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Prevalence and risk of protein-energy wasting assessed by subjective global assessment in older adults with advanced chronic kidney disease: results from the EQUAL study

Objectives: Prevalence and risk factors for protein energy wasting (PEW) are poorly studied in the non-dialysis, older population with advanced chronic kidney disease (CKD). Our aim was to evaluate the prevalence of PEW in advanced stage CKD patients above 65 years of age. Further, we aimed to describe risk factors for PEW in the overall study population and among obese individuals.

Design: Prospective observational cohort study.

Methods: The EQUAL study, a European Quality Study on treatment in advanced chronic kidney disease, is a multicenter prospective observational cohort study in six European countries. We included patients aged >65 years with incident glomerular filtration rate <20mL/min/1.73m2 not on dialysis attending nephrology care. PEW was assessed by 7-point Subjective Global Assessment (7-p SGA).

Results: In general, the study cohort (n=1334) was overweight (mean body mass index (BMI) 28.4 kg/m²). The majority of the patients had a normal nutritional status (SGA 6-7), 26% had moderate PEW (SGA 3-5) and less than 1% had severe PEW (SGA 1-2). Muscle wasting and loss of fat tissue were the most frequent alterations according to the SGA subscales, especially in those >80 years of age. The prevalence of PEW was higher among women, increased with age, and was higher in those with depression/dementia. PEW was most common in those with underweight (BMI <22 kg/m²); 55%) or normal weight (BMI 22-25 kg/m²); 40%). In obese individuals (BMI >30 kg/m²), 25% were diagnosed with protein wasting. Risk factors for SGA≤5 in obese people were similar to those for the overall study population.

Conclusion: This European multicentre study shows that the prevalence of PEW is high in patients with advanced CKD above 65 years of age. The risk of PEW increases substantially with age and is commonly characterized by muscle wasting. Our study suggests that focus on nutrition should start early in the follow-up of older adults with CKD.

Keywords: Chronic kidney disease, malnutrition, protein-energy-wasting, obesity, elderly, 7 point SGA

Introduction

About one third of European older adults admitted to hospitals are classified as malnourished. Even more of them are at risk of malnutrition [1-3]. Malnutrition is associated with several negative outcomes, such as declined functional ability, frailty, falls, prolonged length of stay in hospital, and mortality [4,5]. Many of these patients also have chronic kidney disease (CKD), as this is a frequent condition in the older population with a prevalence approaching 30% in those above 75 years of age [6,7].

Nutritional problems in CKD are even more complex than in the general population and have many different components. Inadequate nutrient intake, along with factors, such as inflammation, acidosis, and endocrine disorders, leads to increased net breakdown of protein or fat. This is well described in the literature [8-12] and categorized as protein-energy wasting (PEW). The concept of PEW should be discriminated from malnutrition in general. The International Society of Renal Nutrition and Metabolism (ISRNM) suggests the following diagnostic criteria for PEW, of which at least three out of four categories should be documented: biochemical markers in the low range (albumin /pre-albumin/cholesterol), low body weight and/or reduced total body fat or weight loss, decrease in muscle mass, and unintentional low protein or energy intake [10].

The process of nutritional screening and assessment varies in different settings. The Mini Nutritional Assessment tool (MNA) is recommended in older adults without CKD as the basis for nutritional screening[1]. The Subjective Global Assessment (SGA) tool uses the history of the patient as well as a physical examination and was originally created by Detsky, Baker et al [13,14]. It was later expanded to the 7-p scale to rate the severity of malnutrition[15-17]. The ISRNM recommends the SGA in CKD 3-5 patients as one tool to diagnose PEW[10]. It has been widely used in the dialysis population for decades and shows both low intra and inter-observer variability and a good prognostic ability[18,19].

PEW has been associated to increased mortality in CKD patients starting dialysis[11]. A systematic review and meta-analysis [20] concluded that while being underweight is associated with a higher risk of death, being overweight or obese (BMI 25-35 kg/m²) is associated with a lower risk of death in CKD stages 3-5. This is often referred to as the obesity paradox. However, obese patients with protein wasting have the same increased risk of death as those not obese[21]. Recent data suggest that the association between obesity and outcome in dialysis patients is confounded by inflammation[22].

