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The Associations of Muscle Strength, Muscle Mass, and Adiposity with Clinical Outcomes and Quality of Life in Prevalent Kidney Transplant Recipients

Winnie Chan, PhD [1,2.3], Shui Hao Chin, PhD [4], Anna C Whittaker, PhD [3.5], David Jones, PhD [6], Okdeep Kaur, MSc [1], Jos A Bosch, PhD [3,7], Richard Borrows, MA [1,8]

[1] Department of Nephrology & Kidney Transplantation, Area 5, Level 7, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, United Kingdom.

[2] Department of Nutrition & Dietetics, Therapy Services South Suite, 1st Floor, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, United Kingdom.

[3] School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom.

[4] Department of Cardiovascular Sciences, Clinical Sciences Wing, University of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, United Kingdom.

[5] Faculty of Health Sciences and Sport, University of Stirling, Stirling, FK9 4LA, Scotland, United Kingdom

[6] School of Healthcare Science, Manchester Metropolitan University, John Dalton Building, Chester Street, Manchester M1 5GD, United Kingdom.

[7] Department of Clinical Psychology, University of Amsterdam, Weesperplein 4, 1018 XA, Amsterdam, The Netherlands.

[8] Centre for Translational Inflammation Research, University of Birmingham, Edgbaston, Birmingham B15 2WB, United Kingdom.

Corresponding Author:

Dr Winnie Chan
Department of Nutrition & Dietetics, Therapy Services South Suite, 1st Floor, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, United Kingdom.
Tel: +44 (0) 788 195 8822
Fax: +44 (0) 121 371 5858
Email: Winnie.Chan@uhb.nhs.uk ; wlwchan@gmail.com

Author Contributions

Winnie Chan, David Jones, Jos A Bosch, and Richard Borrows designed the research. Winnie Chan, Shui Hao Chin, Anna C Whittaker, Jos A Bosch, and Richard Borrows wrote the manuscript. Winnie Chan, Okdeep Kaur, and Richard Borrows conducted the research. Winnie Chan, Jos A Bosch, and Richard Borrows analysed the data and performed the statistical analysis. Winnie Chan and Richard Borrows had primary responsibility for the final content.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Title

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Abstract

Objective: Sarcopenia, defined as loss of both muscle strength and mass, is associated with inferior clinical outcomes and quality of life (QoL) in chronic kidney disease, but its effects are unknown in kidney transplantation. Obesity confers increased mortality risk and compromises QoL in kidney transplant recipients (KTRs), but the impacts of sarcopenic obesity remain unexplored. This study aimed to evaluate the associations of muscle strength and mass, sarcopenia, and sarcopenic obesity with clinical outcomes and QoL in KTRs.

Methods: This prospective longitudinal study enrolled 128 KTRs ≥1-year post-transplantation. Low muscle strength (by handgrip strength) and mass (by bio-impedance analysis), and a combination of both (sarcopenia) were defined as <reference cut-offs for corresponding indices. Sarcopenic obesity was defined as sarcopenia combined with fulfilment of ≥2 out of 3 criteria from 1) body mass index ≥30 kg/m^2, 2) bio-impedance analysis derived-fat mass >reference cut-offs, and 3) waist circumference >World Health Organisation cut-offs. Prospective follow-up data on mortality and hospitalisation were collected. QoL was evaluated using Medical Outcomes Study Short Form-36 questionnaire.

Results: Median follow-up duration was 64 (60–72) months. Low muscle strength and mass, sarcopenia, and sarcopenic obesity were observed in 64%, 36%, 29% and 16% of KTRs respectively. Low muscle strength was independently associated with the composite endpoint of mortality and hospitalisation (*HR*=2.45; 95% CI=1.30, 4.64; *p*=0.006), and QoL (physical-related: *β*=-12.2; 95% CI=-23.6, -0.8; *p*=0.04; mental-related: *β*=-9.9; 95% CI=-19.6, -0.3; *p*=0.04). Low muscle mass (*β*=-8.8; 95% CI=-16.9, -0.8; *p*=0.04) and sarcopenia (*β*=-14.7; 95% CI=-27.2, -2.5; *p*=0.03) were associated with physical-related QoL only. No independent associations were found between muscle mass, sarcopenia, and sarcopenic obesity with the composite outcome of mortality and hospitalisation.

