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ORIGINAL ARTICLE

Protein energy wasting in children with chronic kidney disease

Alison G. Abraham · Robert H. Mak · Mark Mitsnefes · Colin White · Marva Moxey-Mims · Bradley Warady · Susan L. Furth

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Abstract
Background In adults with chronic kidney disease (CKD), protein-energy wasting (PEW) is a risk factor for hospitalization and death. However, PEW in children with CKD is not well characterized or defined.
Methods Using data from the Chronic Kidney Disease in Children study, we assessed three alternate definitions of PEW using biochemical parameters, body and muscle mass measurements, and reported appetite as described in adults: (1) a minimal PEW definition (≥2 of the four criteria); (2) a standard PEW definition (≥3 of the four criteria); (3) a modified PEW definition (≥3 of the four criteria plus a pediatric-focused criterion of short stature or poor growth).
Results Of the 528 children analyzed in this study (median age 12 years, median glomerular filtration rate 45 mL/min/1.73 m^2, 39 % female, 18 % African American), 7–20 % met the spectrum of definitions for PEW. The unadjusted incidence rates for incident hospitalizations were 1.9-, 2.1-, and 2.2-fold higher for those children diagnosed with PEW using the minimal, standard, and modified definitions, respectively (P=0.08, 0.09 and 0.03). Following adjustment, only the modified PEW definition, which added short stature or poor growth as a criterion, showed modest significance (P=0.06).
Conclusions The inclusion of a criterion based on growth may augment the definition of PEW and improve risk discrimination in children with CKD.

Keywords Cachexia inflammation syndrome · Hospitalization · Chronic kidney disease · Malnutrition · Growth · Glomerular filtration rate

A. G. Abraham (✉)
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205, USA
e-mail: aabraham@jhsph.edu

R. H. Mak
Department of Pediatrics, UC San Diego School of Medicine, San Diego, CA, USA

M. Mitsnefes
Department of Pediatrics, Cincinnati Children's Hospital, Cincinnati, OH, USA

C. White
Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

M. Moxey-Mims
Division of Kidney, Urology and Hematology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

B. Warady
Department of Pediatrics, Children's Mercy Hospitals and Clinics, Kansas City, MO, USA

S. L. Furth
Department of Pediatrics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Introduction

In adults with chronic kidney disease (CKD), especially end-stage renal disease (ESRD), protein-energy wasting (PEW) is highly prevalent and has been implicated as a risk factor for death and accelerated atherosclerotic cardiovascular disease. Using classic measures of nutritional status, evidence of wasting is present in 18–75 % of adult maintenance dialysis patients [1]. PEW occurring in adults with CKD is characterized by four primary components: biochemical criteria such as low serum albumin or low cholesterol, reduced body mass, reduced muscle mass, and decreased protein intake [2]. Although several lines of evidence suggest PEW also exists in the pediatric CKD population, the syndrome is less well characterized in children. Low serum albumin is associated

with higher all-cause mortality in children with ESRD [3] as it is with all-cause mortality and cardiovascular disease in adults [4–6]. Low body mass as assessed by the body mass index (BMI) has been associated with higher mortality in children with ESRD [7] and in adult CKD patients [8–10]. In a cross-sectional study of children at various stages of CKD by Foster et al., body composition assessed by dual-energy X-ray absorptiometry (DEXA) demonstrated significant deficits in leg lean mass in children with advanced CKD on dialysis [11].

Although evidence from these studies is suggestive of a syndrome of PEW in childhood CKD similar to that in adults, criteria for diagnosing this syndrome in children have not been evaluated. We therefore sought to assess the clinical components thought to be important for diagnosing PEW and compare the performance of three classifications of PEW in predicting clinical outcomes in a prospective cohort of children with CKD.

Methods

Study participants and design

The Chronic Kidney Disease in Children (CKiD) study has been described previously [12]. Briefly, children with mild to moderate CKD (30–90 mL/min per 1.73 m^2) based on the original Schwartz formula [13–15] were recruited from 43 participating pediatric nephrology centers. Eligible subjects were those aged 1–16 years who had never been dialyzed or undergone organ transplant. Demographic characteristics and clinical measurements were collected at annual visits. Glomerular filtration rate (GFR) was determined from plasma iohexol disappearance curves at baseline, 1 year later, and every other year thereafter, following methods that have been previously described [16]. GFR values unattainable through direct measurement were estimated using the CKiD equation [17, 18]. Baseline for the current analysis was the second annual visit.