Whereas the prevalence of PEW is well described in patients starting or maintaining dialysis[12,23] there are only a limited number of studies in CKD non-dialysis patients [24-29]. None of these studies had a clear focus on the elderly most vulnerable patients, and most of them were single-centre studies.

We studied a large European inception cohort of patients ≥65 years with stage 4-5 CKD not on dialysis to examine the prevalence and risk factors of PEW assessed by the 7 point SGA method. Further, we aimed to describe the association between PEW and obesity in relation to the patients' baseline characteristics.

Methods

Study design and population

The EQUAL study is an international observational multicentre prospective cohort study [30]. Stage 4-5 CKD patients not on dialysis from 121 nephrology clinics in six European countries (Germany, Italy, Netherland, Poland, Sweden, United Kingdom) were included consecutively between 2012 and 2016. For detailed information regarding the process of study centre and patient selection see **Supplement**. The inclusion criteria were: older adults (≥65 years) with incident estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73m² estimated by the

Modification of Diet in Renal Disease equation (MDRD) [31] who attended a nephrology clinic. The patients were included within six months of their first eGFR in secondary care below the pre-specified limit for inclusion. Patients were excluded if the drop in eGFR resulted from an acute event or if they had received dialysis or a kidney transplant previously. The EQUAL cohort used for the purpose of this analysis includes 1440 patients recruited during the first phase of the study. Data collected at baseline included routine blood and urine biochemistry, demographics, primary renal disease, comorbidities, medication, uremic signs and symptoms (patient questionnaire data) and anthropometry.

Protein-energy wasting

The 7-point SGA tool assessed nutritional status. To ensure good quality and reproducibility, all centres participating in the EQUAL study were offered on-site or group training of the SGA. The SGA method is described in more detail in the **Supplement**. In short, it is a tool assessing the patients' nutritional status based on features from the past six months and a physical examination. It is composed of four domains: history of weight change, history of dietary intake and gastrointestinal symptoms, and a physical examination for loss of fat mass and muscle wasting. Each subscale, and the overall assessment, is scored from 1-7 where score 6-7 corresponds to normal nutritional status, 3-5 to moderate malnourishment and 1-2 to severe malnutrition. For the purpose of the study, an overall SGA score ≤ 5 weas considered as an indication of PEW.

Measures

The primary renal diagnoses assigned by the treating nephrologist were divided into six categories (glomerular disease, tubulointerstitial disease/hereditary, diabetes, hypertension/atherosclerosis, miscellaneous and unknown). The history of all the patients' comorbidities were summarized into the Charlson comorbidity index [32]. Height and weight were measured to compute body mass index (BMI). According to the European Society of

Clinical Nutrition and Metabolism´s (ESPEN) consensus statement for malnutrition in older adults, a BMI < 22 kg/m² was categorized as low body weight [33], BMI 25-29.9 kg/m^2 was considered overweight and BMI ≥30 kg/m² obesity [34]. Waist circumference was measured with a measuring tape, horizontally at the level of umbilical line, after the patients' exhaled. We used the WHO classification of abdominal obesity (102 cm for men and 88 cm for women) also for those with Asian ethnicity (2%) [35]. The 24-hour creatinine and urea clearance were calculated from the 24 hour urinary collection. The protein intake (PCR) was estimated by the Maroni formula[36]

*PCR=Urea nitrogen excretion (g) + 0.031*bodyweight * 6.25*

and the normalized PCR (nPCR) was computed by dividing the PCR with the patients' ideal body weight ((BMI=23 kg/m^2)* height^2). Late referral was defined as seeing a nephrologist less than three months prior to inclusion into the study. All patients were treated by their nephrologists according to their standard protocol in each country. All the participants gave their written informed consent before inclusion. The EQUAL-study was approved by the Ethical Committees in each country.

