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ORIGINAL ARTICLE

Prevalence and outcomes of fragility: a frailty-inflammation phenotype in children with chronic kidney disease

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Abstract

Background Frailty is a condition of decreased physiologic reserve and increased vulnerability to stressors. Frailty in combination with inflammation has been associated with increased mortality risk in adults with advanced chronic kidney disease (CKD). This study aimed to investigate prevalence and outcomes associated with a frailty-inflammation phenotype, or "fragility," in children with CKD.

Methods We analyzed 557 children (age 6–19 years, eGFR 30–90 ml/min/1.73 m^2) from the Chronic Kidney Disease in Children (CKiD) study. Based on adult models, the CKiD fragility model included four indicators: (1) suboptimal growth/weight gain (BMI < 5th percentile-for-height-age, deceleration ≥ 10 BMI-for-height-age percentiles/1 year, height-for-age percentile < 3rd or deceleration ≥ 10 height percentiles/1 year); (2) low muscle mass (mid-upper-arm circumference < 5th percentile or deceleration ≥ 10 percentiles/1 year); (3) fatigue (parent/child report); (4) inflammation (CRP > 3 mg/l). Logistic regression was used to evaluate association of fragility indicators with three adverse outcomes: frequent infection (> 1 per year/3 years), hospitalization (any), and rapid CKD progression (decline in eGFR > 30% or initiation of renal replacement therapy within 3 years).

Results Prevalence of fragility indicators 1 year after study entry were 39% (suboptimal growth/weight gain), 62% (low muscle mass), 29% (fatigue), and 18% (inflammation). Prevalence of adverse outcomes during the subsequent 3 years were 13% (frequent infection), 22% (hospitalization), and 17% (rapid CKD progression). Children with ≥ 3 fragility indicators had 3.16-fold odds of frequent infection and 2.81-fold odds of hospitalization, but did not have rapid CKD progression.

Conclusions A fragility phenotype, characterized by the presence of ≥ 3 indicators, is associated with adverse outcomes, including infection and hospitalization in children with CKD.

Keywords Frailty · Chronic kidney disease · Inflammation · Nutrition · Infection · Kidney disease progression · Children

Introduction

Frailty is a condition of decreased physiologic reserve and increased vulnerability to stressors, which was first described in the geriatric population [1]. The concept of frailty has since expanded, serving as an indicator of increased morbidity and mortality risk in numerous adult disease states, including HIV [2], cardiovascular disease [3], liver disease [4], cancer [5], and chronic kidney disease [6, 7]. Recently, frailty in combination with inflammation has been identified as a marker for increased mortality risk in adults with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) [8]. This study suggested that inflammation is a key component of frailty unique to the CKD population, a disease state in which elevated inflammatory markers are a hallmark of increased morbidity and mortality [8]. In the geriatric population, the relationship of frailty with morbidity and mortality risk may

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be confounded as the symptoms of aging are intermingled with those related to renal disease. The pediatric population may therefore provide a cleaner model for the study of the effects of a frailty-inflammation phenotype on health outcomes in individuals with chronic disease. While frailty has not been well studied in younger populations, evidence of the existence of frailty during childhood and its effects on survival was discovered by a bioarcheological study of skeletal remains of children affected by famine in medieval times in London [9]. Just recently, a model was developed to assess frailty in a cohort of children with chronic liver disease [10]. The concept of frailty has not been investigated in children with CKD. The objective of this study was to investigate the prevalence of and outcomes associated with a frailty-inflammation phenotype, or "fragility," in children with CKD.

Methods

Study design and population

The detailed methods of the Chronic Kidney Disease in Children (CKiD) study, an ongoing prospective multicenter cohort study of North American children with CKD, have been previously described [11]. The CKiD study (NCT00327860) was approved by an external study monitoring board appointed by the National Institute of Diabetes and Digestive and Kidney Diseases and by the institutional review board of each participating center, including Children's National Health System. Informed consent of all individual participants included in the study was obtained by each center and the study was conducted in accordance with the Declaration of Helsinki.