Conclusion: Low muscle strength is common among KTRs, conferring poor prognosis in the medium term. Future research on strength training may prove valuable in improving kidney transplantation outcomes.

Keywords: Muscle Strength; Muscle Mass; Sarcopenia; Sarcopenic Obesity; Hospitalisation; Mortality; Kidney Transplantation

List of Abbreviations

β – Beta Coefficient

BMI – Body Mass Index

CI – Confidence Interval

CKD – Chronic Kidney Disease

CNI – Calcineurin Inhibitors

DEXA – Dual Energy X-ray Absorptiometry

DM – Diabetes Mellitus

eGFR – Estimated Glomerular Filtration Rate

FM – Fat Mass

FTI – Fat Tissue Index

GPPAQ – General Practice Physical Activity Questionnaire

Hb – Haemoglobin

HGS – Handgrip Strength

HR – Hazard Ratio

hsCRP – High-Sensitivity C-Reactive Protein

KTRs – Kidney Transplant Recipients

ICED – Index of Coexistent Disease

IL - Interleukin

IQR – Interquartile Range

LTM – Lean Tissue Mass

LTI – Lean Tissue Index

NODAT – New Onset Diabetes After Transplantation

p – P-value

QoL – Quality of Life

r – Correlation Coefficient

SD – Standard Deviation

SF-36 – Medical Outcome Short Form-36 Questionnaire

SGA – Subjective Global Assessment

τ – Kendall's Tau correlation

WHO – World Health Organisation

Introduction

Sarcopenia was formerly defined as age-related loss of muscle mass[1,2], but has recently been redefined as loss of both skeletal muscle strength and mass[1,3-5]. It is associated with inferior outcomes in quality of life (QoL)[6-9], morbidity and mortality in ageing and chronic kidney disease (CKD) populations[10-12]. Although muscle strength is commonly associated with muscle mass[13], there may be a discordant relationship between the two muscular indices[14]. Studies in ageing and CKD populations suggest that muscle strength represents a more powerful prognostic index than muscle mass[15,16]. Indeed, data available in the general and dialysis populations concluded that muscle strength *per se* is an important prognostic marker[17-21].

Studies on individual muscular indices (i.e. muscle strength or mass) either in isolation or in combination (i.e. sarcopenia) remain scarce in kidney transplantation. The limited literature concludes that muscle strength is impaired in kidney transplant recipients (KTRs) compared with healthy individuals[13]. One study revealed that low muscle strength was found in 20.5% of KTRs, possibly a consequence of decreased vitamin D levels and ageing[22]. On the other hand, decreased muscle mass is a common feature in KTRs, variably attributed to the use of corticosteroid therapy[23,24], presence of diabetes[23], and suboptimal renal function[13]. Low muscle mass at the end of the first year post-transplantation was found to associate with prior episodes of delayed graft function and acute rejection[24]. Furthermore, decreased urinary creatinine excretion, a surrogate marker of low muscle mass, predicts subsequent graft loss and mortality in KTRs[23]. However, no studies to date have scrutinised the relationships

between directly-measured muscular derangement categories (i.e. low muscle strength, low muscle mass, and sarcopenia) and clinical outcomes of kidney transplantation.

Of relevance, deranged muscular indices may co-exist with obesity and weight gain, as both entities are highly prevalent in KTRs[25]. The combination of obesity and sarcopenia is termed as the "sarcopenic obesity" phenotype. Associations of sarcopenic obesity with increased mortality and inferior QoL have been verified in general and CKD populations[26,27], but not in kidney transplantation. Obesity among KTRs is known to be associated with worsened QoL, cardiovascular risk profiles, as well as graft and overall survival[25]. It is therefore possible that the coexistence of obesity and muscular derangements (i.e. sarcopenic obesity) may aggravate these inferior outcomes.

