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Original article

Malnutrition according to GLIM criteria in stable renal transplant recipients: Reduced muscle mass as predominant phenotypic criterion

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SUMMARY

Background & aims: Malnutrition has a negative impact on quality of life and survival in renal transplant recipients (RTR). Therefore, malnutrition detection is important in RTR, but this may be hampered by concomitant presence of weight gain and overweight. Recently, the Global Leadership Initiative on Malnutrition (GLIM) developed a set of diagnostic criteria for malnutrition. We aimed to assess the prevalence of malnutrition according to the GLIM criteria and the distribution of phenotypic criteria in RTR. Additionally, we examined the potential value of 24-h urinary creatinine excretion rate (CER) as alternative measure for the criterion reduced muscle mass.

Methods: We used data from stable outpatient RTR included in the TransplantLines Cohort and Biobank Study (NCT02811835). Presence of weight loss and reduced intake or assimilation were derived from Patient-Generated Subjective Global Assessment (PG-SGA) item scores. Reduced muscle mass was assessed by multi-frequency bio-electrical impedance analysis (MF-BIA) and defined as an appendicular skeletal muscle mass index (ASMI) < 7 kg/m^2 for men and <5.5 kg/m^2 for women, and in additional analysis defined as creatinine-height index (CHI, based on 24 h urine CER) < 80%. Inflammation was present if C-reactive protein (CRP) was >5 mg/L. Malnutrition was defined as presence of at least one phenotypic (weight loss and/or low BMI and/or reduced muscle mass) and one etiologic criterion (reduced intake/assimilation and/or disease burden/inflammation).

Results: We included 599 RTR (55 ± 13 years old, 62% male, BMI 27.2 ± 4.7 kg/m^2) at a median of 3.1 years after transplantation. According to GLIM criteria, 14% was malnourished, of which 91% met the phenotypic criterion for reduced muscle mass. Similar results were found by using CHI as measure for muscle mass (13% malnutrition of which 79% with reduced muscle mass).

Conclusions: Malnutrition is present in one in 7 stable RTR, with reduced muscle mass as the predominant phenotypic criterion. Assessment of nutritional status, most importantly muscle status, is warranted in routine care, to prevent malnutrition in RTR from remaining undetected and untreated. The diagnostic value of 24-h urinary CER in this regard requires further investigation.

1. Introduction

Renal transplantation is considered the treatment of choice for patients with end-stage renal disease, resulting in a better quality of life (QoL) and survival compared with dialysis treatment [1–3]. However, QoL is still lower and long-term outcomes are worse in renal transplant recipients (RTR) compared with the general population [3,4]. Post-transplant weight gain and obesity are well-known and common health problems, related to transplant-specific factors such as cessation of dietary restrictions [5,6], side effects of prednisolone [5] and low physical activity levels [7], and are associated with adverse long-term outcomes in RTR [8–12]. However, less attention is paid to the, possibly concomitant, high risk of malnutrition. Several transplant-related factors increase the malnutrition

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Abbreviations

GLIM	Global Leadership Initiative on Malnutrition
QoL	quality of life
RTR	renal transplant recipients
MUST	Malnutrition Universal Screening Tool
DEXA	dual energy X-ray absorptiometry
BIA	bio-electrical impedance analysis
CT	computed tomography
MRI	magnetic resonance imaging
CER	creatinine excretion rate
PG-SGA	Patient-Generated Subjective Global Assessment
eGFR	estimated glomerular filtration rate
TSAT	transferrin saturation
CRP	C-reactive protein
ASM	appendicular skeletal muscle mass
ASMI	appendicular skeletal muscle mass index
CHI	creatinine-height index
SGA	Subjective Global Assessment
MIS	Malnutrition-Inflammation score

risk in RTR, including the use of immunosuppressive medications, infections, rejection of the graft, insulin resistance and the immune response to the graft [13–15]. Although RTR is an underrepresented population in the scientific literature on malnutrition in chronic kidney disease (CKD) [16], previous research has shown that malnutrition also has a considerable negative impact on QoL and survival in RTR [17,18]. Therefore, malnutrition should not be overlooked in this patient population.

Recently, the Global Leadership Initiative on Malnutrition (GLIM) published updated diagnostic consensus criteria for malnutrition [19]. According to the GLIM consensus, the diagnosis of malnutrition requires the presence of at least one phenotypic and one etiologic criterion. The phenotypic criteria include either weight loss, low Body Mass Index (BMI), or reduced muscle mass, and the etiologic criteria include either reduced food intake or assimilation, or disease burden/inflammation (Table 1). In RTR, the high prevalence of post-transplantation weight gain and obesity [8,11] is accompanied by an altered body composition with an increased fat mass [20] and lower muscle mass [21–23]. Therefore, using low BMI and weight loss alone may lack sensitivity to diagnose malnutrition in RTR, as excess fat mass may obscure underlying depletion of muscle mass. To our knowledge, however, the prevalence of malnutrition according to the GLIM criteria, and the relative contribution of each phenotypic criterion to the diagnosis of malnutrition, has not yet been investigated in this population.