The present study includes a cohort of 557 children who were between the ages 6 and 19 years and had eGFR 30–90 ml/min|1.73 m^2. Fragility data elements (anthropometrics, fatigue, and CRP) were measured over the first year of the CKiD study. Outcome indicators (infections, hospitalizations, and changes in eGFR) were assessed over the subsequent 3-year period. All study data were collected during outpatient CKiD study visits and not during acute illness or hospitalizations. The exclusion criteria of this analysis were the same as those of the CKiD study. Children with eGFR < 30 ml/min|1.73 m^2 at study year 1 were excluded from the analysis.

Construction of the fragility model

We created a pediatric fragility model which was adapted from the Fried Adult Frailty model [1] and the adult CKD Frailty model of McAdams-DeMarco et al. [8]. The Adult Fried Frailty model consists of the following four components: (1) weight loss/shrinking, (2) muscle weakness/sarcopenia, (3) fatigue/exhaustion, and (4) low activity. The adult CKD model of McAdams-Demarco further improved risk prediction by the inclusion of markers of inflammation to detect frailty in adults with CKD [12], and evidence indicates that the inflammatory pathway plays a key role in the pathogenesis of frailty [13, 14]. Therefore, our proposed pediatric fragility model was based on a combination of these validated adult models, and adapted for the pediatric CKiD population. This pediatric CKD fragility model consists of four indicators determined at 1 year after study entry: (1) suboptimal growth and weight gain (BMI < 5th percentile for height-age, deceleration of ≥ 10 BMI for height-age percentiles over 1 year, or poor growth defined by height < 3rd percentile for age or decrease of ≥ 10 height percentiles over 1 year); (2) low muscle mass (mid-upper-arm circumference for height-age-sex < 5th percentile or a decrease of ≥ 10 percentiles over 1 year); (3) fatigue or low energy (moderate/severe parent or child report on the Pediatric Quality of Life Questionnaire [PedsQL Version 4.0] [15] or moderate/severe response to "tiring easily" on the CKiD symptoms questionnaire); and (4) inflammation (CRP > 3 mg/l). Inflammation was assessed by a single CRP measurement per patient, performed at the year 1 CKiD study visit.

Definition of adverse outcomes

While adult frailty studies have commonly used mortality as an adverse outcome, mortality is very uncommon in children; there were no patient deaths in our cohort during the defined 3-year outcome period. As mortality is therefore not an appropriate outcome for this population, we instead selected evidence-based outcomes that are indicative of fragility (decreased physiologic reserve and increased vulnerability to stressors) in this unique population. Adverse outcomes were defined by frequent infection (> 1 infection per year), any hospitalization, and rapid CKD progression (decline in eGFR > 30% or initiation of renal replacement therapy) during the 3-year period after determination of fragility indicators. The calculation of frequent infections included kidney, bladder, ear, and "other" infections. The category of "other infections" included any reported viral, bacterial, or fungal infection. The calculation of hospitalization rate excluded hospitalization for the purpose of initiation of dialysis.

Statistical analysis

Continuous variables were compared by Wilcoxon rank-sum test, and categorical variables were compared using a chi-squared test. Multiple logistic regression analysis was used to evaluate association of fragility indicators with each of the three adverse outcomes (infection, hospitalization, and CKD progression over 3 years), adjusting for age, sex, race, glomerular diagnosis, and eGFR at study entry. The adjusted analysis

evaluated the association of having either 1–2 fragility indicators or 3–4 fragility indicators with each of the adverse outcomes, in comparison with the reference group (no fragility indicators).

Data on inflammation were missing for 42 (8%) subjects, and data on muscle mass were missing for 3 (1%) subjects. When counting fragility indicators to create our primary predictor, these missing values were implicitly imputed as absent, representing the most conservative approach possible. As a sensitivity analysis, we tested the other extreme, imputing all missing fragility indicators as present. This shifted 10 subjects from zero indicators to 1–2, and 12 subjects from 1–2 indicators to 3–4. The resulting models had larger-magnitude odds ratios for both risk groups (1–2 indicators and 3–4 indicators) but did not change in statistical significance. The results presented are those of the most conservative approach.