Therapeutic measures targeting muscle strength, muscle mass, sarcopenia, and sarcopenic obesity individually are not necessarily identical. Therefore, greater insight into each entity and their clinical impacts are prerequisites for developing specific nutritional and physical activity interventions in KTRs. As such, the primary objectives of this study were to investigate the associations of muscle strength, muscle mass, sarcopenia, and sarcopenic obesity with a composite endpoint of all-cause mortality and acute hospitalisation; and secondly, with health-related QoL, in clinically stable KTRs.

Materials and Methods

Study Population, Study Design, and Clinical Outcome

Adult KTRs beyond 1-year post-transplantation with stable graft function (i.e. defined as <10% increase in serum creatinine over the preceding 6 months) were consecutively recruited from renal transplant clinic to this single-centre prospective longitudinal study between April 2010 and April 2013. Written informed consent was obtained from all participants. Detailed biochemical, clinical, anthropometric, dietary, lifestyle, and health-related QoL assessments were performed at initial study evaluation. Following baseline assessment, all KTRs were prospectively followed-up in the context of research visits during routine clinic attendances for ≤84 months or until 31st March 2017, whichever event occurred first. The endpoint of this study was a composite variable for a combined event, consisting of all-cause mortality, or the first occurrence during the study period of a non-elective hospitalisation with acute illness. Exclusion criteria included episodes of acute rejection within the preceding 6 months, evidence of sepsis in the last 6 weeks, presence of active malignancy or chronic infection, history of thyroid disease or adrenal insufficiency, and contraindications for use of bioimpedance-based body composition assessment (i.e. implanted electronic devices, metallic implants, amputations, pregnancy, and lactation). This study was approved by the local research ethics committee and was conducted in accordance with the Declaration of Helsinki.

Definitions of Low Muscle Strength, Low Muscle Mass, Sarcopenia, and Sarcopenic Obesity

Low muscle strength was defined using gender-specific handgrip strength (HGS) cut-offs for low muscle strength derived from a reference population (<30 kg for men; and <20 kg for women)[28], a definition applied in the CKD literature[16]. Low muscle mass was defined as bio-

impedance analysis derived-lean tissue index (LTI) <gender- and age- specific cut-offs obtained from a reference population[29]. Sarcopenia was defined as concurrent presentation of both low HGS and low LTI[3]. Sarcopenic obesity combined the criteria of sarcopenia with the fulfilment of ≥2 out of 3 criteria from 1] body mass index (BMI) ≥30 kg/m^2; 2] bio-impedance analysis derived-fat tissue index (FTI) >gender- and age- specific cut-offs obtained from a reference population[29]; and 3] central obesity, denoted as waist circumference >World Health Organisation (WHO) cut-offs (>102 cm for men; >88 cm for women)[30].

Data Collection at Baseline

Demographic, Clinical, and Lifestyle Parameters

The following demographic and clinical parameters were retrieved from patient's medical records: 1] age; 2] gender; 3] ethnicity; 4] time post-transplantation; 5] presences of diabetes mellitus, either pre-transplantation (pre-transplantation DM) or new onset diabetes after transplantation (NODAT); 6] previous biopsy-proven acute rejection episodes; 7] dialysis vintage; 8] pre-emptive transplantation; 9] statin usage; and 10] immunosuppressive medication usage, either prednisolone, calcineurin inhibitor (CNI), or adjunctive antiproliferative agent. Comorbidity was assessed by Index of Coexistent Disease (ICED), using algorithm described in the HEMO study[31]. Smoking status (non-, current-, and ex-smoker) and alcohol consumption (units per week) were collected by questionnaire. Physical activity level (hours per week) was captured by the General Practice Physical Activity Questionnaire (GPPAQ)[32].