Statistics

Continuous variables at baseline were described as means (standard deviation, SD) and medians (interquartile range, IQR) according to their underlying distribution while categorical variables were described as percentages (%). Descriptive statistics were presented by SGA category (SGA score 6-7 versus score ≤5) and BMI, first for the overall SGA score and then by the four SGA subscales. Comparisons between the groups were made by non-parametric tests (Kruskall Wallis equality of populations rank test). The correlation between 7-point SGA and biochemical markers of PEW was further assessed by the Spearman's correlation coefficient. Furthermore, we used logistic regression to estimate the crude odds ratios (OR)

and 95% confidence intervals (CI) of all relevant clinical variables that are associated with a low (≤5) versus normal (6-7) SGA at baseline. Finally, we computed the age and sex-adjusted ORs. Diabetes and country were additionally adjusted for BMI. In a sub-analysis we further restricted the comparisons between the SGA-groups to those patients with body obesity, i.e. BMI ≥30 kg/m^2. As a sensitivity analysis we repeated the analyses assuming that observations may not be independent within country by using the Stata vce (cluster, clustvar) command. All analyses were performed by Stata12 (StataCorp).

Results

Protein-energy wasting

In total, 1334 patients were included in the analysis. We excluded 110 patients because of missing SGA at baseline. Baseline characteristics are presented in **Table 1**. The median age was 76 years (IQR; 70.6-81.2), 65.5% were male, and the median eGFR was 18.2 ml/min/1.73 m² (IQR; 14.8-21.4). The overall SGA score indicated that most patients had a normal nutritional status (SGA 6-7), 26 % of the patients were moderately malnourished (SGA 3-5) and less than 1% had severe malnutrition (SGA 1-2) (**Table 1**). The SGA subscales showed that 278 (20.8%) patients had experienced recent weight loss, 312 (23.4%) had inadequate food intake and/or gastrointestinal symptoms, 375 (28.1%) had signs of subcutaneous fat loss and 451 (33.8%) had signs of muscle wasting.

Table 2 illustrates the demographics in patients with normal SGA, and overall SGA and muscle wasting subscale <5. Generally, a muscle wasting score <5 was more often present than an overall SGA <5. Both PEW and muscle wasting were increasingly more common among the oldest (36% in those $80 years). In patients with a diagnosis of depression or dementia, almost 60% were diagnosed with PEW.

Table 3 shows the characteristics of the patients according to PEW as indicated by an overall SGA score ≤5. Patients who were classified with PEW had significantly lower BMI, waist circumference, plasma albumin, plasma sodium, haemoglobin, 24-hour creatinine and urea clearance. Patients with PEW also had lower nPCR compared to those without PEW. Overall, the correlation coefficients between 7-point SGA and the biochemical markers for PEW were low but statistically significant. Creatinine and urea clearance, BMI, waist circumference and protein intake had the strongest correlation with 7-point SGA (**Table S1).**

Table 4 illustrates age and sex-adjusted risk factors for PEW. The risk of PEW increased with age, starting already for patients over 70, but was most prominent among the oldest> 80 years (OR 1.87 95% CI 1.33-2.63). Female gender was significantly associated with an increased risk of PEW (OR 1.32 95% CI 1.03-1.69). The prevalence and distribution of abnormal SGA subscales by age category are presented in **Figure 1.** Muscle wasting and loss of fat tissue were the subscales with the largest changes, and the Odds Ratios increased with age (in patients >80 years the OR [muscle wasting] was 2.13 (95% CI 1.53-2.97) and OR [subcutaneous fat loss] 2.53 (95% CI 1.77-3.61 compared with those 65-69.9 years). (**Supplemental Table 2-5**).

The comorbidity burden based on the Charlson comorbidity index did not increase the risk of PEW, while late referral (<1 year before inclusion) showed a borderline statistically significant association with PEW. A history of psychiatric disease (i.e. depression/dementia) had the strongest association with PEW (OR 3.72; 95% CI 2.33-5.95). Furthermore, the risk of PEW somewhat increased in many other comorbid conditions (chronic pulmonary disease, cerebrovascular disease, heart failure, peripheral arterial disease, cancer) but these results did not reach statistical significance. The relationship between diabetes and PEW was confounded by BMI and showed no association in the adjusted model. There were some differences in the risk of PEW between the different countries. In the adjusted models, patients from the

Netherlands, Sweden and Germany had a lower risk of PEW compared to the United Kingdom. The sensitivity analyses showed no significant change in the risk of PEW associated with the various characteristics after clustering for country.