Results

Study population

Demographics and clinical characteristics of the study population at the time of study entry are summarized in Table 1. Study participants were a median of 12.1 years of age with eGFR of 55 ml/min|1.73 m^2. The population was 59% male, 21% African American, and 31% had a glomerular diagnosis. As expected, patients with any fragility indicators were significantly thinner, evidenced by lower BMI *z*-scores ($p < 0.0001$ in each fragility group), and shorter, evidenced by lower height *z*-score ($p = 0.07$ for 1–2 indicators, $p = 0.03$ for 3–4 indicators) compared with those who were deemed non-fragile.

Prevalence of fragility indicators and outcomes

The prevalence of fragility indicators and outcomes are summarized in Table 2. The overall prevalence rates of the four individual fragility indicators within the study population at study year 1 were as follows: (1) 39% had suboptimal growth and weight gain, (2) 62% had low/decelerating muscle mass, (3) 29% had fatigue or low energy, and (4) 18% had inflammation. Further examining these as subgroups, 22% of patients had suboptimal growth, 24% had suboptimal weight gain, 18% had fatigue, and 21% had low energy.

The proportion of patients affected by 0, 1, 2, 3, or 4 fragility indicators was 14%, 40%, 33%, 12%, and 1%, respectively, at study year 1 (Fig. 1). The proportion of children who experienced adverse outcomes over the subsequent 3 years was as follows: 13% with frequent infections, 22% with hospitalizations, and 17% with rapid CKD progression.

Association of fragility with adverse outcomes

Children with ≥ 3 fragility indicators 1 year after study entry had 3.16- and 2.81-fold odds of developing the adverse outcomes of frequent infection ($p = 0.03$) and hospitalization ($p = 0.01$) over the subsequent 3 years, respectively, after adjusting for age, sex, race, glomerular diagnosis, and eGFR (see Table 3). However, these children did not have statistically significant increased odds of rapid CKD progression (odds ratio [OR] 2.01, $p = 0.11$). The presence of 1–2 fragility indicators was not significantly associated with frequent infection (OR 1.45, $p = 0.43$), hospitalization (OR 1.33, $p = 0.41$), or rapid CKD progression (1.31, $p = 0.45$) in the adjusted analysis. With regard to the covariates included in the adjusted analysis, glomerular diagnosis was independently associated with reduced odds of infection (0.17, $p < 0.0001$), and increased odds of rapid CKD progression (OR 3.24, $p < 0.0001$). African American race was also independently associated with increased odds of rapid CKD progression (OR 1.94, $p = 0.01$), while higher eGFR at baseline was associated with decreased odds of rapid CKD progression (OR 0.75, $p = 0.0003$). Hispanic ethnicity was associated with decreased odds of hospitalization (OR 0.45, $p = 0.03$).

Discussion

In older adults, tools such as the Fried Frailty Model and the Clinical Frailty Scale have been developed to identify individuals with decreased physiologic reserve who are at increased risk for poor health outcomes, including disability, hospitalization, and premature death [1, 16]. Elderly adults with CKD are known to be more likely to have the frailty phenotype, with reported prevalence more than 60%, compared with 11% among community-dwelling adults of similar age without CKD [17]. Although the concept of frailty was initially developed for older adults, new applications of frailty to younger adult populations and various chronic disease populations are emerging. The prevalence of frailty in adult (< 65 years) hemodialysis (HD) patients is approximately 35% and has been independently associated with higher risk of hospitalization and mortality, regardless of age [12]. Recently, Lurz et al. tested the Fried Adult Frailty criteria in a cohort of children with chronic or end-stage liver disease [10]. In this study, the overall prevalence of frailty was 24% and was highest (46%) in those with end-stage liver disease [10]. Evidence indicates that frailty occurs as a result of a constellation of dysregulation of multiple physiological functions and biological systems [18]. Given the multi-systemic nature of complications of CKD, the use of a standardized clinical tool to identify markers of frailty in adults with CKD and ESRD may be especially useful and has been recently proposed [8, 19, 20]. The inclusion of an inflammation component in the frailty