Muscle Strength and Body Composition

HGS (kg) was measured to the nearest 0.1kg by a digital handgrip dynamometer (Takei Scientific Instruments, Niigata City, Japan) with the non-dominant arm or non-fistula arm if previously implanted[33]. Prior to measurement, participants were asked to familiarise themselves with the instrument and select the best adjustment. Participants were instructed to stand with both arms hanging at their side and grip the dynamometer with maximum strength in response to a voice command. Three trials were performed with a rest period of at least 1 minute between each measurement, and the highest reading was noted.

Body weight (kg) and height (m) were measured for derivation of BMI (kg/m^2). Waist circumference (cm) was determined using methodology recommended by the WHO[30]. Body composition was assessed by a well-validated multi-frequency bio-impedance based body composition monitor (BCM, Fresenius Medical Care, Germany)[34], providing measurements of lean tissue mass (LTM, kg) and fat mass (FM, kg). Both measurements were normalised to height (m) and therefore expressed as LTI (kg/m^2) and FTI (kg/m^2).

Nutritional Parameters

Dietary intakes encompassing total energy (kcal/day) and protein (g/day) intakes were estimated by a 3-day food diary, a widely accepted dietary assessment tool deemed to be

valid, reliable, and accurate in estimating typical and habitual nutrient intake[35]. Nutritional status was evaluated by 7-point subjective global assessment (SGA).

Laboratory Parameters

Blood samples were taken in the morning following an overnight fast for measurements of creatinine, estimated glomerular filtration rate (eGFR) derived using four-variable modifications of diet in renal disease equation, haemoglobin (Hb), and vitamin D (25-hydroxyvitamin D). Analyses were undertaken in the accredited hospital biochemistry laboratory. High-sensitivity C-reactive protein (hsCRP) was measured using a Tina-quant® cardiac C-reactive protein latex high-sensitive immunoturbidimetric assay (Roche Diagnostics, Switzerland).

Health-related Quality of Life

Health-related QoL was assessed using the well-validated Medical Outcomes Study Short Form-36 questionnaire (SF-36)[36], providing scores for physical- and mental- health-related QoL, ranging from 0 to 100, with higher scores denoting better QoL.

Statistical Analyses

Statistical analyses were performed using SPSS Statistics 23 (Chicago, IL). Descriptive statistics were used to examine baseline characteristics. Results were presented as mean ± standard deviation (SD) or median with interquartile range (IQR). Comparison between two groups were performed using independent-samples t-test, Wilcoxon rank-sum test, or Fisher's Exact test. Pearson (r) or Kendall's Tau (τ) correlations were used to assess relationships. Survival analysis of time to occurrence of composite outcome (all-cause mortality, or first acute hospitalisation) was conducted using Cox proportional hazards regression model and Kaplan-Meier method evaluated by log-rank test. Linear regression analyses were used to determine associations between predictor variables and health-related QoL. Relationships established by Cox proportional hazards and linear regressions were expressed as hazard ratio (HR) and beta coefficient (β) respectively, with 95% confidence interval (CI). A type 1 error rate ≤5% ($p \leq 0.05$) was considered significant.

Measures of muscular parameters (HGS and LTI), adiposity (BMI, FTI, and waist circumference), and categorical/composite indices (low muscle strength, low muscle mass, sarcopenia, and sarcopenic obesity) were assessed individually in separate regression analysis due to possibility of collinearity among these highly correlated variables, as shown in **Supplementary Material, Tables 1a and 1b.** While the categorical/composite variables were examined on categorical scale, all muscular and adiposity measures were assessed on both continuous and categorical scales. Each index was evaluated in three discrete Cox or linear regression models. Model 1 adjustments were made for socio-demographic variables including age, gender, ethnicity, smoking status, and alcohol consumption. In model 2, adjustments were made for variables in model 1 plus clinically relevant variables encompassing ICED, diabetes status, eGFR, dialysis vintage, pre-emptive transplantation, time post-transplantation, acute rejection episodes, use of statin, and use of CNI, or

adjunctive antiproliferative agent, or prednisolone. Finally, model 3 were adjusted for variables in models 1 and 2, plus potential mediators including SGA score, physical activity level, vitamin D, Hb, hsCRP, dietary intakes of protein and energy.