Body and abdominal obesity

Overall, the study cohort was overweight with a mean BMI 28.4 kg/m² and mean waist circumference of 105.8 cm (men), and 100.3 cm (women). According to WHO standards, 435 (34 %) patients were obese, 469 (37%) were overweight and 110 (9 %) were underweight (BMI <22 kg/m²) according to ESPEN recommendations for cut-off values for older persons (>70 years) [33]. Women were more often obese and underweight than men. (**Table S6**). People >80 years were more often underweight, and less often obese. Most patients from Germany and United Kingdom were obese (44% and 43% respectively). In Italy, the Netherlands, Poland and Sweden most patients were overweight. The normalized protein intake increased with increasing BMI and was significantly higher among obese (1.08 g/kg) compared with underweight (0.71g/kg) individuals. As expected, SGA≤5 occurred most frequently in people with BMI <22 kg/m^2 (**Figure 2**). In this group almost everyone had both loss of subcutaneous fat and muscle wasting according to the SGA subscales. On the contrary, in overweight and obese people (both body and abdominal obesity) protein wasting was most common (25%) whereas15% of those with body obesity had both weight loss/loss of subcutaneous fat and muscle wasting according to the SGA subscales. .

The proportion of people with abdominal obesity was almost twice as high (65.9 %) as compared to body obesity. More women were classified with abdominal obesity (78.5%) compared with men (59.4%). Most of the patients classified with abdominal obesity also had body obesity (50.7 %), but a smaller number of those with normal and low BMI also fulfilled the criteria for abdominal obesity (**Table S6**). The analyses restricted to patients with body obesity showed similar associations between biochemical markers of PEW and 7p-SGA

(**Table S7**). Also, the risk factors for an overallSGA score ≤5, and for protein wasting (muscle wasting subscale) among the obese patients were similar to those for the cohort in general (**Table S8**).

Discussion

This study on prevalence of PEW in older European patients with advanced stage CKD shows that one out of four had signs of moderate malnutrition. The risk of PEW increased with age and was also more common among women and those with a history of psychiatric disease. Whereas obesity was common, its prevalence decreased with age. We additionally confirm that the prevalence of protein wasting was high (i.e. obese sarcopenia) among obese and overweight CKD patients[37].

A few previous studies have examined the prevalence of PEW using 7p-SGA in CKD populations[26,29]. In the largest study to date (n=922) from Brazil [26] the prevalence of PEW was estimated to be 11% (13% in CKD 4-5). The majority of the patients had a higher eGFR and were younger than the patients in the present study. In accordance with the current study, those with a SGA ≤5 were older and less often had diabetes as comorbid condition. In contrast, the study by Cuppari et al [26] found no association between gender and PEW. Another recent European study by Westland et al [29] also showed a PEW prevalence of 11% and an association between age and PEW in patients recently referred to nephrology care. As in our study, women had a higher risk of PEW. Westland et al [29] further reported that 16/43 patients (37%) with moderate PEW had a BMI >25 kg/m².

In our inception cohort, eGFR at baseline was not associated with PEW as the first drop of eGFR ≤20 ml/min/1.73m² was an inclusion criterion and therefore all patients had approximately the same eGFR at baseline. However, extensive evidence indicates that

nutritional status deteriorates as renal function declines [38]. We report that the oldest patients (>80 years) are especially vulnerable with a higher risk of developing PEW, also in the presence of body obesity. One limitation of our study is that we did not include a control group and thus were unable to explore to what extent the increased odds of PEW among the oldest patients is contributed by CKD or part of normal aging. In our cohort anyway, BMI decreased with age. This is opposed to the general EU population, where older adults, although generally at higher risk of malnutrition, still show an increasing BMI with age [39]. This is supportive of the hypothesis that in older adults the uremic milieu accelerates the process of fat, muscle mass and renal function decline observed in healthy aging[40].