Table 1 Demographics and clinical characteristics at study entry

	Age (years)	Male sex	African American race	Hispanic ethnicity	Glomerular diagnosis	eGFR (ml/min|1.73 m^2)	BMI *z*-score	Height *z*-score
Overall ($N = 557$)	12.1 (9.0, 14.9)	59%	21%	14%	31%	55 [44, 67]	0.50 [− 0.21, 1.44]	− 0.44 [− 1.20, 0.35]
No fragility indicators ($N = 77$)	11.7 (7.9, 15.1)	64%	30%	14%	36%	58 [45, 70]	1.45 [0.55, 2.06]	− 0.26 [− 1.00, 0.54]
1–2 fragility indicators ($N = 407$)	12.1 (9.1, 14.9)	60%	19%	14%	30%	56 [44, 67]	0.45 [− 0.27, 1.34]	− 0.43 [− 1.18, 0.27]
p value none vs. 1–2 fragility indicators	0.47	0.52	0.03*	0.91	0.25	0.44	< 0.0001*	0.07
Fragile (3–4 fragility indicators) ($N = 73$)	12.0 (8.4, 14.7)	52%	23%	16%	33%	54 [43, 62]	0.37 [− 0.51, 1.02]	− 0.57 [− 1.84, 0.58]
p value none vs. 3–4 fragility indicators	0.76	0.15	0.36	0.71	0.65	0.11	< 0.0001*	0.03*

*p value indicates significant difference between groups ($p < 0.05$). Continuous variables were compared by Wilcoxon rank-sum, and categorical variables were compared by chi-squared test. Continuous variables are reported as median and interquartile range (IQR) in parentheses. Categorical variables are presented as the proportion (%) of children in each group who had the characteristic

model has proven to be particularly sensitive for adult patients with advanced CKD awaiting kidney transplant [8]. No similar tool has been previously developed to evaluate the adverse health outcomes in children with CKD.

In the present analysis, we adapted the concept of the adult frailty model to construct a pediatric model, and demonstrated the ability of this model to identify a frailty-inflammation phenotype among children with CKD. We used the term "fragility" to more accurately describe this unique pediatric phenotype, as it represents the subset of children with CKD who exhibit greater susceptibility to the physiologic stressors compared with other children without fragility. Fragility indicators were based upon classical signs and symptoms of adult frailty, which manifest in children as suboptimal growth and weight gain, muscle wasting/sarcopenia, and fatigue, as well as the CKD-specific frailty marker of inflammation. The inclusion of increased inflammation as an indicator of fragility is supported by previous work indicating that inflammation plays a critical role in the pathogenesis of frailty [13, 14] and is a key component to improve mortality risk prediction in frail adults with CKD [8]. In addition, sarcopenia, which is accelerated in CKD, is an important component of frailty. Low muscle mass is also associated with increased infection risk [21] and contributes to poor bone health due to the lack of skeletal support, further increasing frailty [13]. Fatigue is a particularly debilitating symptom of chronic disease states and has been shown to be a key driving factor in the diagnosis of frailty in both adults and children with chronic liver disease [10].

The concept of frailty is distinct from protein-energy wasting (PEW). A prior study in children with CKD assessed PEW in children using several different biochemical and anthropometric measures [22]. While this study provided important information about nutritional assessment of children with CKD, the concept of fragility provides a more global assessment of poor health and vulnerability to adverse outcomes in this population. Thus, these different assessment tools can be used in a complementary fashion.

