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Global Prevalence of Protein-Energy Wasting in Kidney Disease: A Meta-analysis of Contemporary Observational Studies From the International Society of Renal Nutrition and Metabolism

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Objective: To better define the prevalence of protein-energy wasting (PEW) in kidney disease is poorly defined.

Methods: We performed a meta-analysis of PEW prevalence from contemporary studies including more than 50 subjects with kidney disease, published during 2000-2014 and reporting on PEW prevalence by subjective global assessment or malnutrition-inflammation score. Data were reviewed throughout different strata: (1) acute kidney injury (AKI), (2) pediatric chronic kidney disease (CKD), (3) non-dialyzed CKD 3-5, (4) maintenance dialysis, and (5) subjects undergoing kidney transplantation (Tx). Sample size, period of publication, reporting quality, methods, dialysis technique, country, geographical region, and gross national income were a priori considered factors influencing between-study variability.

Results: Two studies including 189 AKI patients reported a PEW prevalence of 60% and 82%. Five studies including 1776 patients with CKD stages 3-5 reported PEW prevalence ranging from 11% to 54%. Finally, 90 studies from 34 countries including 16,434 patients on maintenance dialysis were identified. The 25th-75th percentiles range in PEW prevalence among dialysis studies was 28-54%. Large variation in PEW prevalence across studies remained even when accounting for moderators. Mixed-effects meta-regression identified geographical region as the only significant moderator explaining 23% of the observed data heterogeneity. Finally, two studies including 1067 Tx patients reported a PEW prevalence of 28% and 52%, and no studies recruiting pediatric CKD patients were identified.

Conclusion: By providing evidence-based ranges of PEW prevalence, we conclude that PEW is a common phenomenon across the spectrum of AKI and CKD. This, together with the well-documented impact of PEW on patient outcomes, justifies the need for increased medical attention.

Introduction

THE SYNDROME OF protein-energy wasting (PEW) encompasses a number of nutritional and metabolic alterations that often coexist in patients with chronic kidney disease (CKD). These alterations result, collectively, in a progressive loss of body stores of protein and energy fuels (i.e., body muscle and fat mass).[1–3] The consequences of PEW are many and important, with a negative impact on not only patients' prognosis, complications, management, and quality of life but also on health economics.[1–3] Despite this evidence, PEW is often undetected and untreated, not being considered a clinical priority. Lack of awareness as well as insufficient knowledge and training are possibly major obstacles. Increased awareness of PEW in kidney disease starts by recognizing its prevalence along the CKD spectrum.

PEW prevalence in kidney disease patients is, to date, poorly defined. Reports often state wide and noninformative wide ranges such as 18-75%. The evaluation of PEW prevalence from existing CKD literature is hampered by multiple factors, including lack of standardized PEW definitions, variability of existing assessment tools, studies with small sample size and differences in the socioeconomic realities of the countries in which the studies took place. An evidence-based and more objective determination of PEW prevalence is necessary to weigh the magnitude of the problem, evaluate the need for increased medical attention and allocation of clinical resources/manpower, and allow assessment of expected PEW prevalence for study planning. The latter is important for both sample size determination for randomized controlled trials and for detectable effect sizes when using existing records. For these purposes, we present, on behalf of the International Society of Renal Nutrition and Metabolism (ISRNM), a meta-analysis of the prevalence of PEW in contemporary observational studies of patients with kidney disease. Such information may raise awareness and enhance the implementation of effective clinical service programs that address PEW in kidney disease at all levels of decision-making.

Methods

Data Sources and Searches

This is a collaborative initiative from the ISRNM. ISRNM members were invited to join and participate in the identification of studies eligible for meta-analysis of PEW prevalence. Selection of 25 study collaborators was based on their publication track record on the topic of investigation and geographical location. We performed a wide search to identify studies reporting on the prevalence of PEW in kidney disease. We searched MEDLINE (PubMed), Embase, backward citation in Web of Science, and language-specific search engines (SCIELO for Spanish papers, CNKI for Chinese studies, and KoreaMed for Korean studies). The search string consisted of two parts: (1) the exposure (i.e., protein energy wasting, PEW, malnutrition, undernutrition, subjective global assessment, SGA, malnutrition inflammation score, MIS) and (2) study population. For the latter, we used the recently published "High-Performance Information Search Filters for CKD Content" algorithm.[4] Different spelling was accounted for, and medical subheadings were incorporated in the PubMed search.

Study Outcome

The outcome of this meta-analysis was the prevalence of PEW. Given the lack of gold-standard methods/definitions to diagnose PEW, we decided *a priori* to focus on prevalence estimates derived from either subjective global assessment (SGA) or malnutrition inflammation score (MIS). The rationale is that SGA is a validated and well-established nutritional assessment score widely used internationally in many disciplines beyond nephrology,[5]

and MIS is an SGA-based semiquantified score specific to CKD.[6] Initially, we included all variations of the SGA score (ABC SGA, 7 points SGA, CANUSA SGA, and semiquantitative SGA) used within the CKD literature (summarized in the study by Steiber et al.[7]) and defined PEW as the combined proportion of patients having mild, moderate, or severe malnutrition (any kind of malnutrition). During qualitative data analysis, we modified the initial protocol and excluded studies using the semiquantitative SGA score.[8] This was carried out because the original publication did not define a PEW cutoff, and subsequent papers applying this method used arbitrary definitions that hampered their comparison. Furthermore, we found that there was no universally agreed upon cutoff for PEW in the MIS. To define a common cutoff, we contacted the primary investigators of the three largest studies to date using MIS[9-12] and accessed raw patient data to perform receiver operator characteristic curve analyses for mortality prediction. We defined PEW by a MIS cutoff (MIS score equal or higher than 5) that resulted in equal sensitivity and specificity (symmetry point of receiver operator characteristic curve).