Anthropometry and tanner staging

Age- and sex-specific *Z* scores for height and weight were calculated using National Center for Health Statistics 2000 Center for Disease Control growth data [19]. BMI-for-height-age and sex *Z* scores were also calculated, as recommended in the 2008 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) nutrition guidelines [20]; height-age is the age at which the child's height is at the 50th percentile. The mid-upper arm circumference (MUAC) was taken as the mean of three measurements when available and expressed relative to height-age- and sex-stratified norms obtained from the National Health and Nutrition Examination Survey 2007–2008 sample [21]. Skinfold thickness data were not available from the cohort, but very few of the patients had clinically significant edema (*N*=15, 3 %) at the second annual visit. Pubertal status was dichotomized into Stage 1 and >Stage 1, with the stages defined by Tanner [22].

Biomarker assays

At the study visit where the iohexol GFR was measured, an intravenous line or butterfly needle was used to administer 5 ml of iohexol. A second intravenous line was saline locked and used for obtaining blood samples for biomarker measurements. Blood samples were collected at four time points (10, 30, 120, and 300 min) following the infusion of iohexol (GE Healthcare, Amersham Division, Princeton, NJ) with the iohexol concentration determined by high-performance liquid chromatography. Body surface area for GFR standardization was determined using the formula of Haycock et al. [23]. Inflammation was assessed with wide-range C-reactive protein (CRP). Cystatin C was measured using a Siemens BN II nephelometer (Siemens Diagnostics, Tarrytown NY), and serum creatinine (enzymatic) and serum total cholesterol (TC) were analyzed—following an overnight fast—at a central location (CKiD laboratory at the University of Rochester Medical Center) on a Bayer Advia 2400 (Siemens Diagnostics). Assay results were entered by the Central Biochemistry Laboratory into a web-based data management system (Nephron) developed by the Data Coordinating Center of the University of Rochester.

Defining PEW

Using data from the first two annual visits of the study, indicators for PEW were created based upon the International Society of Renal Nutrition and Metabolism diagnostic criteria [1] with modifications and additions to provide greater applicability to children [24]. The criteria for clinical diagnosis of PEW included the following:

(1) Biochemical: TC<100 mg/100 mL; serum albumin <3.8 g/100 mL, which was approximately the 5th percentile of the data; serum transferrin <140 mg/dL [25]; CRP >3 mg/L
(2) Reduced body mass: defined by a BMI for height-age and sex of less than the 5th percentile at entry into CKiD or a decrease in BMI for height-age and sex percentile of ≥10 % between the first and second annual visits from an initial BMI for height-age and sex percentile of <80th
(3) Reduced muscle mass: MUAC for height-age and sex of <5th percentile or a decrease in MUAC for height-age and sex percentile of ≥10 % between the first and second annual visits;

(4) Decreased appetite as a surrogate for dietary protein intake: fair, poor, or very poor appetite reported over the week prior to the study visit.

We also evaluated the improvement in prediction gained with using a pediatric-specific metric:

(5) Poor growth: defined as either short stature (a height for age and sex percentile of <3 % [26]) or poor growth velocity (a decrease in height for age and sex percentile of ≥10 % between the first and second annual visits).

Using combinations of the indicators described above, three definitions of PEW were created: a minimal PEW definition requiring any positive test in ≥2 of categories (1) through (4) to be met; a standard PEW definition requiring any positive test in ≥3 of categories (1) through (4); a modified PEW definition requiring any positive test in ≥3 of categories (1) through (5), such that poor growth was also included as a separate indicator category.

Statistical analysis

To avoid a loss of information on those with incomplete data on some indicators, multiple imputation was used to complete missing laboratory and self-report data of PEW indicators integral to classifying the participants. Missing values were imputed five times based on the distribution of covariates (Tanner stage, BMI percentile, height percentile, serum creatinine, serum transferrin, cystatin C, hemoglobin, bicarbonate, albumin, urine creatinine, urine protein, low-density lipoprotein cholesterol, CRP, appetite score, GFR, MUAC, and low birth weight) using a Markov chain Monte Carlo method [27, 28] and assuming multivariate normality. Non-fasting lipid measurements were also assumed to be missing and imputed. Established methods for combining estimates from each imputed dataset were used to appropriately adjust standard errors [27, 28]. Trends across categories of imputed variables were tested using linear or logistic regression, assuming an ordinal relationship between the independent variable and the categorical dependent variable.