Further exploratory analyses were performed to identify the predictors of HGS. Plausible socio-demographic, clinical, biochemical, lifestyle, and dietary parameters were assessed as potential explanatory variables. Linear regression analyses were performed in 2 stages. Initially, the effect of each variable was assessed in a series of univariate analyses. Subsequently, the joint effect of variables was examined in a multivariate analysis including only the explanatory variables with univariate association of $p<0.20$. A backward selection procedure was performed to derive the final model, retaining only those variables found to be statistically significant.

Results

Population Characteristics

Of 138 patients approached, 10 did not participate due to work commitment (93% consent rate). Mean age was 49±15 years; 56% was male; 78% was Caucasian; median time post-transplantation was 5 (2–11) years; and mean eGFR was 45±18 mL/min/1.73m^2. **Table 1** indicates the baseline characteristics of the entire study population and stratified according to normal or low muscle strength. KTRs with low muscle strength were older (p=0.008), presented with longer transplant (p=0.005) and dialysis (p=0.04) vintage, and more likely to

receive prednisolone (p=0.002). In addition, decreased physical activity level (p=0.04), lower circulating concentrations of Hb (p=0.04) and vitamin D (p=0.001), reduced dietary protein intake (p=0.04), decreased LTI (p=0.002), and increased FTI (p=0.04) were observed in KTRs with low muscle strength.

Median prospective follow-up duration was 64 (60–72) months. Crude rates of mortality and hospitalisation were 10% and 47% respectively. Low muscle strength and mass were evident in 82 and 46 patients (64% and 36%) respectively. Concurrent presentation of low muscle strength and mass, i.e. sarcopenia, were present in 37 patients (29%). Obesity, determined by fulfilling ≥2 out of 3 criteria from BMI, FTI, and waist circumference measurements, was found in 52 patients (41%). Sarcopenic obesity, based on sarcopenia combined with obesity, was found in 20 patients (16%).

Associations of Muscle Strength and Mass, Sarcopenia, and Sarcopenic Obesity with the Risk of Mortality and First Acute Hospitalisation

A composite endpoint of time to death or first acute hospitalisation was modelled as the outcome of interest. Hospitalisation attributed to kidney transplant dysfunction were excluded. During follow-up, mortality and hospitalisation rates were 10% (n=13) and 47% (n=60) respectively. Causes of death were malignancy (n=4), acute ischaemic cardiac events (n=4), heart failure (n=3), stroke (n=1), and sepsis (n=1). Causes of hospitalisation were sepsis (40%, n=51), acute ischaemic cardiac events (4%, n=5), and gastro-intestinal infection (3%, n=4).

Univariate Cox associations of muscular, adiposity, categorical/composite indices, and relevant covariates with combined mortality and hospitalisation risk are shown in **Supplementary Material, Tables 2a and 2b**.

When the muscular and adiposity indices were analysed as *continuous*ly-distributed measures in multivariate Cox regression analyses, shown in **Table 2**, only decreased HGS displayed significant association with higher risk of combined mortality and hospitalisation in all adjusted models (models 1, 2 and 3). Although lower LTI demonstrated significant adjusted association with higher risk of combined mortality and hospitalisation in models 1 and 2, the association did not persist in model 3 when further adjustment was made. No association was found between adiposity measures (BMI, FTI, and waist circumference) and combined mortality and hospitalisation risk in all adjusted models.

In the multivariate Cox regression analyses pertaining *categorical/composite* indices (**Table 2**), only low muscle strength revealed significant association with higher risk of combined mortality and hospitalisation in all adjusted models. In fact, the risk is almost 2.5 times higher in KTRs presented with low muscle strength compared to those with normal muscle strength (*HR*=2.45; 95% CI=1.30, 4.64; p=0.006). Kaplan-Meier survival estimates depicted higher rate of combined mortality and hospitalisation in KTRs with low muscle strength, as shown in **Figure 1** (p<0.01). Although low muscle mass, sarcopenia, and sarcopenic obesity showed significant adjusted associations with combined mortality and hospitalisation risk in model 1, these associations were not retained with further adjustment in models 2 and 3. No

adjusted association was found between obesity and the combined endpoint of mortality and hospitalisation.