Study Population, Inclusion/Exclusion Criteria

The study population included the following groups of patients within the spectrum of kidney diseases that were analyzed separately: (1) acute kidney injury (AKI), (2) pediatric CKD patients, (3) adult nondialysis-dependent patients with CKD stages 3-5, (4) adult dialysis-dependent patients, and (5) in patients undergoing kidney transplantation (Tx). We also separated studies performed in patients undergoing hemodialysis (HD) and peritoneal dialysis (PD). We did not consider CKD stages 1-2.

Study Selection

Studies eligible for meta-analysis were those with an observational design and including patients affected by kidney disease, published between January 2000 and December 2014 and recruiting a minimum of 50 patients. Abstracts or other materials in conference proceedings, case reports, case series, and review articles were excluded. Language selection was applied to English, Chinese, Spanish, and Korean. A study protocol was developed and distributed to study collaborators. Collaborators were asked to perform study searchers in their assigned geographical areas or within their assigned subpopulations (Supplemental information 1).

We follow the United Nation's association of countries with geographical regions and refer to countries by their short forms, which may or may not coincide with the name used by that country in official documents (United Nations standard for statistical uses M49; https://unstats.un.org/unsd/methodology/m49/). For brevity in our tables and figures, we make the following exceptions from the M49 Standard names: (1) "Hong Kong" refers to China, Hong Kong Special Administrative Region; (2) "Korea" to the Republic of Korea; (3) "Taiwan" to the island of Taiwan; (4) "UK" to the United Kingdom of Great Britain and Northern Ireland; (5) "USA" to the United States of America; (6) "Iran" to Iran (Islamic Republic of).

Studies identified during this first selection phase were imported to Microsoft Excel software. For each study, the PDF file was saved in an online repository. The following information was abstracted from each study and entered into the MetaXL data set: (1) first author's name, (2) PubMed-Indexed for MEDLINE number, (3) year of publication, (4) country, (5) geographical region, (6) type of population (pediatric, AKI, Tx, CKD, or dialysis), (7) total number of patients, (8) number of patients with PEW, and (9) method of PEW definition (SGA or MIS). For studies with insufficient data, email requests were sent to the corresponding authors. If no response was received after three email reminders, the study was excluded for further analysis. Because PEW may reflect underlying country-specific malnutrition, studies including dialysis patients were in addition classified according to their countries' gross national income (GNI). Using the 2014 classification by the World Bank Atlas (https://datahelpdesk.worldbank.org/knowledgebase/articles/378832-what-is-the-world-bank-atlas-method), countries were grouped into high-income countries, upper-middle-income countries, and low-income countries (low-income + lower middle-income countries). Finally, two investigators (M.Z.M. and K.N.) developed and applied a Quality Index assigning a quality score of 0–1 to each study. The quality score was calculated on the basis of five aspects of a study (Supplemental Information 2). The maximum raw score was 8 points, representing the highest methodological quality. Disagreements in the scores were resolved by discussion and consensus. The quality index was then "normalized" to the range 0-1 by dividing the raw score by 8 (maximum achievable). At this point, a second selection phase was performed by three investigators (J.J.C., M.Z.M., and K.N.) to verify that inclusion-exclusion criteria were met and to exclude duplicates from the same cohort. In cases of (partially) duplicated reports, we retained the more recent report or the report with the largest sample size.

Data Analysis and Synthesis

We first performed random-effect meta-analysis of the reported PEW prevalence and confirmed that the residual heterogeneity and unaccounted variability across these studies is very high ($I^2 = 97\%$; $P < .001$). This was expected as we were already aware of widely diverse proportions of study participants reported to have PEW and hypothesized that these differences might be explained by the type of dialysis patients were receiving (HD and PD), the way PEW was assessed (MIS, SGA 3 points, or SGA 7 points), or the geographic region of the study population. Because

we *a priori* did not assume functionally equivalent studies, we anticipated using meta-regression as our fundamental modeling approach that would allow investigating systematic effects on the proportion of participants with PEW by study traits that we could identify from the respective publications. Additional factors explored as sources of heterogeneity were the study sample size (<100, 100-250, and >250 patients), the year of publication (2010-2014, 2005-2009, 2000-2004), and the study quality (normalized quality index score <5/8 and ≥5/8). Our mixed-effects meta-regression[13] estimates the (expected) mean of PEW prevalence in the identifiable subgroups including a standard error of such a summary effect. Funnel plots were used to assess publication bias. All analyses were repeated with logit transformed PEW proportion without appreciably different findings (not shown).