Insight in the distribution of the different malnutrition phenotypes in RTR is important, as this may have implications for the assessment of malnutrition in clinical practice. Most validated malnutrition screening instruments, which are often used as a first step in the detection of malnutrition, include screening for low BMI and weight loss, but do not include screening for low muscle mass [24,25]. Therefore, malnourished RTR with reduced muscle mass as phenotypic criterion may currently remain undetected in this consecutive two-step process of screening and assessment. Furthermore, while standard anthropometric measurements, such as weight and height, are routinely performed at outpatient visits, the assessment of muscle mass, for example with dual energy x-ray absorptiometry (DEXA) or bio-electrical impedance analysis (BIA) as recommended by GLIM, is usually not part of routine care due to practical and time constraints [26]. In several renal transplant care centers, however, 24-h urine samples are routinely collected during outpatient visits, enabling measurement of 24-h urinary creatinine excretion rate (CER), which has shown to be a reliable marker of muscle mass in RTR [21,22]. Therefore, it is worthwhile to explore its potential value for the assessment of reduced muscle mass in diagnosing malnutrition in this population.

The aim of this study was to investigate the prevalence of malnutrition in stable outpatient RTR using the GLIM criteria and to examine the relative contribution of each phenotypic criterion, i.e., weight loss, low BMI and reduced muscle mass, to the diagnosis of malnutrition. Additionally, the prevalence of malnutrition and relative contribution of the phenotypic criterion low muscle mass with use of 24-h CER was examined.

2. Methods

2.1. Study design and population

For this cross-sectional analysis of data from a cohort of RTR, data was extracted from the TransplantLines Biobank of the University Medical Center Groningen (UMCG) (ClinicalTrials.gov Identifier: NCT03272841). Rationale and design of this cohort study has been described previously [27]. In brief, since June 2015, all eligible transplant candidates and transplant recipients were invited to participate in the TransplantLines study. Written informed consent was obtained before inclusion. The Medical Ethical Committee of the UMCG approved the TransplantLines study protocol (METc 2014/077) and all study procedures were performed in line with the principles of the Declaration of Helsinki. For the current study, we included adult RTR (≥18 years) enrolled in the TransplantLines study, with a functioning graft ≥ 1 year after

Table 1
Operationalization of the phenotypic and etiologic criteria for the diagnosis of malnutrition in the current study.

	Phenotypic criteria			Etiologic criteria	
	Weight loss	Low BMI	Reduced muscle mass	Reduced food intake or assimilation	Disease burden/ inflammation
Current study	>5% within the past 6 months based on self-reported weights in PG-SGA Box 1	<20 kg/m^2 if age <70 years, or <22 kg/m^2 if age ≥70 years Asia: <18.5 kg/m^2 if age <70 years, or <20 kg/m^2 if age ≥70 years	ASMI <7 kg/m^2 (men) and <5.5 kg/m^2 (women) Additional analysis: CHI < 80%	PG-SGA Box 2 score ≥ 1 (reduced food intake in the last month) PG-SGA Box 3 score ≥ 1 (≥1 nutrition impact symptom)	1. CRP >5 mg/L 2. All RTR based on chronic disease burden

Abbreviations: ASMI: appendicular skeletal muscle mass index; BMI: Body Mass Index; CHI: creatinine-height index; CRP: C-reactive protein; RTR: renal transplant recipients; PG-SGA: Patient-Generated Subjective Global Assessment.

transplantation and a scheduled study visit between June 2015 and December 2019. Participants with missing data in the variables that are used in the operationalization of the GLIM criteria for malnutrition ($N = 339$) were excluded for analyses.

2.2. Data collection

During the study visits, anthropometric measures and assessment of nutritional status were performed by trained student researchers. Height, weight, waist and hip circumference were assessed using a wall-secured stadiometer, a digital scale, and a retractable measurement tape, respectively. Body composition was assessed using a multi-frequency BIA device (Quadscan 4000, Bodystat, Douglas, British Isles). The Dutch version of the Patient-Generated Subjective Global Assessment (PG-SGA version 3.7 NL, as available on http://www.pt-global.org/) was used to assess nutritional status [28,29]. The PG-SGA is a validated nutrition assessment tool and available in multiple language versions, based on translation and cultural adaptation processes using the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR's) "Principles of Good Practice for the Translation and Cultural Adaptation Process for PRO Measures" [30,31]. The first part of the PG-SGA (PG-SGA Short Form, SF) was completed by the patient and included items on weight history (Box 1), food intake (Box 2), nutrition impact symptoms (Box 3), activities and function (Box 4).

