likely due to the study being underpowered to assess those outcomes [49]. Monteserin et al. in a larger study of 620 participants, found that a higher percentage of participants reversed their frailty risk after receiving interventions aimed at health promotion as compared to controls receiving usual care [50]. Studies in pediatric Fontan patients have shown improvement in cardiac output and quality of life following endurance training, suggesting potential benefits of interventions even in children [51, 52]. It is conceivable that identification of the frailty phenotype in children could be beneficial in identifying those individuals at risk and designing specific interventions to potentially reverse their risk for adverse health outcomes. The frailty measures do take time to administer, especially in a busy clinic practice.

While this study adds important knowledge to the literature, it does have some limitations. It is a single-site study with a small sample drawn from a limited geographic area. The controls were selected mostly from children of employees, potentially leading to selection bias. Because of the small sample size and lack of longitudinal follow-up, this study is a first step towards the creation of a frailty score in CCD. The performance of our healthy controls on the 6MWT was below the published population norms. This could potentially be from the methodology used, wherein we had participants walk back and forth across a small hallway and they may have lost time in turning around thereby affecting the total distance covered. Although we cannot be entirely sure, it is also possible that the control participants performed at a level lower than expected for the 6MWT due to lack of motivation to complete the test to the best of their ability despite encouragement. While none of the Fontan participants had activity restrictions imposed by their cardiologist, it is not possible to exclude self-restriction by the patient or family due to anxiety surrounding their cardiac diagnosis, which could have affected the scores on the activity questionnaires and accelerometer.

In summary, the domains of frailty, as described in the elderly, can be assessed in the pediatric population using developmentally appropriate methods. CCD perform worse across all the domains of frailty as compared to than age and gender matched healthy controls, suggesting the relevance of frailty as a phenotype in this population. Additional research is warranted to delineate thresholds to define the phenotype

of frailty by correlating frailty measures with longitudinal health outcomes.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee (Children's Mercy Hospital Institutional Review Board-16060468) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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