Results

We identified 193 eligible original articles (Fig. 1). Upon consultation of their full text, 92 studies were excluded due to not fulfilling inclusion criteria (n = 23), incorrect use of methods or no response to our email requests (n = 20), different exposure definitions or PEW prevalence not possible to calculate from presented data (n = 18), articles derived or presumably derived from the same patient material (n = 16), data collection prior to year 2000 (n = 7), report of mixed CKD populations (n = 5), and inclusion criteria biasing estimates (e.g., the study selection criteria specifically involved recruiting patients with some degree of malnutrition; n = 3). The remaining 101 studies were included in a qualitative synthesis analysis and scored individually. In this step, we modified our initial protocol and decided to exclude 6 studies that used a semiquantitative

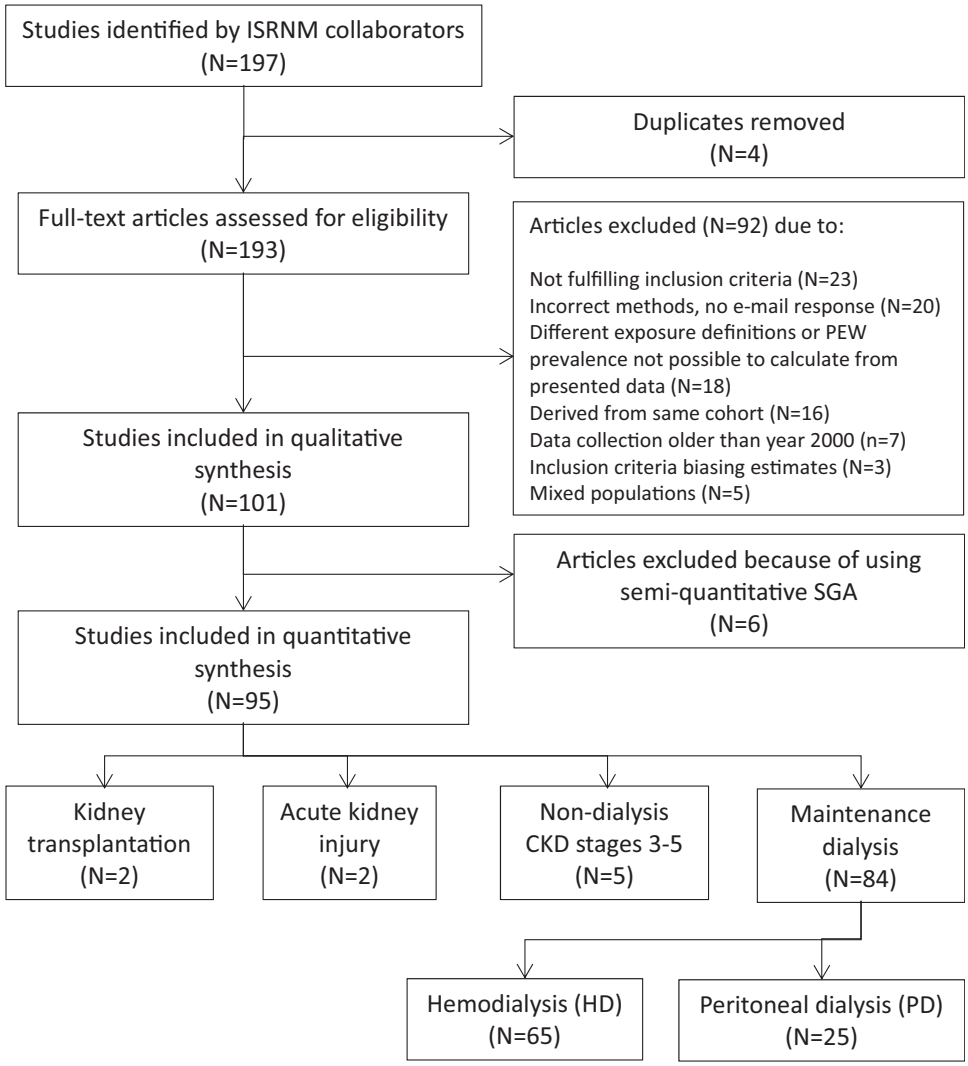

Figure 1. Flow of studies through the different phases of the systematic review. 84 studies including maintenance dialysis patients resulted in a higher number of separate estimates given that some studies included cohorts of HD and PD patients and/or estimates from various countries. CKD, chronic kidney disease; ISRNM, International Society of Renal Nutrition and Metabolism; PEW, protein-energy wasting; SGA, subjective global assessment.

SGA scale. After completed study identification and selection, 95 studies were analyzed, including 2 studies of AKI patients, 2 studies of Tx patients, 5 studies of nondialysis CKD patients, and 84 studies including maintenance dialysis patients (formally resulting in 90 separate estimates given that two studies[14,15] included combined cohorts of HD and PD patients and a multinational analysis[16] reported PEW prevalence in cohorts from 5 different countries). No eligible study of pediatric CKD patients was identified. The complete data set for analysis can be accessed along with the supplementary information to this study.

Studies including patients with AKI, Tx, and nondialysis CKD patients of stages 3-5 are described in Tables 1 and 2, parts A-C, and their respective PEW prevalence data are depicted in Fig. 2. The two studies including Tx patients[10,17] (n = 1067 patients) reported wide difference in PEW prevalence (28% and 52%). The prevalence of PEW among AKI studies[18,19](n = 189 patients) was higher but again with broad variability between studies (60% and 82%).

Five studies included nondialysis-dependent CKD patients with stages 3-5[9,20-23] (n = 1776 patients). Four of those studies[20-23] used SGA and reported PEW prevalence that ranged from 11% to 18%. One additional study[9] that used the MIS reported a PEW prevalence of 54% for a combined estimate of 22.5% (95% confidence interval, 6.9-38%). However, the high ratio of true heterogeneity $I^2 = 98.5\%$ (test for heterogeneity $P < .001$) strongly suggests that more than random fluctuation is needed to explain this variability of PEW prevalence.