Prior to each TransplantLines study visit, fasted blood samples and 24-h urine samples were collected and analyzed by using standard laboratory procedures. Incomplete 24-h urine samples ($N = 53$), due to missed urine portions, were excluded for the data analysis. The serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) algorithm was used to calculate the estimated glomerular filtration rate (eGFR) [32]. Creatinine clearance in mL/min was calculated by dividing 24-h urinary creatinine excretion (mmol/24 h) by serum creatinine (μmol/L), multiplied by 694 to account for the translation from mL/24-h to mL/minutes. Second, creatinine clearance in mL/min/1.73 m^2 was calculated by multiplying creatinine clearance by 1.73 divided by the body surface area (BSA) according to the formula of du Bois [33]. Proteinuria was defined as a urinary protein excretion $\geq$0.5 g/24 h. Other laboratory measures included for analysis in this study were hemoglobin, ferritin, transferrin saturation (TSAT), C-reactive protein (CRP), and albumin from blood samples, and urea and creatinine excretion from 24-h urine samples. Protein intake in grams per day (g/d) was calculated from 24-h urinary urea excretion using the Maroni-equation [34]. For protein intake in grams per kilogram per day (g/kg/d), in subjects with underweight (BMI < 20 kg/m^2) and obesity (BMI >30 kg/m^2) the body weight corresponding to a BMI of 20 and 27.5 kg/m^2, respectively was used [35,36].

Demographic variables and data on disease history, including the primary renal disease, dialysis treatment, medication and transplant characteristics, were extracted from the UMCG Renal Transplant Database. Other lifestyle parameters, including smoking behavior and alcohol consumption, were based on self-reported validated questionnaires administered during or prior to a TransplantLines study visit [27].

2.3. Diagnosis of malnutrition using the GLIM criteria

Criteria for the diagnosis of malnutrition according to GLIM criteria and operationalization of variables in the current study based on these criteria are shown in Table 1. Malnutrition diagnosis was based on presence of at least one phenotypic criterion (weight loss, low BMI, and/or reduced muscle mass) in combination with at least one etiologic criterion (reduced food intake or assimilation and/or disease burden/inflammation) as indicated by GLIM consensus [19].

2.3.1. Weight loss

The phenotypic criterion for weight loss was defined as weight loss of >5% within past 6 months and based on the self-reported weights in Box 1 of the PG-SGA.

2.3.2. Low BMI

BMI was calculated by dividing measured weight in kilograms by measured height in squared meter. For patients with Caucasian, African or unknown ethnicity, the phenotypic criterion for low BMI was defined as a BMI < 20 kg/m^2 in patients <70 year old and BMI < 22 kg/m2 in patients $\geq$70 year old. For patients with Asian ethnicity, the phenotypic criterion for low BMI was defined as a BMI < 18.5 kg/m^2 in patients <70 year old and BMI < 20 kg/m2 in patients $\geq$70 year old.

2.3.3. Reduced muscle mass

BIA measurements were used to assess muscle mass. Using resistance and reactance measured by BIA, appendicular muscle mass (ASM) was calculated using the formula by Sergi et al. [37]. Appendicular muscle mass index (ASMI, kg/m^2) was calculated by dividing ASM by height in squared meter. The phenotypic criterion for reduced muscle mass was defined as an ASMI < 7 kg/m^2 for men and <5.5 kg/m^2 for women according to GLIM recommendations [19,38].

2.3.4. Reduced food intake or assimilation

Scores on PG-SGA Box 2 and Box 3 were used to assess food intake and assimilation. The etiologic criterion for reduced food intake was defined as either 1) PG-SGA Box 2 score $\geq$ 1, indicating food intake less than usual over the past month, or 2) PG-SGA Box 3 score $\geq$ 1, indicating presence of 1 or multiple nutrition impact symptoms (including gastro-intestinal symptoms, such as dysphagia, nausea, vomiting and diarrhea).

2.3.5. Disease burden/inflammation

As recommended by the GLIM Working Group, CRP was used as a supportive measure for the inflammation criterion [19,39] for which we used a cut-off of >5 mg/L [40]. However, as all RTR are considered to have chronic renal disease with low grade inflammation [41] and therefore inherently meet the disease burden/inflammation criterion as stated in the GLIM consensus [19], we also assessed the prevalence of malnutrition in all RTR.

2.4. Use of 24-h CER in assessment of muscle mass

For the additional analysis using 24-h CER for the operationalization of the reduced muscle mass criterion, the creatinine-height index (CHI) as described by Blackburn et al. [42] was used: CHI (%) = measured total urinary creatinine excretion (mg)/(ideal total urinary creatinine excretion for patient of the same sex and height) * 100. Reduced muscle mass was defined as a CHI < 80% [42,43].