Using longitudinal data on the GFR trajectory of the children following the second annual visit, the annual percentage change in GFR was estimated using a segmented linear mixed effects model with a random intercept and slope. The model estimated the effect on the GFR slope separately for the period from baseline to 2 years and after 2 years to examine both proximate and longer term effects of PEW on CKD progression. In addition to progression of kidney dysfunction, self-reported incident hospitalization events were also examined. Poisson regression was used to assess the association between definitions of PEW (defined at the second annual visit) and the rate of incident hospitalizations within 2 years after the PEW assessment, with each definition assessed in a separate model. Generalized estimating equations were used to account for repeated reports of hospitalization from a single individual [29]. Models were adjusted for age (as continuous), CKD stage (45<=GFR<60, 30<=GFR<45, GFR<30, as indicator variables) glomerular diagnosis, a urine protein to creatinine ratio of >2, anemia (hemoglobin level <5th percentile for age and sex), and low birth weight (birth weight <2,500 g).

Results

There were 528 children who contributed to the analysis. Of these, data were missing on TC laboratory measurements, including non-fasting measurements, from 61 (12 %) children, on albumin measurements from 23 (4 %) children, on serum transferrin from 254 (48 %) children, on CRP from 78 (15 %) children, on BMI for height-age and sex percentile at one or both of the first two annual visits from 67 (13 %) children, on MUAC for height-age and sex percentile at one or both of the first two annual visits from 94 (18 %) children, on appetite information from 43 (8 %) children, and on height for age and sex percentile at one or both of the first two annual visits from 87 (16 %) children. The demographic and disease characteristics of the 528 children are shown in Table 1. The overall cohort had a median age of 12 years and a median GFR of 45 mL/min/1.73 m^2; 39 % were female and 18 % were African American.

Using the data augmented through multiple imputation, we compared the characteristics of those who met each definition of PEW with the overall cohort (Table 1). Children meeting the minimal PEW definition represented 20 % [95 % confidence interval (CI) 16, 24] of the cohort. These children were more likely to have a lower median BMI for height-age and sex *Z* score (P=0.02), a lower MUAC height-age and sex *Z* score (P=0.02), and a higher urine protein to creatinine ratio (P=0.04). Children meeting the standard PEW definition represented 7 % (95 % CI 5, 10) of the cohort. These children were more likely to have a lower median BMI for height-age and sex *Z* score (P<0.001) and a lower MUAC height-age and sex *Z* score (P<0.001). Children meeting the modified PEW definition represented 15 % (95 % CI 12, 18) of the cohort. They were more likely to have a lower median weight for age and sex *Z* score (P=0.03), a lower BMI for height-age and sex *Z* score (P=0.02), a lower MUAC height-age and sex *Z* score (P=0.02), and a higher percentage of children with a protein to creatinine ratio of >2 (P=0.03).

When the prevalence of the various indicators of PEW were examined in the overall cohort and by CKD stage, the data suggested trends towards higher prevalence with lower GFR in hypoalbuminemia (P_{trend}=0.04), decreased appetite (P_{trend}<0.001), reduced muscle mass (P_{trend}=0.20), and reduced body mass (P_{trend}=0.16), although

Table 1 Baseline[a] characteristics of the overall cohort and those meeting each of the three protein-energy wasting (PEW). Children meeting each definition were compared to the overall cohort