The remaining 90 studies/estimates included maintenance dialysis patients (including collectively 16434 patients) from 10 geographical regions (Tables 1 and 2, Part D), and this larger number of studies allowed further meta-analysis. The 34 countries that are represented by at least one study represent most but not all parts of the world (Fig. 3): 47 (52%) studies come from Asia, 20 (22%) from Europe, 16 (18%) from the America, 4 (4.4%) from Oceania (Australia), and 3 (3.3%) from Africa. Most studies (n = 65, 72%) included patients undergoing HD, and the remaining (n = 25, 28%) included patients undergoing PD. Thirty-nine studies (43%) reported fewer than 100 patients, 36 (40%) between 100 and 250 patients and 15 (17%) more than 250 patients. In 10 studies (11%), PEW was determined by MIS, and in 80 (89%) studies, it was determined by SGA. About half of the studies, 47 (52%), came from high-income countries, 39 (43%) from middle-income countries, and only 4 (4.4%) from low-income countries. Most studies were reported/published between 2010 and 2014 (52 studies, 58%), followed by 28 (31%) studies published between 2005 and 2009, and only 10 studies (11%) published between 2000 and 2004. The

Table 1. Contributing Studies by Regions and Type of Patients

Region	Countries	No. of Studies	Combined Cases	Combined N	Raw % Cases
Part A: Kidney transplant studies					
Europe	Hungary, Poland	2	321	1067	30.1
Part B: Acute kidney injury studies					
Latin America/Caribbean	Brazil	2	126	189	66.7
Part C: Nondialysis CKD stages 3-5 studies					
Oceania	Australia	1	10	56	17.9
Europe	Netherlands	1	43	376	11.4
Latin America/Caribbean	Brazil	3	286	1344	21.3
Total (part C)		5	339	1776	19.1
Part D: Maintenance dialysis studies					
Oceania	Australia	4	92	414	22.2
Eastern Asia	China, Hong Kong, Japan, Korea, Taiwan	31	2197	4634	47.4
Western Asia	Iraq, Israel, Jordan, Lebanon, Saudi Arabia, Turkey	11	883	1866	47.3
Southeastern Asia	Indonesia, Malaysia, Thailand	3	143	271	52.8
Southern Asia	India, Iran	2	357	548	65.1
Northern Africa	Egypt	1	23	100	23.0
Sub-Saharan Africa	Nigeria, South Africa	2	60	101	59.4
Northern America	USA	3	510	995	51.3
Europe	France, Germany, Italy, Poland, Portugal, Romania, Spain, Sweden, UK	20	1100	4765	23.1
Latin America/Caribbean	Brazil, Colombia, Jamaica, Mexico	13	1128	2740	41.2
Total (part D)		90	6493	16434	39.5

CKD, chronic kidney disease.
Some studies are split up due to reporting of several studies/patient groups (see the Methods Section for details).

Table 2. References for Included Studies Arranged by Country

Country	Reference
Part A: Kidney transplant studies	
Hungary	Molnar MZ, 2011[10]
Poland	Malgorzewicz S, 2014[17]
Part B: AKI studies	
Brazil	Berbel MN, 2014;[18] Guimarães SM, 2008[19]
Part C: nondialysis CKD stages 3-5 studies	
Australia	Campbell KL, 2008[20]
Brazil	Amparo FC, 2014;[9] Cuppari L, 2014;[21] Sanches FMR, 2008[22]
Netherlands	Westland GJ, 2014[23]
Part D: Maintenance dialysis studies	
Australia	Campbell KL, 2009;[24] Campbell KL, 2013;[25] Desbrow, 2005;[26] Todd A, 2013[27]
Brazil	Barros A, 2011;[28] Leinig CE, 2011;[29] Nascimento M, 2004;[30] Nerbass F,2011;[31] Oliveira CM, 2010;[32] Oliveira GT, 2012;[33] Pereira R, 2013;[34] Vannini F, 2009;[35] Vavruk MA, 2012[36]
China (mainland)	Dong J, 2006;[37] Du, 2012;[38] Gu Y, 2008;[39] Gui, 2010;[40] He T, 2013;[39] Li Y, 2009;[41] Lu, 2011;[42] Shao Y, 2013;[43] Shi, 2012;[44] Wang, 2008;[45] Wang, 2009;[46] Wang, 2012;[47] Wu, 2012;[48] Ying, 2013;[49] Zou, 2014[50]
China (Hong Kong)	Chan JY, 2007;[51] Chow VC, 2007;[52] Wang AY, 2003[53]
Colombia	Sanabria M, 2008a (HD estimate); Sanabria M, 2008b (PD estimate)[14]
Egypt	Salwa I, 2010[54]
France	Hecking E, 2004[16]
Germany	Fiedler R, 2009;[55] Fiedler R, 2011;[56] Hecking E, 2004b[16]
India	Sharma R, 2013[57]
Indonesia	Suhardjono S, 2006[58]
Iran	Ashabi A, 2014[59]
Iraq	Al-Saedy AJ, 2011[60]
Israel	Beberashvili I, 2010;[61] Beberashvili I, 2013;[62] Beberashvili I, 2014;[63] Blumberg S, 2014[64]
Italy	Bossola, 2009;[65] Sclauzero P, 2013;[66] Hecking E, 2004[16]
Jamaica	Dewar D, 2012[67]
Japan	Honda H, 2010[68]
Jordan	Tayyem RF, 2008[69]
Korea	Choi HY, 2010;[70] Choi MJ, 2012;[71] Chung SH, 2010;[72] Kim BS, 2005;[73] Koo HM, 2011;[74] Lee JE, 2004;[75] Lhee HY, 2006[76]
Lebanon	Mirey K, 2014[77]
Malaysia	Md Yusop NB, 2013[78]
Mexico	Martín del Campo F, 2012[79]
Nigeria	Liman HM, 2012[80]
Poland	Malgorzewicz S, 2004[81]
Portugal	Bernardo AP, 2009[82]
Romania	Garneata L, 2014;[83] Segal L, 2009[84]
Saudi Arabia	Al Saran K, 2011[85]
South Africa	Abdu A, 2011[86]
Spain	Hecking E, 2004d[16]
Sweden	Carrero JJ, 2007;[87] Cobo, 2014[88]
Taiwan	Hung CY, 2005;[89] Tsai HB, 2012;[90] Tsai HJ, 2011;[91] Yang FL, 2007;[92] Wu TT, 2011[93]
Thailand	Pisetkul C, 2010[94]
Turkey	Afsar B, 2006;[95] Arslan Y, 2010;[96] Sezer S, 2012[97]
UK	Brown EA, 2010a (HD estimate), Brown EA, 2010b (PD estimate);[15] Gurreebun F, 2007;[98] Jones CH, 2004;[99] Hecking E, 2004e;[16] Elliott HA, 2009[100]
USA	Han H, 2013;[101] Rambod M, 2009;[12] Wilson G, 2006[102]