2.5. Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0. Descriptive statistics are presented as means ± standard deviations (SD) for normally distributed variables, median [interquartile range] for non-normally distributed variables, and number (percentage) for categorical variables. The study population was then divided in two groups according to the GLIM malnutrition diagnosis to show differences in baseline characteristics between well-nourished and malnourished RTR. Differences in patient characteristics between the two groups (well-

nourished versus malnourished) were analyzed with the independent T-test for normally distributed continuous data, the Mann–Whitney *U*-test for non-normally distributed data, and the chi-square test for nominal data. A *P*-value < 0.05 (two-tailed) was considered as statistically significant. The BioVenn web application [44] was used to produce a Venn diagram, to visualize (overlap between) phenotypic criteria for the diagnosis of malnutrition.

3. Results

3.1. Patient characteristics

A total of 599 RTR were included, with a mean age of 55 ± 13 years, of which 372 (62%) were male. The most common primary renal disease was cystic kidney disease or other congenital diseases in 151 RTR (25%), followed by glomerulonephritis in 146 RTR (24%), of which 2 patients underwent a re-transplantation because of recurrent glomerulonephritis. Median time after transplantation was 3.1 [1.0–10.0] years. In total, 237 (40%) of the patients received pre-emptive transplantation and 360 (60%) received dialysis treatment prior transplantation. Of all RTR 334 (56%) received a transplant from a living donor irrespective of prior dialysis treatment. Other patient characteristics and parameters are shown in Table 2.

3.2. Prevalence of malnutrition and distribution of phenotypic and etiologic GLIM criteria

Based on the presence of at least one phenotypic criterion and at least one etiologic criterion, 85 (14%) RTR were malnourished (Table 3). Of these malnourished patients, 77 (91%) met at least the phenotypic criterion for reduced muscle mass, and all but one (99%) met either the phenotypic criterion for reduced muscle mass or weight loss or both. Although mean BMI was lower in RTR with malnutrition ($p < 0.001$), 22% of malnourished RTR were classified as overweight or obese, compared with 72% of well-nourished RTR (Table 2).

Regarding the phenotypic criteria, 166 (28%) met at least one phenotypic criterion for the diagnosis of malnutrition (Table 3). Of these patients, 92% (153/166) met the criterion for reduced muscle mass, 9% (15/166) the phenotypic criterion for weight loss and 11% (19/166) the phenotypic criterion for low BMI. Most of the patients (17/19) that met the criterion for low BMI also met the criterion for reduced muscle mass (Table 3 and Fig. 1).

When considering all RTR as meeting the etiologic criterion for disease burden/inflammation based on presence of chronic disease, 166 (28%) were malnourished, of which 153 (92%) met the phenotypic criterion for reduced muscle mass, and all but two (99%) met either the phenotypic criterion for reduced muscle mass or weight loss or both.

Regarding the etiologic criteria, 295 (49%) met at least one etiologic criterion for the diagnosis of malnutrition, of which 226 (38%) patients met the etiologic criterion for reduced food intake or assimilation, and 119 (40%) met the etiologic criterion for disease burden/inflammation based on CRP.

3.3. Association between malnutrition according to GLIM and clinical and nutritional parameters

RTR that were classified as malnourished according to GLIM criteria had a higher education level ($p = 0.03$), and had proteinuria less often ($p = 0.01$). Whereas eGFR was significantly higher in malnourished patients ($p = 0.008$), creatinine clearance was not different for malnourished and well-nourished RTR. Regarding nutritional intake, a lower sodium intake (126 ± 55 mmol/24 h versus 147 ± 59 mmol/24 h, $p = 0.005$), potassium intake (73 ± 24 mmol/24 h versus 67 ± 23 mmol/24 h, $p = 0.05$) and total protein intake (76 ± 18 g/d versus 85 ± 22 g/d, $p = 0.001$), but not protein intake in g/kg/d, was observed in RTR with malnutrition compared with those without malnutrition (Table 2).

3.4. CHI as measure for reduced muscle mass

Data on CHI were available in 526 patients, with a mean age of 55 ± 13 years, of which 322 (61%) were male. No significant differences were found between characteristics of patients with and without CHI available with regard to age, sex, ethnicity, education level, primary renal disease, type of transplantation, renal function, BMI, smoking behavior, or alcohol consumption.

Mean CHI was 106 ± 29, and 99 patients (19%) had a CHI < 80% and therefore met the criterion for reduced muscle mass based on the operationalization with CHI. Using CHI as a criterion for reduced muscle mass in the GLIM framework, 67 (13%) patients were classified as malnourished, of which 53 (79%) met the phenotypic criterion for reduced muscle mass, and 61 (91%) met either the phenotypic criterion for reduced muscle mass or weight loss or both. When considering all RTR as meeting the etiologic criterion for disease burden/inflammation based on presence of chronic disease, 121 (23%) patients were malnourished, of which 99 (82%) met the phenotypic criterion for reduced muscle mass and 110 (91%) met either the phenotypic criterion for reduced muscle mass or weight loss or both.