In studies of CKD 5 patients, SGA has correlated well with anthropometric measures, laboratory features of malnutrition, and survival[24,41]. We overall found significant correlations, although small in absolute terms, between SGA and nutritional markers such as plasma albumin, creatinine appearance, urea appearance and body weight. There was also a significant correlation between lower plasma sodium and PEW. This may be related to the slightly higher prevalence of heart failure among patients with PEW. Other factors such as more frequent over-hydration or a shift of fluid between the intracellular and extracellular compartment (as has been demonstrated in malnourished haemodialysis patients[42]) are other possible explanations. Importantly, whereas energy wasting was a more common in patients with low BMI, muscle or protein wasting was more common among those with overweight, body obesity and abdominal obesity. In patients initiating dialysis, muscle mass and muscle strength are important prognostic factors to predict negative outcome[43-46]. Although obese patients in general have better survival in dialysis, the survival benefit does not include obese patients with protein wasting[21]. This accords with the finding that persistent inflammation (a common finding in PEW) modifies the association between obesity and outcome[22].

We report that the risk of PEW was associated with other comorbidities, although we did not incorporate the severity of the diseases and we therefore were unable to allocate extra weight to certain comorbid conditions. As seen in the Brazilian cohort[26], which included earlier stages of CKD, patients with diabetes had a lower risk of PEW. However, the majority of the patients in our cohort had diabetes type 2, which is more common in overweight or obese people. When adjusting for BMI, we found no association between diabetes and PEW. Previous studies have indicated that diabetic haemodialysis patients have increased muscle breakdown compared to non-diabetic patients on haemodialysis [47], higher risk of loss of lean body mass [48] and more often PEW [49]. This apparent discordance in the risk of PEW in non-dialysis and dialysis patients may indicate that diabetic patients are especially prone to wasting after dialysis is initiated. However, different methods to assess PEW were used in studies before and after dialysis[26,29,47-49] which may have affected the results.

Among the other comorbidities, a diagnosis of depression/dementia was the most important risk factor. Depression and cognitive dysfunction have been linked to nutritional problems in the elderly population in general[50-52]. However, the importance of mental health in relation to nutritional status may be even more significant in older patients with CKD, as shown in our present study. Furthermore, it is a modifiable factor, often possible to treat[53].

The present study has several strengths. First, we included older individuals from many different EU-countries, making our study the largest to evaluate the prevalence of PEW in CKD-patients so far. The large variation in previously published prevalences studies may be due to variation in both the incidence of CKD, prevalence of obesity, and referral pattern of older adults across the world[54]. Our study further has the advantage of including incident patients (who for the first time passed a pre-specified eGFR level), which decreased the risk that prevalent survivors biased our estimates. The 7p-SGA was evaluated against other nutritional measures with good correlation, and the assessment was performed by trained

nurses or dieticians at each clinic. Although not all nurses/dieticians performing the evaluation were trained by the same person, the training followed the same instructional program. However, small differences in how the training was formed may have affected the results, in particular between countries. One limitation is that the generalizability of our results may have been affected by the way patients were recruited. As in all studies, but specifically those focusing on geriatric patients, there is the risk that those with a higher co-morbidity burden and more severe illness decline participation. For our results it means that, in reality, the prevalence of PEW could even be higher in older CKD individuals than we describe here. It might also be that motivated people with significant comorbidity were more likely to take part and that those individuals are different compared to those without significant comorbidity. This may then explain the relatively small difference in SGA between patients with high comorbidity burden versus low.

In summary, this European multicentre study of older patients with incident CKD shows that the overall prevalence of PEW is 26%, and it increases with age (36% in those >80 years). PEW is most commonly indicated by loss of muscle mass, and is more common in women. Whereas one third of the patients were obese, almost 25% of the obese had concomitant signs of protein wasting; i.e. obese sarcopenia. We conclude that monitoring for PEW is important in patients with advanced CKD, especially in the very elderly, in women and in patients with a psychiatric disease. Further research is needed to study if interventions directed towards the elderly will improve the nutritional status and decrease the risk of developing PEW.