AKI, acute kidney injury; CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis.

assigned quality index score was less than 5/8 for 52 (58%) of the studies and greater than or equal to 5/8 for 38 (42%) studies.

Studies of maintenance dialysis patients showed a large variation in PEW prevalence across countries and regions and excess heterogeneity (I^2 = 97%, $P < .001$) strongly indicating that simple pooled estimates would be inappropriate (Fig. 3). The observed average PEW prevalence was 42% (raw prevalence across all studies irrespective of study size). Individual studies reported prevalence ranging from 9% to 98%, with half of the studies reporting a prevalence above 40% (median PEW prevalence, 40%). The 25th-75th percentile range was 28-54% (Figs. 3 and 4). This was similar in HD (range, 9.2-81%; 25th-75th percentiles, 28-56%; median, 43%) and PD (range, 16-98%; 25th-75th percentiles, 32-49%; median, 36%) studies, and dialysis modality was not a statistically significant factor for PEW prevalence ($P = .915$; Supplemental information 3.1).

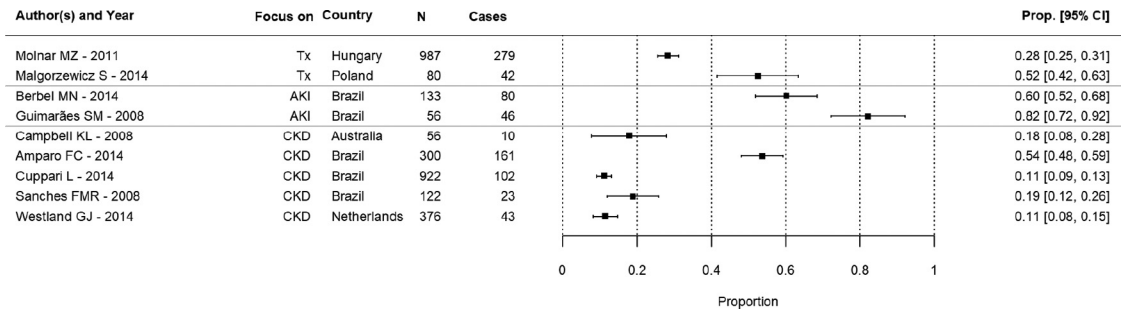

Figure 2. PEW prevalence results reported from studies including kidney transplant (Tx), acute kidney injury (AKI), and nondialysis chronic kidney disease (CKD) stages 3-5 patients. CI, confidence interval; PEW, protein-energy wasting.

Differences in PEW prevalence were not due to random fluctuation attributable to study size ($P = .1$; Supplemental information 3.2), method used ($P = .2$; Supplemental information 3.3), or the GNI of the associated country ($P = .4$; Supplemental information 3.4) that might reflect on overall patient populations. The differences cannot be "explained" by the quality of the study as described by our quality index score ($P = .9$; Supplemental information 3.5) or the year of publication. Specifically, we did not see evidence for that more recent studies would start to agree more on overall PEW prevalence ($P = .3$; Supplemental information 3.6). Visual inspection of an ordering of studies according to PEW prevalence did not suggest any noteworthy patterns as well (Supplemental information 3.7). In these analyses, no systematic variation of PEW prevalence emerged when studies were ordered by any of such variables, and not much light was shed on possible origins of these diverse PEW prevalence estimates. This was verified by our mixed-effects meta-regression analysis, in which the only statistically significant fixed effect was geographical region ($P < .001$), which explained about 23% of the observed heterogeneity between the studies (Supplemental information 4). The residual heterogeneity remained very high in that model ($I^2 = 96\%$; $P < .001$), and these model-based best estimates are presented in Supplemental information 4 together with the