4. Discussion

In the present study, we assessed the prevalence of malnutrition and distribution of phenotypic criteria in RTR according to the GLIM criteria. Using these criteria, malnutrition is present in one in 7 stable outpatient RTR. Importantly, in the vast majority of malnourished RTR the phenotypic criterion for reduced muscle mass was present, while most malnourished RTR had a BMI within the normal range, and one fifth had a BMI within the overweight or obese range.

The malnutrition prevalence of 14% in this cohort is lower compared to previous reported prevalence rates of 28–52%, as measured by the Subjective Global Assessment (SGA) and the Malnutrition-Inflammation Score [18,45,46]. Although absolute numbers differ between studies, due to the use of different instruments and differences in patient characteristics between the samples, these prevalence rates indicate that malnutrition is a common issue in RTR that warrants attention, including at routine outpatient visits. The current study is, to the best of our knowledge, the first to apply the GLIM criteria in RTR, contributing to the body of knowledge on both malnutrition in RTR and malnutrition according to the GLIM criteria in different patient populations [47–51].

Our findings indicate that the inclusion of the phenotypic criterion for reduced muscle mass is most important to detect malnutrition in stable outpatient RTR. Contribution of the criterion for weight loss and especially low BMI were very low in our study sample. This may be explained by the high prevalence of overweight and obesity (i.e., 65% in the current study) and post-transplant weight gain, which are known to specifically increase fat mass [8,11,20,23]. Underlying muscle mass depletion and malnutrition may therefore easily be overlooked, possibly negatively impacting health outcomes. Previous studies showed that reduced muscle mass, assessed by either serum creatinine or 24-h urinary CER, is associated with higher mortality rates and graft failure in RTR [21,52,53]. Lower muscle mass as determined by BIA was also found to be associated with a worse renal function [54].

Table 2
Characteristics of total population and across well-nourished and malnourished RTR following the GLIM-criteria.

Number of subjects	Total	Well-nourished	Malnourished	*P*-value
	599 (100)	514 (86)	85 (14)	–
Sociodemographic characteristics				
Age (years)	55 ± 13	55 ± 13	55 ± 15	0.96
Male sex	372 (62)	313 (61)	59 (69)	0.13
Ethnicity				
Caucasian	418 (70)	357 (69)	61 (72)	0.30
African	6 (1)	4 (1)	2 (2)	
Asian	8 (1)	8 (2)	0 (0)	
Other	8 (1)	6 (1)	2 (2)	
Unknown	159 (27)	139 (27)	20 (24)	
Education level				0.03
Low	207 (34)	181 (35)	26 (30)	
Medium	189 (32)	168 (33)	21 (25)	
High	154 (26)	121 (23)	33 (39)	
Unknown	49 (8)	44 (9)	5 (6)	
Renal and transplant characteristics				
Primary renal disease				0.88
Glomerulonephritis	146 (24)	127 (25)	19 (22)	
Interstitial nephritis	51 (9)	42 (8)	9 (11)	
Cystic kidney disease and other congenital/hereditary	151 (25)	128 (25)	23 (27)	
Renal vascular disease, diabetes mellitus and other multisystem disease	129 (22)	113 (22)	16 (19)	
Other/unknown	122 (20)	104 (20)	18 (21)	
Time after transplantation (years)	3.1 [1.0–10.0]	3.1 [1.0–10.0]	2.5 [1.0–10.5]	0.95
Type of transplantation				0.11
Pre-emptive transplantation	237 (40)	197 (38)	40 (48)	
Dialysis prior transplantation	360 (60)	316 (62)	44 (52)	
Missing	2 (0)	1 (0)	1 (0)	
Type of donor				0.24
Living donor	334 (56)	282 (55)	52 (62)	
Deceased-donor donor	263 (44)	231 (45)	32 (38)	
Missing	2 (0)	1 (0)	1 (0)	
Immunosuppressive drugs				
Tacrolimus	402 (67)	342 (67)	60 (71)	0.48
Ciclosporin	93 (16)	82 (16)	11 (13)	0.47
Mycophenolic acid	459 (77)	397 (77)	62 (73)	0.37
Azathioprine	49 (8)	39 (8)	10 (12)	0.20
Prednisolone	584 (98)	502 (98)	82 (97)	0.43
eGFR (mL/min/1.73m^2)	51 ± 18	51 ± 17	56 ± 19	0.008
Creatinine clearance[c]				
in mL/min	70 ± 25	71 ± 26	66 ± 20	0.12
in mL/min/1.73m^2	62 ± 22	62 ± 22	62 ± 20	0.95
Proteinuria[c]	77 (13)	73 (14)	4 (4)	0.01
Hematological and inflammation parameters				
Hemoglobin (mmol/L)	8.4 ± 1.1	8.4 ± 1.1	8.4 ± 1.1	0.89
Ferritin (mmol/L)	88 [41–175]	89 [41–176]	84 [50–166]	0.88
TSAT (%)	24 ± 10	24 ± 10	23 ± 10	0.35
CRP (mg/L)	1.9 [0.7–4.6]	1.7 [0.7–4.3]	2.7 [0.8–7.0]	0.03
Albumin (g/L)	43.7 ± 2.9	43.6 ± 2.9	43.8 ± 3.2	0.75
Anthropometry and body composition				
Height (cm)	174 ± 9	174 ± 9	175 ± 10	0.40
BMI (kg/m^2)	27.2 ± 4.7	27.9 ± 4.6	23.4 ± 2.8	<0.001
BMI category				<0.001
Underweight	15 (3)	7 (1)	8 (9)	
Normal weight	195 (32)	136 (27)	59 (69)	
Overweight	230 (38)	215 (42)	15 (18)	
Obesity	159 (27)	156 (30)	3 (4)	
Waist circumference (cm)				
Male	102 ± 13	103 ± 13	94 ± 11	<0.001
Female	94 ± 14	96 ± 13	81 ± 9	<0.001
ASMI (kg/m^2)				
Male	7.46 ± 0.97	7.46 ± 0.93	6.50 ± 0.50	<0.001
Female	6.35 ± 0.86	6.47 ± 0.82	5.43 ± 0.60	<0.001
24-h urinary CER (mmol/24 h)[c]				
Male	14.0 ± 3.8	14.3 ± 3.8	12.2 ± 3.4	<0.001
Female	10.4 ± 2.9	10.6 ± 2.9	9.1 ± 2.2	0.03