Associations of Muscle Strength and Mass, Sarcopenia, and Sarcopenic Obesity with Health-related Quality of Life

Mean summary scores for SF-36 physical- and mental- health-related QoL were 62±25 and 69±22 respectively. The scores were normally distributed and were analysed on the original scale. Univariate linear associations of muscular, adiposity, categorical/composite indices, and relevant covariates with physical- and mental- health-related QoL are shown in **Supplementary Material, Tables 3a-3d**.

When all the muscular and adiposity measures were analysed on *continuous* scale in the multivariate linear regression analyses, only increased HGS was associated with improvements in both physical- (**Table 3a**) and mental- (**Table 3b**) health-related QoL in all adjusted models, illustrated in **Figure 2**. While increased LTI revealed significant association with improving physical health-related QoL in all adjusted models, its positive association with mental health-related QoL was only apparent in models 1 and 2, and this association failed to persist in the fully adjusted model. None of the adiposity measures were associated with physical- and mental- health-related QoL.

When all categorical/composite indices were examined as *categorical* variables individually in the multivariate linear regression analysis, only low muscle strength were associated with

reductions in both physical- (**Table 3a**) and mental- (**Table 3b**) health-related QoL in all adjusted models. While low muscle mass and sarcopenia were associated with decreased physical health-related QoL in all adjusted models, their independent associations with reduced mental health-related QoL were only observed in models 1 and 2, and these associations were not retained in the fully adjusted model. Finally, neither obesity nor sarcopenic obesity were associated with physical- and mental- health-related QoL in all adjusted models.

Predictors of Muscle Strength

Further exploratory analyses were performed to identify the predictors of HGS, justified by the independent clinical impacts of HGS on mortality, morbidity, and health-related QoL; and the clinical relevance of identifying modifiable measures for improving HGS.

The univariate and multivariate analyses showing the predictors of HGS are indicated in **Table 4**. In the adjusted model, higher LTI, younger age, male gender, increased Hb and vitamin D concentrations, higher physical activity level, and increased protein intake were identified as independent predictors for increased HGS. Of note, a substantial proportion of the variation in HGS was explained by the variables contained within the final multivariate model (R^2=63%).

Discussion

This study revealed that low muscle strength is common among a prevalent cohort of clinically stable KTRs. Importantly, only decreased muscle strength was identified as an independent risk factor for a composite endpoint of all-cause mortality and morbidity, as well as health-related QoL. Muscle mass, sarcopenia, and sarcopenic obesity did not demonstrate meaningful prognostic impact in this study.

This study addresses two important phenomena. Firstly, muscle strength *per se* was found to be an important prognostic marker, affirming the emerging data from the general, other diseased, and non-transplant CKD populations[17-21]. Secondly, muscle strength demonstrated superiority over muscle mass in predicting the composite outcome of mortality and morbidity, as well as health-related QoL, a conclusion similarly drawn from both healthy and diseased populations[15,16,23,37]. The latter finding may be justified by the additional qualitative data derived from muscle strength evaluation that was not captured by muscle mass assessment, such as muscle quality, health and excitability[38,39].

In particular, a previous study showed that lower urinary creatinine excretion, a proxy for reduced muscle mass, was associated with increased mortality in KTRs[23]. This finding is in contrast to the current investigation where no predictive association was found between muscle mass and the composite outcome of mortality and morbidity. Although the present study may be hampered by a relatively short follow-up duration, it provides a direct estimation of muscle mass using bio-impedance analysis, a methodology for muscle mass measurement that demonstrated higher correlation with dual energy x-ray absorptiometry (i.e. the gold standard) compared with urinary creatinine excretion[39]. Of relevance, a prior study in non-transplant CKD supported the findings of this study, by which muscle mass assessed

using bio-impedance analysis was not predictive of mortality[39]. Instead, reduced urinary creatinine excretion was found to be a predictor of death independent of bio-impedance analysis-derived muscle mass. The authors speculated that urinary creatinine excretion may capture information about muscle quality independently of muscle mass e.g. creatine content[39], suggesting that other muscular factors such as muscle function and muscle metabolism may play important roles in driving clinical outcomes. This reasoning corroborates the findings of the present study showing that muscle strength was predictive of all-cause mortality and morbidity irrespective of quantities of muscle mass.