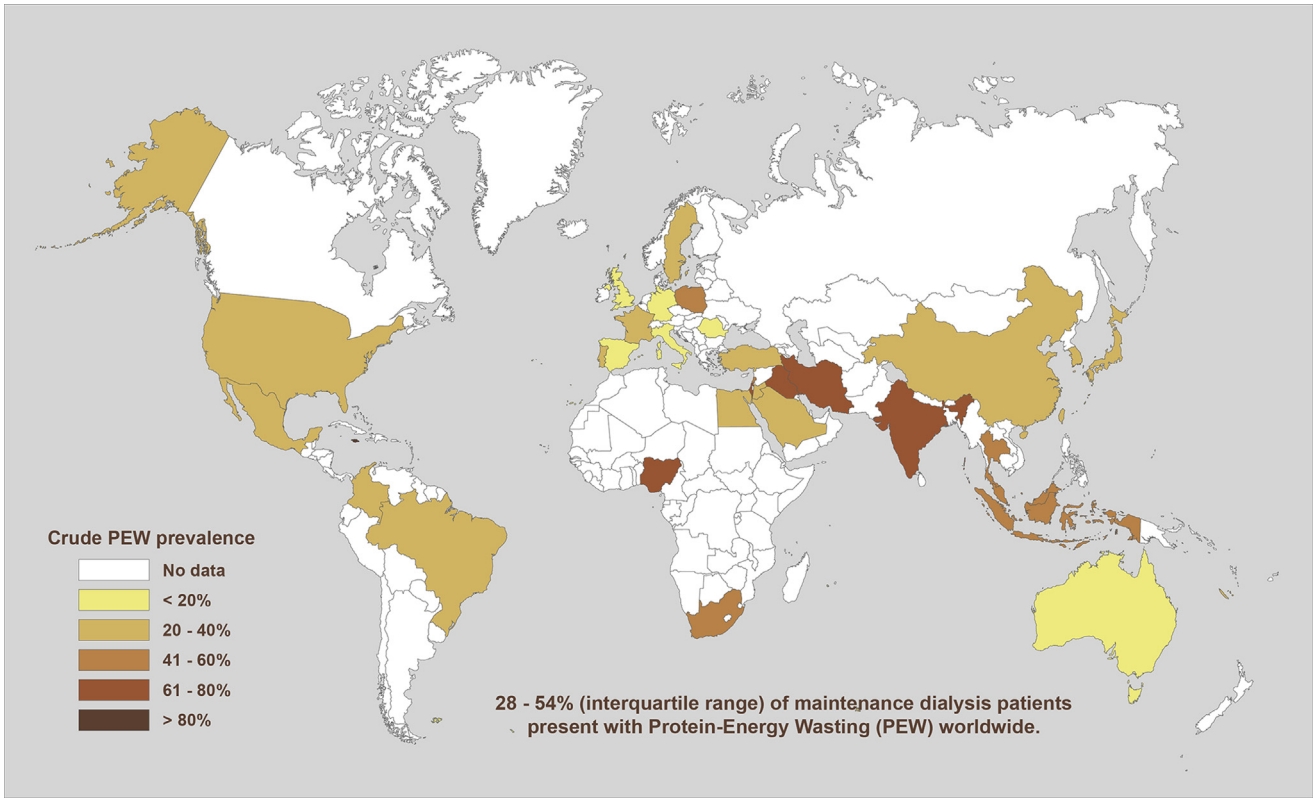

Figure 3. Prevalence of PEW among patients undergoing maintenance dialysis worldwide reported from studies published during 2000-2014. Color gradation reflects PEW prevalence in all included studies from each country (weighted averages within countries). PEW, protein-energy wasting.