Table 2 (*continued*)

Number of subjects	Total	Well-nourished	Malnourished	*P*-value
	599 (100)	514 (86)	85 (14)	–
Nutritional intake[c]				
Protein intake[a]				
in g/kg/d[b]	1.08 ± 0.26	1.08 ± 0.26	1.07 ± 0.26	0.89
in g/d	84 ± 22	85 ± 22	76 ± 18	0.001
24-h urinary sodium excretion rate (mmol/24 h)	144 ± 59	147 ± 59	126 ± 55	0.005
24-h urinary potassium excretion rate (mmol/24 h)	72 ± 24	73 ± 24	67 ± 23	0.05
Other lifestyle parameters				
Smoking status				0.17
Current smoker	47 (8)	36 (7)	11 (13)	
Non-(current) smoker	450 (75)	390 (76)	60 (70)	
Unknown	102 (17)	88 (17)	14 (17)	
Alcohol consumption				0.27
Yes	385 (64)	336 (65)	49 (58)	
No	60 (10)	48 (9)	12 (14)	
Unknown	154 (26)	130 (26)	24 (28)	

Note: Data are presented as mean ± SD, number (%) or median [IQR].
Abbreviations: ASMI: appendicular skeletal muscle mass index; BMI: body mass index; 24-h CER: 24-hour urinary creatinine excretion rate; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; IQR: interquartile range; TSAT: transferrin saturation; Tx: transplantation.
[a] Protein intake was calculated from 24-h urinary urea excretion using the Maroni-equation [34].
[b] Protein intake in g/kg/d with adjustment for underweight and obesity: a BMI < 20 kg/m^2 is adjusted to a BMI of 20 kg/m^2 and a BMI > 30 kg/m^2 is adjusted to a BMI of 27.5 kg/m^2.
[c] Due to incomplete 24-h urine samples or missing data the number (*N*) available for analysis for creatinine clearance was *N* = 536, for proteinuria *N* = 502, for 24-h creatinine excretion *N* = 534, for 24-h sodium excretion rate *N* = 534, for 24-h potassium excretion rate *N* = 520 and for protein intake (24-h urea excretion) *N* = 501.

Table 3
GLIM criteria for malnutrition in RTR.

	RTR *N* = 599		
	N	% within group	% of total
Phenotypic criterion present	**166**	**-**	**28**
1. Weight loss	15	9	3
2. Low BMI	19	11	3
3. Reduced muscle mass	153	92	26
Combinations of phenotypic criteria present			
Weight loss + low BMI	0	0	0
Weight loss + reduced muscle mass	3	2	1
Low BMI + reduced muscle mass	16	10	3
Weight loss + low BMI + reduced muscle mass	1	1	0
Etiologic criterion present	**295**	**-**	**49**
a. Reduced food intake/assimilation	226	77	38
Reduced food intake	180	61	30
Reduced assimilation	79	27	13
b. Inflammation, CRP > 5 mg/L	119	40	20
Combination of etiologic criteria present			
Reduced food intake/assimilation + inflammation	50	17	8
Malnutrition according to GLIM criteria (at least 1 phenotypic + 1 etiologic criterion present)	**85**	**-**	**14**
1. Weight loss + reduced food intake/assimilation or inflammation	10	12	2
2. Low BMI + reduced food intake/assimilation or inflammation	11	13	2
3. Reduced muscle mass + reduced food intake/assimilation or inflammation	77	91	13

Abbreviations: BMI: Body Mass Index; CRP: C-reactive protein; GLIM: Global Leadership Initiative on Malnutrition; RTR: renal transplant recipients.
*Number of patients, % within group of patients that either meets at least one phenotypic criterion, meets at least one etiologic criterion or is classified as malnourished, and % of total is shown.