Practical application

This European, multicentre study reports that the prevalence of protein-energy wasting (PEW) is 26% in older adults with chronic kidney disease (CKD 4-5) not on dialysis. Patients especially at risk are elderly (>80 years), women and those with psychiatric disease. Protein wasting was common (25%) among the obese; i e obese sarcopenia. We conclude that it is very important to detect early signs of PEW in older adults with CKD, and further research is needed to study interventions directed specific towards elderly.

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Table 1. Baseline characteristics

Demographics	
Age, years, median (IQR)	76.0 (70.6-81.2)
Men, n (%)	874 (65.5)
Country, n (%)	
Germany	115 (8.6)
Italy	297 (22.3)
Netherlands	124 (9.2)
Poland	17 (1.3)
Sweden	300 (22.5)
United Kingdom	481 (36.1)
Primary renal diagnosis, n (%)	
Glomerular disease	113 (8.5)
Tubulointerstitial disease + hereditary	155 (11.6)
Diabetes	271 (20.3)
Hypertension/atherosclerosis	496 (37.2)
Miscellaneous	48 (3.6)
Unknown	194 (14.5)
Missing	57 (4.3)
Laboratory data, median (IQR)	
eGFR mL/min/1.73 m² [n=1327]	18.2 (14.8 – 21.4)
Systolic blood pressure, mmHg [n=1322]	140 (130-157)
Diastolic blood pressure mmHg [n=1322]	72 (66-80)
Nutritional and anthropometric data Mean (SD)	
BMI [n=1268]	28.4 (5.5)
<22 kg/m^2	110 (8.7)
22-24.9 kg/m^2	254 (20.0)
25-29.9 kg/m^2	469 (37.0)
≥30 kg/m^2	435 (34.3)

Waist circumference, cm, Men [n=791]	105.8 (13.2)
Waist circumference, cm, Women [n=409]	100.3 (15.4)
Abdominal obesity	791 (65.9)
SGA mean score (SD)	5.9 (1.02)
SGA 6-7, n (%)	943 (65.4)
SGA 3-5, n (%)	380 (26.3)
SGA 1-2, n (%)	13 (0,9)
Weight loss, n (%)	278 (20.8)
GI symptoms/inadequate intake, n (%)	312 (23.4)
Loss of subcutaneous fat, n (%)	375 (28.1)
Muscle wasting, n (%)	451 (33.8)
Daily protein intake (g/kg) [n=548]	0.91 (0.71-1.13)
Comorbidity, n (%)	
Charlson index, median (IQR) [n=1330]	4.0 (3-6)
Stroke/TIA	198 (14.8)
Heart failure	228 (17.1)
Myocardial infarction/angina	425 (31.9)
Peripheral arterial disease	213 (16.0)
Depression/Dementia	80 (6.0)
Diabetes (type 2; n=514)	539 (40.4)
Asthma/COPD	176 (13.2)
Systemic inflammatory disease	47 (3.5)
Referral, n (%) [1334]	
> 5 years before inclusion	327 (24.5)
>1-5 years before inclusion	518 (38.8)
1 year or less before inclusion	483 (36.2)

Continuous variables presented as median (IQR; interquartile range), Categorical variables presented as percentages (%); BMI (body mass index), SGA (Subjective global assessment), GI (gastrointestinal), TIA (transitory ischemic attack), COPD (chronic obstructive pulmonary disease), eGFR (estimated glomerular filtration rate), SD (standard deviation)

Table 2. Characteristics by presence of SGA ≤5 overall and for the muscle wasting subscale