Characteristics	Overall cohort (*N*=528)	Definitions of PEW[b]		
		Minimal PEW	Standard PEW	Modified PEW
African-American (%)	18	22	15	23
Female (%)	39	35	26	35
Pre-pubertal status (%)	48	46	57	51
Glomerular diagnosis (%)	21	23	15	22
Age, year (median [IQR])	12 [8, 16]	12 [8, 16]	10 [6, 14]	12 [7, 16]
Height for age and sex *Z* score (median [IQR])	−0.7 [−1.4, −0.0]	−0.8 [−1.7, −0.1]	−0.7 [−1.7, 0.2]	−1.1 [−2.0, −0.2]
Weight for age and sex *Z* score (median [IQR])	−0.2 [−0.9, 0.7]	−0.5 [−1.3, 0.3]	−0.8 [−1.6, −0.1]	−0.7 [−1.6, 0.2]*
BMI for height-age and sex *Z* score (median [IQR])	0.5 [−0.3, 1.3]	0.1 [−0.5, 0.9]*	−0.4 [−0.7, −0.1]*	0.0 [−0.5, 0.8]*
Mid upper arm circumference for height-age and sex *Z* score (median [IQR])	−0.8 [−3.3, 2.6]	−2.2 [−4.6, −0.5]*	−3.2 [−4.8, −1.4]*	−2.5 [−4.7, −0.7]*
Urine protein to creatinine (UPC) ratio (median [IQR])	0.5 [0.2, 1.2]	0.8 [0.2, 1.8]*	0.8 [0.2, 1.6]	0.8 [0.2, 1.8]
UPC ratio > 2.0 (%)	14	24*	18	24*
Anemia (%)	39	43	32	45
Acidosis (%)	32	38	28	39
Hypertension (%)	48	45	41	46
Dyslipidemia (%)	51	54	62	57
Low birth weight (%)	19	25	27	28
Growth hormone use (%)	13	13	13	14
ieGFR (median [IQR])	45 [33, 58]	42 [30, 56]	42 [31, 55]	43 [30, 56]
CKD stage (%)				
Stage 1 or 2	23	24	22	23
Stage 3a	26	19	22	20
Stage 3b	31	32	30	31
Stage 4 or 5	20	25	25	26

*Indicates a statistically significantly difference from the overall cohort using an alpha level of 0.05

IQR, Interquartile range; BMI, body mass index; ieGFR estimated glomerular filtration rate based on plasma iohexol disappearance; CKD, chronic kidney disease

[a] Baseline was defined as the second annual CKD visit

[b] For the definitions of PEW used in this study, see section Defining Pew

only hypoalbuminemia and decreased appetite were significant by a linear trend (Fig. 1). Low transferrin and TC levels were virtually non-existent in the cohort. The prevalence of high CRP appeared to increase with increasing GFR category but was not significant (P_{trend}=0.28). There was no statistically significant increase in the prevalence of PEW with CKD stage regardless of definition (Fig. 2). Notable increases in prevalence of PEW were only seen in patients with a GFR of <30 mL/min and PEW appeared to be stable in earlier stages of CKD. Collapsing the GFR categories to focus on the threshold of 30 mL/min, the odds of having PEW based on a GFR of <30 mL/min versus a GFR of ≥30 mL/min were 1.5 (95 % CI 0.7, 2.8) 1.4 (95 % CI 0.5, 3.5), and 1.5 (95 % CI 0.8, 2.9), respectively, by the minimal, standard, and modified definitions.

We were primarily interested in longitudinal risk associations with CKD progression and hospitalization to establish whether any of the definitions of PEW were predictive of clinically important endpoints. First we looked at the annual GFR percentage decline to see if meeting the criteria for one or more of the PEW definitions at baseline (the second annual CKiD visit) was associated with faster kidney function decline. GFR decline was assessed in both the first 2 years after PEW assessment and thereafter, which included data up to 7 years after baseline (V2) with an interquartile range (IQR) of 1–4 years of follow-up. From segmented linear mixed effects models broken at 2 years from baseline, the cohort experienced approximately a 3.5 % annual decline in overall GFR level, and there was no evidence that children meeting any of the PEW definitions experienced greater declines (Table 2).