Although this study revealed reduced muscle mass as the dominant phenotype of malnutrition in RTR, diagnostic assessment of muscle mass has several limitations. Currently, no consensus exists about the optimal measurement tool for muscle mass in clinical practice [19]. Computed tomography (CT) and magnetic resonance imaging (MRI) are considered the gold standards for assessment of muscle mass, but are not often used for nutritional assessment in clinical practice because of the high costs and practical limitations [38,55]. The GLIM therefore recommends using other indirect body composition measures, such as DEXA or BIA [19], and a previous study in RTR, with mostly a healthy BMI, showed that estimations of muscle mass by CT, DEXA and BIA were well-correlated [56]. However, the use of BIA to estimate muscle mass may include errors caused by changes in hydration status and, importantly, may overestimate muscle mass in obesity [57,58]. Given the high rate of obesity in our cohort (27%), the prevalence of low muscle mass by use of BIA is probably underestimated in this study population. In addition to the recommended body

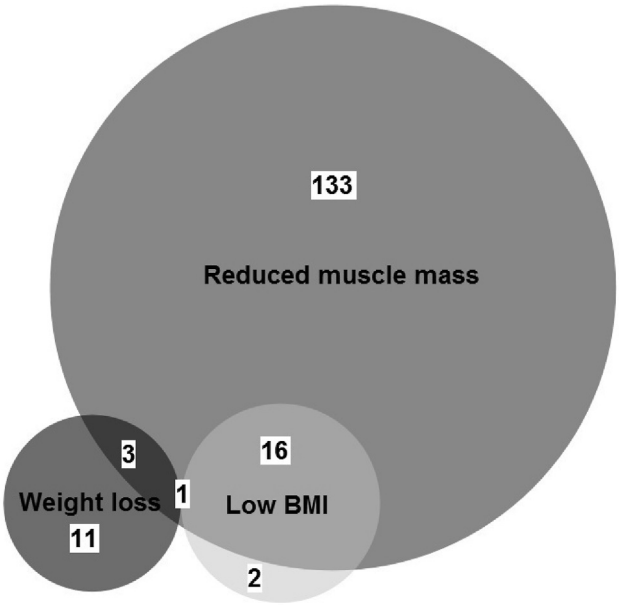

Fig. 1. *Co-existence of phenotypic criteria for malnutrition in all RTR* [44]. Abbreviations: BMI: Body Mass Index; RTR: renal transplant recipients. * Number of patients that meet either the phenotypic criterion for weight loss, low BMI, reduced muscle mass or combinations of those criteria, is shown.

composition measures, when applied properly, 24-h urinary CER is a reliable non-invasive method to assess muscle mass in the general population and RTR [21,22,59]. However, validated age- and gender specific cut-off values for low muscle mass based on 24-h CER are not yet available, which hampers its clinical use for the diagnosis of malnutrition. In the current study we therefore used the CHI, which was previously used to detect malnutrition in lung transplant candidates [60] and patients on prolonged mechanical ventilation [43], and we found very similar malnutrition prevalence numbers when using CHI as measure for reduced muscle mass.

Several clinical and nutritional parameters were associated with malnutrition in the present study. Regarding the clinical parameters, the higher eGFR in malnourished RTR seems counterintuitive, as worse renal function can impair nutritional status [18]. However, eGFR is overestimated in subjects with low muscle mass, as eGFR is based on serum creatinine level, which reflects not only removal (renal excretion) but also supply of creatinine which is predominantly derived from muscle turnover [61]. Creatinine clearance is not subject to this particular bias, and in fact, has been recommended as better measure of renal function in patients with low muscle mass or malnutrition [61]. In our cohort, the similar creatinine clearance in well-nourished and malnourished RTR supports the assumption that the higher eGFR in malnourished RTR is due to overestimation by low muscle mass. Currently, eGFR is a main parameter for renal monitoring in RTR. The overestimation of renal function by eGFR in malnourished patients may lead to underestimation of renal risk in these patients. Whereas this assumption requires further investigation, it nevertheless underscores the importance of routine nutritional assessment in RTR, to prevent malnutrition from remaining undetected, and to prevent bias in renal monitoring. Second, the lower proportion of proteinuric patients among malnourished RTR also seems counterintuitive, as proteinuria can compromise the nutritional status. However, in patients with overt proteinuria, reduction of dietary protein intake is known to reduce proteinuria [62], and the same holds true for reduction of dietary sodium intake [63]. Hence, the lower proportion of proteinuria in malnourished RTR may well be due to their lower intake of protein and sodium. Finally, the significant association between high education level and malnutrition was due to higher rates of the phenotypic criterion 'low muscle mass' in RTR with high education level (data not shown). With simultaneous lower rates of obesity in this group, this may well be explained by less overestimation of muscle mass by BIA in RTR with high education level [58]. In additional analysis with use of CHI instead of BIA for muscle mass assessment, this significant association was indeed lost (data not shown).