	Overall SGA 6-7 n=943	Overall SGA ≤5 n=391	SGA for muscle wa ≤5 n=451
Age classes			
65-69.9	224 (76.7)	68 (23.3)	75 (25.7)
70-74.9	226 (*72*.0)	88 (28.0)	104 (33.1)
75-79.9	245 (72.3)	94 (27.7)	107 (31.9)
≥80	248 (63.7)	141 (36.3)	165 (42.4)
Men	637 (72.88)	237 (27.12)	273 (31.3)
Women	306 (66.5)	154 (33.5)	178 (38.7)
Country United Kingdom	315 (65.5)	166 (34.5)	177 (35.6)
Sweden	220 (73.3)	80 (26.7)	110 (36.7)
Germany	86 (74.8)	29 (25.2)	31 (27.0)
Italy	210 (70.7)	87 (29.3)	108 (36.5)
Netherlands	102 (82.3)	22 (17.7)	25 (20.2)
Poland	10 (58.8)	7 (41.2)	6 (40.0)
Primary renal disease			
Glomerular disease	74(65.5)	39 (34.5)	42 (37.2)
Tubuloint/ heredity	102 (65.8)	53 (34.2)	63 (40.7)

Hypertension /arteriosclerosis	353 (71.2)	143 (28.8)	170 (34.5))
Diabetes nephropathy	204 (75.3)	67 (24.7)	84 (31.0)
Miscellaneous	35 (72.9)	13 (27.1)	13 (27.1)
Unknown	132 (68.0)	62 (32.0)	63 (32.5)
eGFR (per unit change)	18.1 (14.7-21.2)	18.3 (14.9-22.5)	18.5 (14.9-22.1)
Referral >5 years	236 (72.2)	91 (27.8)	108 (33.0)
1 year – 5 years	383 (73.9)	135 (26.1)	160 (31.0)
< 1 year	319 (66.1)	164 (34.0)	182 (37.8)
Comorbidity			
Diabetes	402 (74.6)	137 (25.4)	170 (31.6)
Myocardial infarction	314 (73.9)	111 (26.1)	133 (31.4)
Peripheral arterial disease	143 (67.1)	70 (32.9)	76 (35.9)
Pulmonary Disease	113 (64.2)	63 (35.8)	62 (35.4)
Cerebrovascular disease	134 (67.7)	64 (32.3)	77 (38.9)
Heart failure	156 (68.4)	72 (31.6)	90 (39.5)
Depression/ dementia	33 (41.2)	47 (58.8)	40 (50.0)
Cancer	184 (68.4)	85 (31.6)	
Charlson	4.0 (3-6)	4.0 (3-6)	4.0 (3-6)

Comorbidity score			
nPCR (g/kg/bodyweight)	0.96 (0.75-1.16)	0.78 (0.61-0.97)	0.80 (0.63-1.06)

Categorical variables are expressed as number (n) and percentage (%). Continous variables are expressed as median (Interquartile range)

Table 3. Associations between 7-point SGA and biochemical and clinical markers

	SGA 6-7 n=943	SGA ≤5 n=391	p value
BMI kg/m², mean (SD) [n=1268]	29.1 (5.3)	26.5 (5.3)	<0.001
Waist circumference cm, mean (SD) [n=1200]	105.8 (14.0)	99.4 (13.9)	<0.001
GFR, mean (SD) ml/min/1.73 m²	18.1 (5.6)	18.3 (6.1)	0.39
Hemoglobin g/dl [n=1316]	11.5 (1.6)	11.3 (1.7)	0.01
Sodium mmol/L [n=1308]	140.3 (3.2)	139.5 (3.5)	<0.001
Potassium mmol/L [n=1322]	4.6 (0.6)	4.6 (0.6)	0.25
Calcium mmol/L [n=1289]	2.3 (0.2)	2.3(0.3)	0.55
Phosphate mmol/L [n=1270]	1.3 (0.3)	1.3 (0.4)	0.29
Urea mmol/L [n=1294]	20.4 (7.8)	20.8 (9.7)	0.88
Albumin g/L [n=1223]	38.0 (5.6)	36.2 (6.7)	<0.001
Cholesterol mmol/L [n=1029]	4.5 (1.2)	4.5 (1.3)	0.71
PTH pmol/L, median (IQR) [n=1101]	13.1 (5.5-21.6)	13.6 (5.6-23.7)	0.50
Standardbicarbonate mmol/l [n=989]	23.1 (3.8)	23.1 (4.3)	0.75
U-Creatinine appearance mmol/24h [n=633]	9.4 (4.9)	8.12 (5.8)	<0.001
U-Urea appearance mmol/24h [n=558]	285.1 (170.1)	231.9 (134.4)	<0.001

BMI (body mass index), SGA (Subjective global assessment), GFR (glomerular filtration rate), SD (standard deviation), PTH (parathyroid hormone) nPCR (normalized protein catabolic rate) IQR (interquartile range).