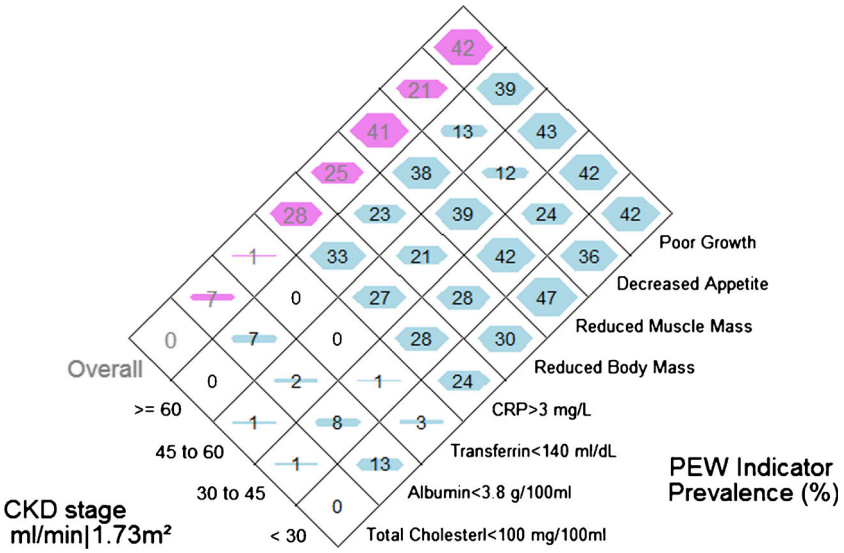

Fig. 1 The prevalence of indicators of protein-energy wasting (PEW) used to form the three definitions. The prevalence is presented stratified by chronic kidney disease (CKD) stage GFR>=60, 45<=GFR<60, 30<=GFR<45, and GFR<30 ml/min/1.73 m2 and also overall. *CRP* C-reactive protein

The annual percentage decline was approximately 2.7 % per year after 2 years from baseline, suggesting a modest deceleration in decline on average. Again there was no evidence of a difference in the rate of decline among children meeting any of the PEW definitions. Age, CKD stage, urine protein to creatinine ratio of >2, and anemia (hemoglobin level <5th percentile for age and sex) were significantly associated with lower GFR in the multivariate models.

Secondly, we examined the incidence rate of hospitalization during the 2 years following baseline using Poisson regression analysis. The unadjusted estimated incidence rate ratios were 1.9-, 2.1-, and 2.2-fold higher for those children classified as PEW using the minimal, standard, and modified definitions, respectively (P=0.08, 0.09, and 0.03, respectively). Following adjustment, the estimates became 1.8, 2.1, and 2.0, respectively, with the modified PEW definition maintaining modest significance (P=0.06). The estimates are compared in Fig. 3. We also examined poor growth as a predictor of hospitalization and found it to be less predictive in adjusted models than the modified PEW definition, of which it was one component (incidence rate ratio 1.8; P=0.11). In the multivariate models with PEW, only CKD stage was a significant predictor of hospitalization in the adjusted models (P=0.05 in all models).

Discussion

There is a dearth of studies examining the occurrence of PEW in children with CKD. Wasting/cachexia syndrome is very common in ESRD in adult populations (30–75 %) and consists of anorexia, increased energy expenditure, decreased

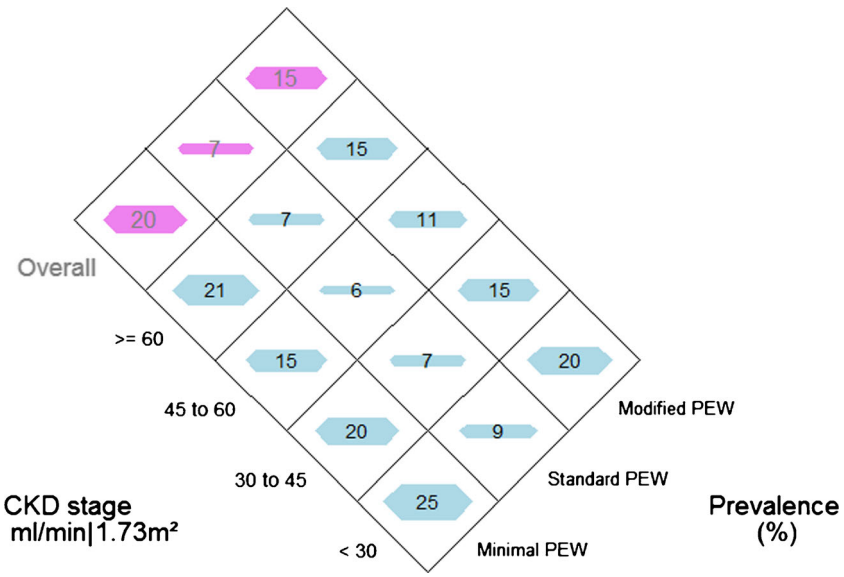

Fig. 2 The prevalence of protein-energy wasting (PEW) as classified using the three definitions adopted in this study: minimal PEW, defined as that requiring at least one test in ≥2 of the four original categories; standard PEW, defined as that requiring at least one test in ≥3 of the four original categories; modified PEW, defined as that requiring at least one test in ≥3 of the five categories (4 original plus poor growth). The prevalence is presented stratified by chronic kidney disease (CKD) stage GFR>=60, 45<=GFR<60, 30<=GFR<45, and GFR<30 ml/min/1.73 m2 and also overall