The children in our CKD cohort who had ≥ 3 fragility indicators 1 year after study entry had roughly 3-fold increased odds of developing adverse outcomes of infection (OR 3.16, $p = 0.03$) and hospitalization (OR 2.81, $p = 0.01$) during the subsequent 3-year period, as compared with those who were non-fragile. Therefore, these children may be considered to have a "fragility phenotype" indicative of a subset of the pediatric CKD population who are more likely to experience adverse health outcomes. In contrast, in the aforementioned pediatric study of models to diagnose PEW in children with CKD, the models did not have a statistically significant association with the primary adverse outcome of hospitalization ($p = 0.06$), and association with infection was not analyzed [22]. Similarly, studies in children and adults with chronic liver disease have shown that frailty assessments identify a broader condition of fragile health that is distinct from and

Table 2 Prevalence of fragility indicators and outcomes

Fragility indicators*		Prevalence (%)
Fragility indicator 1	Suboptimal growth and weight gain	39%
Fragility indicator 2	Low muscle mass/deceleration in muscle mass percentile	62%
Fragility indicator 3	Fatigue or low energy	29%
Fragility indicator 4	Inflammation (CRP > 3 mg/l)	18%
Fragility phenotype	3–4 fragility indicators present	13%
Adverse outcomes**		
Outcome 1	Frequent infection	13%
Outcome 2	Hospitalization	22%
Outcome 3	Rapid CKD progression	17%

*Presence of fragility indicators were identified 1 year after study entry. **Adverse outcomes occurred during the subsequent 3-year period, after determination of the fragility indicators

goes beyond what is captured by standard assessments for malnutrition or severity of chronic disease [10, 23]. In particular, the element of "fatigue or low energy" is not captured by typical nutritional or health risk assessments. Therefore, our proposed fragility model provides a new tool to gauge overall comprehensive health in children with CKD.

Our findings mirror those of adult studies linking frailty with a wide spectrum of adverse clinical outcomes in those with CKD [7]. While frailty is strongly associated with mortality in adults, this outcome is uncommon in children, and there were no deaths in our study cohort. We therefore selected evidence-based outcomes that are indicative of fragility, or "decreased physiologic reserve and increased vulnerability to stressors," in this unique population. Hospitalization is one such adverse outcome that has been independently associated with frailty in adult studies [12, 24]. Frequent infection is another indicator of increased vulnerability to stressors, and the frailty phenotype has been associated with impaired immune response, failure to mount adequate response to immunizations, and increased risk for common infections [25]. Rapid progression of kidney disease was shown to be associated with earlier initiation of dialysis in adults with frailty [26]. However, our results indicated that this fragility model does not identify those children at risk for rapid CKD progression as this process appears to be more driven by glomerular disease and African American ethnicity in the pediatric population.

Our results confirm an association between the presence of ≥3 fragility indicators ("fragility phenotype") with subsequent development of adverse outcomes of infection and hospitalization. Our analysis was strengthened by the use of longitudinal data to demonstrate a temporal relationship between the fragility indicators and the adverse outcomes. Our results also suggest a dose-response gradient, evidenced by the increasing magnitude of the association between having 1–2 fragility indicators vs. 3–4 fragility indicators with the adverse outcomes. As a caveat, although the children with and without the fragility phenotype were similar in terms of age, gender,

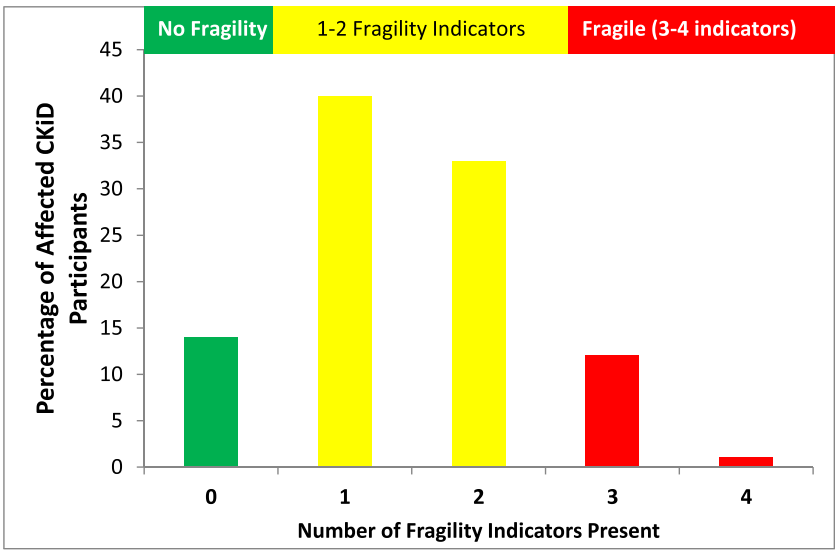

Fig. 1 The percentage of CKiD participants (total $n = 557$) affected by 0, 1, 2, 3, or 4 out of the 4 possible fragility indicators are shown. Patients with ≥3 indicators are considered to have the fragility phenotype