Of importance, the findings from this study implies causal relationships of muscle strength with clinical outcomes and health-related QoL, justifying interventional strategies to improve muscle strength in KTRs. Whilst such relationships cannot be confirmed with the current observation data, other investigations have provided tantalising mechanistic pathways. An intriguing body of literature has emerged over the past decade in relation to soluble mediators released from contracting skeletal muscles particularly during exercise, termed as "myokines"[40-42], including interleukin (IL)-5, brain-derived neurotropic factor, irisin, gelsolin, and IL-6. These myokines are known to possess potent anti-inflammatory, antioxidant, and cytoprotective properties, exerting pleotropic modulating effects in metabolic and cardiovascular diseases[40-42]. Although studies conducted in the general, CKD and kidney transplant populations showed that resistance training confers positive changes on cardiovascular risk profiles[43-45], real-life translational improvement in mortality and morbidity are yet to be observed. Additionally, the associations between increased muscle strength and improved mental health-related QoL may be explained by the irisin-mediated muscle-brain crosstalk, supported by the proposed upstream effect at the level of central

nervous system[46]. Indeed, studies from the general population affirm that strength training improves specifically the mental aspects of QoL[47].

The current study found that decreased muscle strength, decreased muscle mass, and sarcopenia were all independently associated with inferior physical health-related QoL. This is because muscle strength and mass are intuitively required to perform physical activities measured by the SF-36 physical functioning. In support of this, studies conducted in the ageing, CKD and kidney transplant populations showed that resistance training can improve muscle strength and mass, physical capacity, overall- and physical- health-related QoL[43,44,48].

Increased muscle mass, higher concentrations of vitamin D and Hb, increased physical activity level, and higher protein intake were identified as modifiable independent predictors of increased muscle strength in this study. The positive correlation between muscle mass and strength has been well-established. However, it is important to note that higher muscle mass may not necessarily translate into greater muscle strength, and gains in muscle strength may be achieved without corresponding increases in muscle mass. It is therefore crucial to consider other lifestyle modifications beyond enhancing muscle mass. Studies in the general population showed that promoting physical activity through resistance training with protein supplementation may increase muscle mass and strength[49]. Vitamin D deficiency and anaemia are both common among KTRs. Literature in general[50] and CKD[51] populations indicated that vitamin D supplementation may improve muscle mass and strength, especially those with vitamin D deficiency[50]. Although the exact mechanisms have not been fully elucidated, it is postulated that the biologically active form of vitamin D binds to the vitamin D receptors located on skeletal muscle fibres, triggering *de novo* protein synthesis within the

muscle, possibly resulting in changes in muscle cell morphology and hence overall muscular performance[52]. Lastly, literature in the general population revealed an association between lower Hb levels and reduced muscle strength, particularly in the presence of anaemia[53], possibly with resultant decreased muscular tissue oxygenation ultimately manifesting as reduced muscular strength[53]. This implicates the correction of anaemia in KTRs as a potential means for improving muscle strength. Other possible factors influencing muscular strength should be considered, including muscle fibre type and contractility, the architectural arrangement of muscle fibres, muscle aerobic capacity, neuromuscular activation, and presence of intermuscular adipose tissue and muscle fibrosis[38]. Although these potential underlying mechanisms are beyond the scope of this study, findings from the current study should be considered as hypothesis-generating prequels to future research to elucidate the pathogenesis of reduced muscle strength at tissue level.