Table 2 Adjusted estimates of the annual percentage change in glomerular filtration rate (GFR) from segmented mixed effect models[a]

GFR/PEW	% Annual Change in GFR Slope (95% Confidence Interval)[b]		
	Minimal PEW	Standard PEW	Modified PEW
From baseline to 2 years			
Annual decline in GFR	−3.3 (−5.7, −0.8)*	−3.6 (−5.8, 1.4)*	−3.5 (−5.8, 1.2)*
Change in slope for PEW	−1.0 (−7.6, 6.0)	2.3 (7.7, 13.5)	0.0 (5.8, 7.1)
After 2 years			
Annual decline in GFR	−2.9 (−4.1, −1.6)*	−2.6 (−3.7, −1.5)*	−2.7 (−3.9, −1.6)*
Change in slope for PEW	1.6 −1.6, 4.9)	0.0 (−4.4, 5.4)	1.1 (−1.1, 4.5)

*Indicates significance at the α=0.05 level

PEW, Protein-energy wasting; CKD, chronic kidney disease

[a] The effect of meeting a definition of PEW on the GFR slope was assessed for each PEW definition for two periods of time: within 2 years of baseline (CKD second annual visit) and after 2 years from baseline

[b] Adjusted for age, CKD stage, glomerular diagnosis, a urine protein to creatinine ratio of >2, anemia (a hemoglobin level of <5th percentile for age and sex), and low birth weight (birth weight <2,500 g)

protein stores, and loss of weight and muscle mass [30]. While this syndrome in its various forms (PEW vs. cachexia which has been considered a more severe state of PEW) has been described for adults, and diagnostic criteria have been proposed [1, 8], the applicability of these clinical features to children with CKD has not been established. In this study we examined the prevalence of adult diagnostic criteria as well as pediatric focused indicators of PEW in a pediatric CKD cohort and assessed the degree to which varying definitions using these criteria predict incident hospitalizations and CKD progression. We found that the incidence of PEW ranged from 7 to 20 % in the overall cohort depending upon the definition, and an increase in prevalence (corresponding to an odds ratio of 1.5) was suggested in advanced CKD stages 4 and 5, although the increase was not statistically significant. The lack of statistical significance may be the result of relatively small numbers of children meeting any one PEW definition in our cohort. Several of the indicators of PEW tended to increase with decreasing GFR, with hypoalbuminemia and poor appetite having the strongest association. These results may