Table 3 Association of fragility indicators with adverse outcomes

Predictor	Frequent infection		Rapid CKD progression		Hospitalization	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (years)	1.01 (0.93, 1.09)	0.82	0.96 (0.90, 1.03)	0.31	0.98 (0.92, 1.04)	0.54
Male sex	0.75 (0.44, 1.28)	0.29	1.58 (0.97, 2.57)	0.07	0.97 (0.64, 1.49)	0.91
African American race	1.21 (0.62, 2.35)	0.57	1.94 (1.14, 3.28)	0.01*	0.90 (0.54, 1.51)	0.70
Hispanic ethnicity	1.29 (0.62, 2.67)	0.50	1.61 (0.88, 2.96)	0.12	0.45 (0.22, 0.92)	0.03*
Glomerular diagnosis	0.17 (0.07, 0.42)	< 0.0001*	3.23 (1.91, 5.47)	< 0.0001*	1.14 (0.70, 1.86)	0.60
eGFR, per 10 ml/min/1.73 m^2	0.95 (0.79, 1.14)	0.60	0.75 (0.64, 0.88)	0.0003*	1.00 (0.87, 1.15)	0.99
1–2 fragility indicators	1.45 (0.58, 3.60)	0.43	1.31 (0.65, 2.64)	0.45	1.33 (0.68, 2.60)	0.41
Fragile 3–4 Fragility indicators	3.16 (1.12, 8.90)	0.03*	2.01 (0.86, 4.72)	0.11	2.81 (1.27, 6.22)	0.01*

*p value < 0.05 indicates significant independent association with the adverse outcome by logistic regression analysis, adjusted for age, sex, race, glomerular diagnosis, and eGFR. Results are reported as odds ratio (OR) with 95% confidence intervals in parentheses

race, disease etiology, and eGFR, there may be other unmeasured variables or events which contributed to the adverse outcomes of frequent infection and hospitalization that we observed in the fragile patients. In addition, while hospitalizations for initiation of dialysis were excluded from the analysis, the specific reasons for other hospitalizations were not collected by the CKiD study, and therefore the causes for these are not known. As noted in the "Methods" section, imputation and sensitivity analyses were employed to address missing data. We are comfortable reporting the results of the most conservative statistical model, recognizing that our sensitivity analysis indicates that the true effects may be slightly stronger than indicated.

Pediatric tools of fragility may be useful in clinical decision-making as these children will need additional interventions to prevent adverse outcomes. Targeted therapies to improve outcomes in fragile children may include optimization of nutrition and/or growth hormone therapy to promote muscle accretion, weight gain and growth, as well as exercise and physical therapy to increase physical fitness and build muscle mass. Recent evidence suggests that the combination of exercise with growth hormone therapy enhances IGF-1 signaling, trabecular bone formation, and growth [27]. Other anabolic hormones and anti-inflammatory agents may also hold promise to attenuate muscle atrophy in children with CKD [28–30], but more research is needed in this area.

The major strength of this study was the use of CKiD study data, which was prospectively and longitudinally collected according to standardized protocols at 54 sites across North America. The analysis was limited by the general exclusion criteria of the CKiD study, which excluded children with genetic syndromes involving the central nervous system and those with severe intellectual disability (IQ < 40, significant impairment in adaptive functioning, and/or inability to independently execute self-care skills). These children represent a growing yet vulnerable subset of the CKiD population likely to be at high risk for the fragility phenotype. Future studies should aim to validate a pediatric clinical tool to identify fragile children at risk for adverse outcomes and strategies to address fragility.