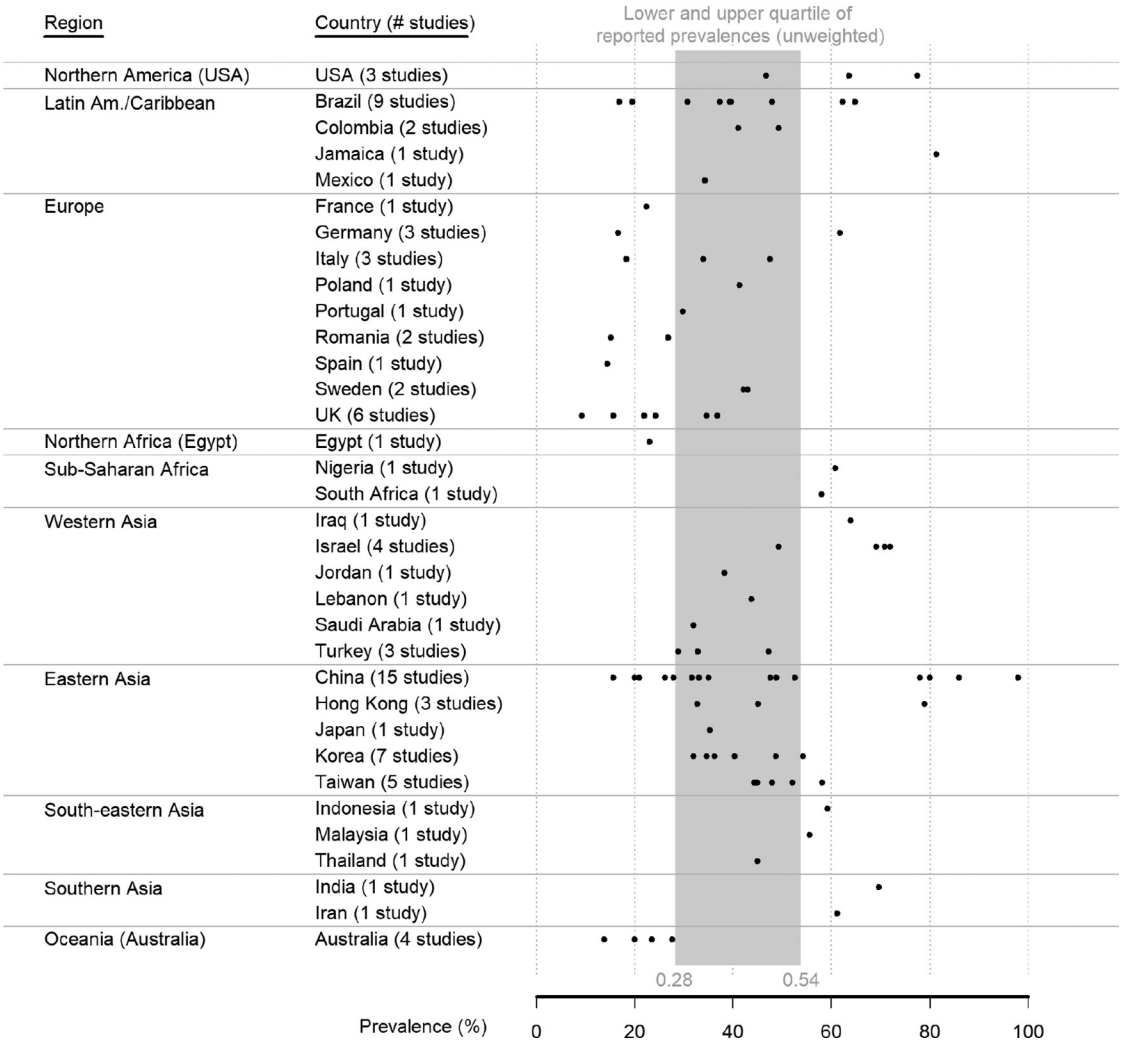

Figure 4. PEW prevalence results in studies including patients on maintenance dialysis, depicting reported prevalence of individual studies by country within region and marking in gray the interquartile range of the studies' reported PEW prevalence (i.e., 50% of the studies reported a prevalence within the highlighted area). See supplemental figures for expanded versions including confidence intervals (Germany and Korea have two studies each with prevalence too close to each other to discern as separate points in the figure). PEW, protein-energy wasting.

raw prevalence proportions for various grouping summaries in Supplemental information 5.1-5.5. We anticipate that these numbers might be helpful for planning future studies in the respective areas.

Discussion

This meta-analysis of PEW prevalence in patients with kidney disease provides more precise evidence-based estimates than previously reported, which credibly illustrate the commonness of this syndrome in patients at all stages of disease severity. We found that the prevalence of PEW is insufficiently studied in some scenarios, such as pediatric CKD, Tx, or AKI. Furthermore, we also found wide variability in the reported PEW estimates, which has implications in the design of future studies.

The main results of our work involve an abundance of studies including maintenance dialysis patients, which allowed further exploration and stratification. Our principal finding is that 28-54% of dialysis patients present with PEW. This estimate is based on the interquartile range of distribution of 90 studies and is the first evidence-based prevalence range of PEW reported for this patient population, offering more precision and emphasizing the burden of wasting alterations in these patients. Another important finding is our inability to provide moderators for PEW prevalence estimates in this patient population due to remaining high residual heterogeneity and diversity between the studies. We feel that our meta-analysis is large enough to conclude that neither the type of dialysis, nor PEW determination, a country's GNI, or an overall quality of the reported study "explains" the observed PEW prevalence

variability. The only identified major contributor to the diverse PEW prevalence rates is geographical region, but this only explained about 23% of the observed heterogeneity between the studies.

Explanations for the high heterogeneity observed may lie in the subjectivity of the exposure, naturally affected by interobserved and intraobserved variability.[103] In addition, it may be affected by the individual health-care professional's education, knowledge, and experience, as well as on the approach used to define patients with PEW (i.e., reporting of PEW by methods other than SGA/MIS). We acknowledge that other potential modifiers such as dialysis vintage and access to a renal dietitian were not available in the majority of studies identified and could not be accounted for. Contrary to our expectations, GNI of the countries represented in our study did not differentiate studies with different PEW prevalence. A plausible explanation could be that studies identified in our searches are not representative of the reality of their respective countries. For instance, studies addressing PEW prevalence and outcomes may come from hospitals/centers with interest/awareness of this problem and be taking more actions to detect/combat PEW than other centers in the same country. Studies derived from developing countries and emerging economies may come from selected hospitals with the resources to perform these determinations or that receive insured or financially affluent individuals not representative of the majority of the population in that country. We are not able to address this possible "representation bias", which in our analysis is simply absorbed into the remaining variability in the observed PEW prevalence. Similarly, we were not able to systematically assess specific enrollment criteria for published studies that may or may not explain some of the variability in the empirically observed PEW prevalence. A final consideration is that because most, if not all, CKD studies included clinically stable patients, the reported ranges would be, if anything, an underestimation of the true PEW prevalence.