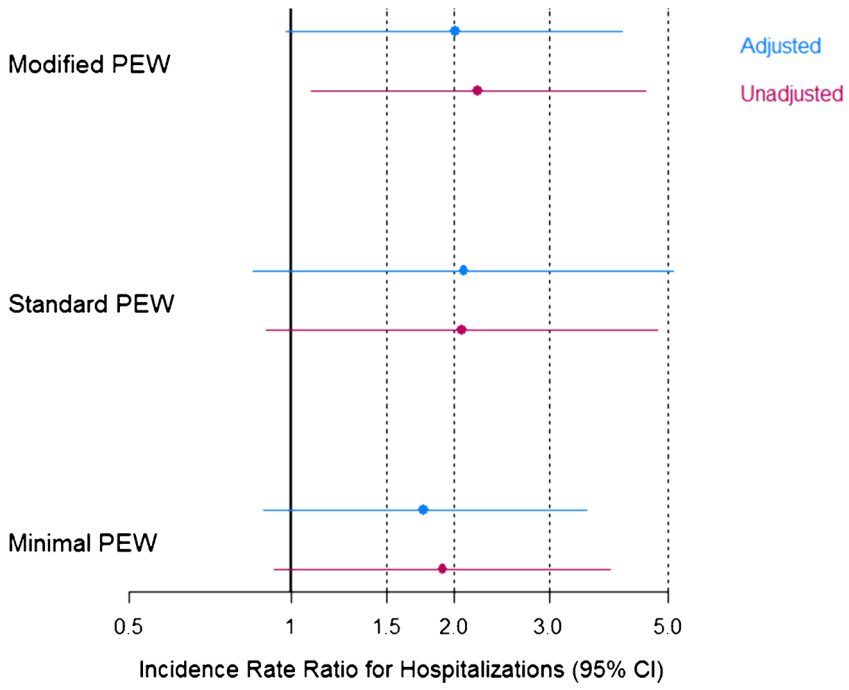

Fig. 3 The unadjusted and adjusted incidence rate ratios for hospitalization within the 2 years from baseline comparing the three protein-energy wasting (PEW) definitions used in this study

suggest that, of the four laboratory measures assessed, hypoalbuminemia is the most sensitive indicator of PEW in our pediatric cohort. Both low transferrin and cholesterol levels were exceedingly rare. It is possible that low transferrin and cholesterol levels may be more valuable indicators in children with more severe disease or those on dialysis. In contrast to what has been reported in adult studies of CKD, high CRP in the CKiD cohort seemed to be more common in children with milder disease. While PEW is thought to be a process driven by inflammation, a recent report by Foster et al. [11] examining children with more advanced CKD also reported a lack of association between markers of inflammation and wasting based on leg lean mass *Z* scores, as measured by DEXA scans, except in the most advanced stages of CKD in children. Notably, these authors reported no significant skeletal muscle wasting in children with CKD stages 2–3.

There is no clinical consensus as to the optimal assessment of PEW in children. We used both baseline and longitudinal information to classify participants in terms of their muscle mass, body mass, and growth status. As multiple prior studies have implicated short stature and poor growth as predictors of adverse outcomes in children with CKD, we included an assessment of growth status in our modified definition of PEW. However, the sensitivity of this poor growth measure may be compromised if small but non-wasted children are captured in the definition. Similarly, using decreasing BMI percentiles, may capture overweight children who have intentionally lost body mass. In addition, BMI is an imperfect surrogate of lean mass. BMI can result in questionable measurements of wasting in CKD, which is ideally defined as diminished lean body mass. Fluid overload, which is common in CKD, confounds BMI and lean/skeletal mass measurements [31]. Furthermore, calorie supplementation, which is commonly prescribed in CKD children with a weight deficit or linear growth failure, may not correct true lean mass deficits in CKD and may instead increase body weight by increasing fat mass and water content. Rashid et al. [32] measured body composition by DEXA scan in growth-retarded children with advanced CKD on energy supplementation and showed that a normal BMI can be associated with reduction in lean mass and that reduced BMI can be associated with increased fat mass in these children.

The most important test of a PEW definition is the prediction of clinical outcomes. The modified definition of PEW, which included criteria for poor growth specific to a pediatric context, was the only definition associated with incident hospitalizations within 2 years of classification. This finding suggests that growth may be a better standard for diagnosing PEW in children than weight-based criteria. Adding poor growth to the definition also increased the prevalence of PEW from 7 to 15 %. Indeed, the Society for Cachexia and Wasting Disorders (SCWD), which includes participants with diverse backgrounds encompassing many of the diseases states that result in cachexia (such as cancer, human immunodeficiency virus infection, heart failure, CKD, and chronic obstructive pulmonary disease), identified growth failure as the most important clinical feature of cachexia in children [33].

There are limitations to our analysis that should be noted. The CKiD cohort comprised children with moderate CKD and, therefore, the prevalence of PEW was relatively low, limiting our ability to look at associations with outcomes and discriminate between PEW definitions. In addition, a direct measurement of GFR was not available every year by study design, and thus estimated GFRs were used in intervening years to supplement iohexol GFR measurements. Estimated GFRs from CKiD's internally derived equation have shown good agreement with iohexol GFR measurements [18]. However, using estimated and directly measured GFR interchangeably could result in bias in estimated GFR decline over time.

In summary, our results suggest that diagnosing PEW syndrome in children with CKD requires pediatric-specific criteria. The addition of an indicator of growth failure or poor growth velocity added to the existing adult criteria improved the prediction of hospitalizations. Clinicians should consider growth in their assessment of children at risk for PEW.

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Conflict of interest None.

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