In conclusion, we developed the first pediatric model to identify fragility in children with CKD. This fragility phenotype, characterized by the presence of ≥ 3 indicators, is associated with adverse outcomes, including infection and hospitalization. The model provides a new tool for the evaluation of overall health of children with CKD and the identification of at-risk children who may benefit from additional interventions.

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Data availability Data in this manuscript were collected by the Chronic Kidney Disease in children prospective cohort study (CKiD) with clinical coordinating centers (Principal Investigators) at Children's Mercy Hospital and the University of Missouri–Kansas City (Bradley Warady, MD) and Children's Hospital of Philadelphia (Susan Furth, MD, PhD), Central Biochemistry Laboratory (George Schwartz, MD) at the University of Rochester Medical Center, and data coordinating center (Alvaro Muñoz, PhD and Derek Ng, PhD) at the Johns Hopkins Bloomberg School of Public Health. The CKiD website is located at https://statepi.jhsph.edu/ckid.

Compliance with ethical standards

The CKiD study (NCT00327860) was approved by an external study monitoring board appointed by the National Institute of Diabetes and Digestive and Kidney Diseases and by the institutional review board of each participating center, including Children's National Health System. Informed consent of all individual participants included in the study was obtained by each center and the study was conducted in accordance with the Declaration of Helsinki.