With respect to the nutritional parameters, lower daily protein intake in g/d, but not in g/kg/d, was also independently associated with malnutrition. This discrepancy can be explained by differences in body weight between well-nourished and malnourished RTR, but this comparison may be obscured by not considering differences in body composition. A previous study found that the association between low protein intake and mortality in RTR was mediated by lower muscle mass [64]. Although there are currently no recommendations for optimal protein intake for RTR, it can be hypothesized that, RTR with low muscle mass and/or malnutrition may benefit from increments in protein intake, similarly to the protein recommendations for elderly to maintain optimal muscle function [65]. However, more research is required for determining optimal protein recommendations for RTR, as a causal relationship between protein intake and malnutrition cannot be determined from the present study, and reversed causation cannot be excluded. As sodium and potassium intake were also significantly lower in malnourished RTR, the lower protein intake may well be a consequence of an overall lower food intake in the patients with malnutrition.

As reduced muscle mass is independently associated with increased mortality and graft failure in several populations, including RTR [21,52,53], it may be an important factor to target with interventions to improve long-term outcomes in RTR. In addition to nutritional interventions, other types of interventions may be effective, including physical activity programs, which show some positive results in improving muscle performance and strength in RTR [66–68]. However, most of these interventions were targeted at attenuating weight gain and reducing cardiovascular risk factors after transplantation rather than maintaining or increasing muscle mass. Future combined lifestyle intervention studies in RTR may benefit from targeting both sides of the coin, aiming for both reduction of fat mass and cardiovascular risk factors, as well as an increase of muscle mass and improvement or maintenance of an adequate nutritional status [69].

This study has several limitations. Firstly, the information on weight loss was derived from patient-reported data, which is prone to bias and may result in either under- or overestimation of weight loss. Secondly, although the GLIM criteria has provided a useful framework to create more consistency in measurement of malnutrition, there is lack of consensus about the best way to measure muscle mass which hampers its assessment in both research and clinical setting. Especially for patient populations with high rates of obesity, including our population, it is important to find a reliable way to assess muscle mass, as BIA tends to overestimate muscle mass in obese individuals [57,58] and malnutrition based on reduced muscle mass may consequently be overlooked. The use of CHI in the current study can be debated, since reference values for ideal CER are outdated, and not validated against currently used diagnostic techniques. Updated reference values and/or age- and gender specific cut-off values for 24-h CER validated against a golden standard for muscle mass assessment would be preferred, but are currently not available. Thirdly, only a limited amount of nutritional parameters were available for this study, and e.g. caloric intake was documented. Further studies are needed to better examine the role of nutritional intake in malnutrition in RTR. Lastly,

with the lack of longitudinal data, we were not able to assess the prevalence of malnutrition over time and study its association with important health outcomes, e.g., graft and patient survival. However, the long-term follow-up of participants in TransplantLines cohort and biobank study will enable this in the coming years.

Several implications for clinical practice can be derived from our findings. Given the estimated prevalence of malnutrition of one out of 7 stable outpatient RTR, or a doubled number depending on the operationalization, structural nutritional assessment during outpatient visits is of paramount importance. Clinicians should be aware that BMI and critical weight loss alone lack sensitivity to detect malnutrition in RTR. General screening and assessment tools that only include these phenotypic criteria [24,25], when not followed by additional assessment of muscle mass, should be interpreted with caution in this population for the same reason. Instead, as low muscle mass is the most important driver of the malnutrition diagnosis in RTR, the assessment of muscle mass should be incorporated in outpatient visits. However, more research is needed to determine the most reliable assessment tool for this specific population, in which overweight and obesity are highly prevalent. In our opinion, 24-h urinary CER is a promising tool for muscle mass assessment, which can easily be incorporated in a clinical and outpatient setting. We do acknowledge that more research is needed, e.g., to determine optimal cut-off values for CER, and to compare the predictive value of different existing screening and assessment tools and measurement techniques in RTR.

In conclusion, malnutrition is present in one in 7 stable outpatient RTR and is predominantly characterized by reduced muscle mass. Therefore, routine assessment and monitoring of muscle status is warranted in RTR, to prevent malnourished RTR from remaining undetected and untreated.

Author contributions

K.B. and I.M.Y.V. conceptualization, methodology, formal analysis, investigation and writing – original draft; A.G.N. resources and writing – review and editing; M.F.C.J.: writing – review and editing; S.J.L.B.: funding acquisition, resources and writing – review and editing; H.J.W.: writing – review and editing and supervision; G.J.N. conceptualization, writing – review and editing and supervision. The final draft of the manuscript have been read and approved by all authors.

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Conflicts of interest

The authors declare no conflicts of interest.

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