Our analysis also identified five studies performed in patients with CKD stages 3-5[9,20-23] with a PEW prevalence range of 11-54%. This range, albeit broad, is in line with studies that described PEW by other definitions[104] and consistent with the observed gradually increasing prevalence in PEW as the severity of CKD worsens.[104] Most studies used SGA,[20-23] and their reported PEW prevalence was lower than that reported by the only study using MIS.[9] Reasons for this discrepancy could lie in the between-study variability, but also in the fact that typically, MIS tends to report a larger proportion of PEW by considering hypoalbuminemia, which is almost ubiquitous in these patients, in its scoring. Furthermore, we used a score cutoff based on mortality prediction, which is not necessarily the cutoff for best PEW diagnostic performance. The lack of a gold standard method for measuring PEW makes the determinations for such diagnostic cutoff difficult at present.[105]

It became evident in our analysis that some populations have not been sufficiently characterized with regard to their PEW. This pertains to Tx patients, AKI, and pediatric CKD. PEW may have not received sufficient attention in the Tx literature, as only two eligible studies were identified in our searches.[10,17] In a side-by-side comparison, it has been noted that the burden of PEW features in Tx patients is similar to that of nondialysis CKD patients with similar eGFR.[106] Our results, if any, may support this contention, as the prevalence estimates of the two identified Tx studies (28% and 52%) are not dissimilar to those of nondialysis CKD (11% to 54%). However, the scarcity of data precludes any strong conclusion and suggests the need of further characterization of the PEW status in this population. It is possible that differences in health systems or clinical approaches to transplant recipients and other factors such as racial or cultural differences may impact at this level. Nonetheless, PEW features alike in other CKD patient populations, also impact on the outcome of Tx patients, such as mortality risk and allograft rejection,[11] presence of anemia,[107] risk of depression,[108] and poor quality of life.[109]

Although several lines of evidence suggest that features of PEW exist in the pediatric CKD population, this syndrome seems to be less well characterized in children, and our study could not identify any eligible report. As discussed elsewhere,[110] characterizing PEW in children is challenging, and existing studies are biased by their small sample size as well as inclusion of patients with generally early forms of CKD (where PEW is seldom encountered).[111] Nonetheless, indicators of PEW tend to increase with decreasing GFR in CKD children, such as hypoalbuminemia and poor appetite.[112] It is possible that factors such as short stature and poor growth may be more relevant manifestations of PEW in children with CKD.[112] As in adults, PEW surrogates are important outcome predictors in CKD children, such as low serum albumin,[113] low body mass index,[114,115] or growth failure.[116]

Finally, we recognize that evaluating nutritional status is particularly difficult in AKI patients, with no single nutritional tool credited with enough sensitivity and specificity in this clinical context, similar to critically ill patients in general. Studies identified in our search used SGA, which, as an intrinsic limitation, cannot be used for repeated evaluations at short intervals of time; thus, its use is not to be recommended for monitoring short-term changes in nutritional status or to evaluate the immediate effects of nutritional support. Based on currently available evidence, PEW seems to be a frequent problem in AKI (60-82% PEW prevalence observed[18,19]). Complementing these estimates, additional reports were excluded from our analysis but ought to be mentioned for contextualization;

an Italian study reported severe malnutrition (SGA score C) in 36.8% of AKI patients not requiring renal replacement therapy and in 47.4% of AKI patients requiring renal replacement therapy.[117] Furthermore, 32.2% of consecutive cases of mechanically ventilated patients with AKI were severely malnourished.[118] PEW has adverse consequences in these patients, as the length of hospital stay, the risk of complications (sepsis, bleeding, arrhythmia, respiratory failure, and so forth), and in-hospital mortality risk significantly increased in AKI patients with PEW compared with AKI patients without PEW.[119]

Our study has additional limitations that need consideration, starting with the fact that the quality of our estimates depends on the evidence available to analyze. We find it unlikely that we may have missed studies so different from the included ones that would alter our conclusions. We recognize that both SGA and MIS are imperfect measures of PEW and more so in children and AKI. The lack of gold-standard methods to diagnose a complex syndrome such as PEW precludes making definitive conclusions on this issue. We restricted our search to these two methods of nutritional assessment to allow comparison across studies; otherwise, PEW prevalence varies considerably depending on the assessment tools and cutoffs used.[29]

Clinically, we believe that our results are relevant to raise awareness on the importance of PEW for CKD patients, relatives, and health-care professionals; motivate the development of effective programs to implement PEW screening, planning, and monitoring in health-care centers; and justify the prioritization of this common complication in terms of resource allocation and utilization. From a research point of view, our findings also have implications with regard to required sample sizes in prospective studies or detectable effect sizes in retrospective studies or for secondary analyses of existing data. With the exception of Australia, no geographic region has a narrow range of plausible PEW prevalence conditional on the characteristics explored in our meta-regression analysis. Therefore, the entire range of historically observed and reported prevalence rates for a specific region/country should be considered when planning for a study in any of the included regions.

By providing evidence-based estimates from contemporary studies, we conclude that PEW is an unacceptably prevalent complication across the spectrum of acute kidney disease as well as CKDs. This commonness of PEW deserves increased medical attention. Establishing proper PEW screening tools is an important starting point for improving PEW care. Nutritional assessment, by means of widely available questionnaires, SGA, or MIS requires minimal resources. However, strategies to tackle PEW and subsequently integrating them into daily clinical routines demand organizational issues that need to be ranked higher in the list of clinical priorities for these patients. Ultimately, these results also highlight the need for well-designed intervention studies targeting PEW for improving clinical outcomes of these patients.

Practical Application

This meta-analysis of PEW prevalence in patients with kidney disease provides evidence-based estimates than illustrating the commonness of this syndrome in patients at all stages of disease severity. This information is useful for health-care planning, allocation of resources, and for the design of future interventions.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2018.08.006.

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