Table 4. Risk factors for protein-energy wasting assessed by 7p SGA overall score

	Unadjusted Odds Ratio for PEW	Adjusted Odds Ratio* for PEW	P-value
Age classes, n (%)			
65-69.9	1.00	1.00	
70-74.9	1.28 (0.89-1.85)	1.28 (0.89-1.85)	0.17
75-79.9	1.26 (0.88-1.81)	1.26 (0.88-1.81)	0.22
≥80	1.87 (1.33-2.63)	1.87 (1.33-2.63)	<0.001
Men, n (%)		1.00	
Women	1.35 (1.06-1.73)	1.32 (1.03-1.69)	0.03
Country United Kingdom		1.00	
Sweden	0.69 (0.50-0.95)	0.64 (0.45-0.89)	0.001
Germany	0.64 (0.40-1.01)	0.67 (0.42-1.09)	0.11
Italy	0.79 (0.58-1.07)	0.66 (0.47-0.92)	0.02
Netherlands	0.41 (0.25-0.67)	0.37 (0.21-0.64)	<0.001
Poland	1.33 (0.50-3.56)	1.17 (0.42-3.23)	0.76
Primary renal disease			
Glomerular disease		1.00	
Tubuloint/ heredity	0.99 (0.59-1.64)	0.95 (0.57-1.60)	0.86

Hypertension /arteriosclerosis	0.77 (0.50-1.19)	0.67 (0.43-1.04)	0.07
Diabetes nephropathy	0.62 (0.39-1.00)	0.61 (0.38-0.99)	0.05
Miscellaneous	0.70 (0.33-1.49)	0.68 (0.32-1.44)	0.32
Unknown	0.89 (0.54-1.46)	0.76 (0.46-1.26)	0.29
eGFR (per unit change)	1.01 (0.99-1.03)	1.00 (0.98-1.03)	0.59
Referral >5 years	1.00		
1 year – 5 years	0.91 (0.67-1.29)	0.91 (0.66-1.24)	0.53
< 1 year	1.33 (0.98- 1.81)	1.29 (0.95-1.76)	0.10
Comorbidity			
Diabetes	0.72 (0.56-0.92)[#]	1.02 (0.78-1.34)	0.90
Myocardial infarction	0.79 (0.61-1.02)	0.79 (0.60-1.02)	0.07
Peripheral arterial disease	1.21 (0.89-1.67)	1.25 (0.91-1.72)	0.17
Pulmonary Disease	1.41 (1.00-1.96)	1.38 (0.98-1.93)	0.06
Cerebrovascular disease	1.18 (0.85-1.63)	1.17 (0.84-1.62)	0.36
Heart failure	1.13 (0.83-1.54)	1.11 (0.81-1.52)	0.50

Depression/ dementia	3.76 (2.37-5.98)	3.7 (2.33-5.95)	<0.001
Cancer	1.14 (0.85-1.52)	1.17 (0.87-1.57)	0.66
Charlson Comorbidity score per unit increase in score	1.01 (0.92-1.11)	1.00 (0.95-1.88)	0.997
nPCR (g/kg/bodyweight) per 0.1g/kg increase	0.89 (0.83-0.94)	0.89 (0.84-0.95)	<0.001

*Adjusted for age and sex. Country and Diabetes comorbidity were additionally adjusted for body mass index.

OR (Odds Ratio), CI (Confidence interval), eGFR (estimated glomerular filtration rate by MDRD equation)

FIGURE LEGENDS

Figure 1. Prevalence and distribution of SGA subscales according to age-classes

Figure 2. Prevalence and distribution of overall protein-energy wasting and its different components (SGA subscales)