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

References

1. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, Cardiovascular Health Study Collaborative Research Group (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146–M156
2. Kelly SG, Wu K, Tassiopoulos K, Erlandson KM, Koletar SL, Palella FJ, ACTG A5322 Study Team (2018) Frailty is an independent risk factor for mortality, cardiovascular disease, bone disease and diabetes among aging adults with HIV. Clin Infect Dis. https://doi.org/10.1093/cid/ciy1101
3. Stewart R (2019) Cardiovascular disease and frailty: what are the mechanistic links? Clin Chem 65:80–86
4. Haugen CE, McAdams-DeMarco M, Holscher CM, Ying H, Gurakar AO, Garonzik-Wang J, Cameron AM, Segev DL, Lai JC (2019) Multicenter study of age, frailty, and waitlist mortality among liver transplant candidates. Ann Surg. https://doi.org/10.1097/SLA.0000000000003207
5. Geessink N, Schoon Y, van Goor H, Olde Rikkert M, Melis R, TOPICS-MDS consortium (2017) Frailty and quality of life among older people with and without a cancer diagnosis: findings from TOPICS-MDS. PLoS One 12:e0189648
6. Nixon AC, Bampouras TM, Pendleton N, Mitra S, Dhaygude AP (2019) Diagnostic accuracy of frailty screening methods in advanced chronic kidney disease. Nephron 141:147–155
7. Nixon AC, Bampouras TM, Pendleton N, Woywodt A, Mitra S, Dhaygude A (2018) Frailty and chronic kidney disease: current evidence and continuing uncertainties. Clin Kidney J 11:236–245
8. McAdams-DeMarco MA, Ying H, Thomas AG, Warsame F, Shaffer AA, Haugen CE, Garonzik-Wang JM, Desai NM, Varadhan R, Walston J, Norman SP, Segev DL (2018) Frailty, inflammatory markers, and waitlist mortality among patients with end-stage renal disease in a prospective cohort study. Transplantation 102:1740–1746
9. Yaussy SL, DeWitte SN (2018) Patterns of frailty in non-adults from medieval London. Int J Paleopathol 22:1–7
10. Lurz E, Quammie C, Englesbe M, Alonso EM, Lin HC, Hsu EK, Furuya KN, Gupta NA, Venkat VL, Daniel JF, Leonis MA, Miloh T, Telega GW, Yap J, Menendez J, Book LS, Himes RW, Sundaram SS, Parekh R, Sonnenday C, Bucuvalas J, Ng VL, Kamath BM (2018) Frailty in children with liver disease: a prospective multicenter study. J Pediatr 194:109–115 e104
11. Furth SL, Cole SR, Moxey-Mims M, Kaskel F, Mak R, Schwartz G, Wong C, Munoz A, Warady BA (2006) Design and methods of the chronic kidney disease in children (CKiD) prospective cohort study. Clin J Am Soc Nephrol 1:1006–1015
12. McAdams-DeMarco MA, Law A, Salter ML, Boyarsky B, Gimenez L, Jaar BG, Walston JD, Segev DL (2013) Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. J Am Geriatr Soc 61:896–901
13. Chen X, Mao G, Leng SX (2014) Frailty syndrome: an overview. Clin Interv Aging 9:433–441
14. Yao X, Li H, Leng SX (2011) Inflammation and immune system alterations in frailty. Clin Geriatr Med 27:79–87
15. Varni JW, Seid M, Kurtin PS (2001) PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 39:800–812
16. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A (2005) A global clinical measure of fitness and frailty in elderly people. CMAJ 173:489–495
17. Berger JR, Jaikaransingh V, Hedayati SS (2016) End-stage kidney disease in the elderly: approach to dialysis initiation, choosing modality, and predicting outcomes. Adv Chronic Kidney Dis 23:36–43
18. Fried LP, Xue QL, Cappola AR, Ferrucci L, Chaves P, Varadhan R, Guralnik JM, Leng SX, Semba RD, Walston JD, Blaum CS, Bandeen-Roche K (2009) Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J Gerontol A Biol Sci Med Sci 64:1049–1057
19. Kallenberg MH, Kleinveld HA, Dekker FW, van Munster BC, Rabelink TJ, van Buren M, Mooijaart SP (2016) Functional and cognitive impairment, frailty, and adverse health outcomes in older patients reaching ESRD-a systematic review. Clin J Am Soc Nephrol 11:1624–1639
20. Musso CG, Jauregui JR, Macias Nunez JF (2015) Frailty phenotype and chronic kidney disease: a review of the literature. Int Urol Nephrol 47:1801–1807
21. Krell RW, Kaul DR, Martin AR, Englesbe MJ, Sonnenday CJ, Cai S, Malani PN (2013) Association between sarcopenia and the risk of serious infection among adults undergoing liver transplantation. Liver Transpl 19:1396–1402
22. Abraham AG, Mak RH, Mitsnefes M, White C, Moxey-Mims M, Warady B, Furth SL (2014) Protein energy wasting in children with chronic kidney disease. Pediatr Nephrol 29:1231–1238
23. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K (2014) Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant 14:1870–1879
24. Johansen KL, Chertow GM, Jin C, Kutner NG (2007) Significance of frailty among dialysis patients. J Am Soc Nephrol 18:2960–2967
25. Yao X, Hamilton RG, Weng NP, Xue QL, Bream JH, Li H, Tian J, Yeh SH, Resnick B, Xu X, Walston J, Fried LP, Leng SX (2011) Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine 29:5015–5021
26. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL (2012) Frailty, dialysis initiation, and mortality in end-stage renal disease. Arch Intern Med 172:1071–1077
27. Troib A, Guterman M, Rabkin R, Landau D, Segev Y (2016) Endurance exercise and growth hormone improve bone formation in young and growth-retarded chronic kidney disease rats. Nephrol Dial Transplant 31:1270–1279
28. Yu R, Chen JA, Xu J, Cao J, Wang Y, Thomas SS, Hu Z (2017) Suppression of muscle wasting by the plant-derived compound ursolic acid in a model of chronic kidney disease. J Cachexia Sarcopenia Muscle 8:327–341
29. Sun LJ, Sun YN, Chen SJ, Liu S, Jiang GR (2017) Resveratrol attenuates skeletal muscle atrophy induced by chronic kidney disease via MuRF1 signaling pathway. Biochem Biophys Res Commun 487:83–89
30. Niemczyk S, Sikorska H, Wiecek A, Zukowska-Szczechowska E, Zalecka K, Gorczynska J, Kubik M, Czerwienska B, Gosek K, Veldhuis JD, Wagner DA, Gaudreau P, Hakonen T, Kay SW, Jouhikainen T, Schaefer F (2010) A super-agonist of growth hormone-releasing hormone causes rapid improvement of nutritional status in patients with chronic kidney disease. Kidney Int 77:450–458