Notably, the prevalence of obesity (i.e. 41%) in this study remains comparable to the current literature[25,54,55], yet only 16% of KTRs fulfilled the criteria of sarcopenic obesity. In contrast to muscle strength, measures of adiposity and the composite phenomenon of sarcopenic obesity failed to demonstrate associations with clinical outcomes and health-related QoL. These findings are in partial agreement with Kovesdy, *et al.*, where no association was evident between BMI and mortality in KTRs[56]. The authors postulated that the "obesity paradox" observed in multiple chronic diseases including CKD may in part be responsible for this association. However, Kovesdy, *et al.*, found an association between mortality and central obesity measured by waist circumference[56], which differs from the results of this study. Whilst this discrepancy may be attributed to differences in patient characteristics of the study cohorts, the importance of central and generalised obesity should not be dismissed, as their adverse effects on kidney transplant outcomes tend to be reported in cohorts with

longer transplant vintage and follow-up duration. Nevertheless, it is crucial to highlight the emerging clinical importance of muscular indices, particularly muscle strength, in the medium term. Future evaluations should incorporate concurrent measurements of muscular and adiposity indices in resemblance to the methodology in the current study, aiming to dissect their relative importance and contributions to various clinical outcomes.

Although this study presents the first compelling association between decreased muscle strength and adverse clinical outcomes in kidney transplantation, it is hampered by a small sample size in a single centre. The inherent observational nature of the study precludes the establishment of causality between muscle strength and clinical outcomes. Further validations with prospective clinical trials are required to elucidate the potential beneficial effects of strength training in KTRs, thereby circumventing the confounding role of muscle strength in the co-morbidities that may directly impact on clinical outcome. Such studies should involve exercise interventions, incorporating resistance training and possibly adjunctive nutritional supplementation such as protein and vitamin D supplements.

In conclusion, this study shows that low muscle strength represents a common and clinically relevant problem in an otherwise stable kidney transplant population. Muscle strength assessment in routine clinical practice may serve as a novel tool for improving risk stratification in prevalent KTRs. Future clinical trials should evaluate the effectiveness of strength-based exercises on improving clinical outcomes and QoL in kidney transplantation.

Practical Application

This study presents the first compelling independent association between decreased muscle strength and adverse clinical outcomes in kidney transplantation. Muscle strength assessment in routine clinical practice may serve as a novel tool for improving risk stratification in prevalent KTRs, setting the scene for future interventional research and therapeutic strategies.

References

1. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *Journal of the American Medical Directors Association.* 2011;12(4):249-256.
2. Evans WJ, Campbell WW. Sarcopenia and age-related changes in body composition and functional capacity. *The Journal of nutrition.* 1993;123(2 Suppl):465-468.
3. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age and ageing.* 2010;39(4):412-423.
4. Morley JE, Abbatecola AM, Argiles JM, et al. Sarcopenia with limited mobility: an international consensus. *Journal of the American Medical Directors Association.* 2011;12(6):403-409.
5. Muscaritoli M, Anker SD, Argiles J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clinical Nutrition.* 2010;29(2):154-159.
6. Sayer AA, Syddall HE, Martin HJ, Dennison EM, Roberts HC, Cooper C. Is grip strength associated with health-related quality of life? Findings from the Hertfordshire Cohort Study. *Age and ageing.* 2006;35(4):409-415.
7. Kull M, Kallikorm R, Lember M. Impact of a new sarco-osteopenia definition on health-related quality of life in a population-based cohort in Northern Europe. *Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry.* 2012;15(1):32-38.
8. Noori N, Kopple JD, Kovesdy CP, et al. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. *Clinical journal of the American Society of Nephrology : CJASN.* 2010;5(12):2258-2268.
9. Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA. Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function. *Kidney international.* 2003;63(1):291-297.
10. Pereira RA, Cordeiro AC, Avesani CM, et al. Sarcopenia in chronic kidney disease on conservative therapy: prevalence and association with mortality. *Nephrology Dialysis Transplantation.* 2015;30(10):1718-1725.

11. Cawthon PM, Marshall LM, Michael Y, et al. Frailty in older men: prevalence, progression, and relationship with mortality. *Journal of the American Geriatrics Society.* 2007;55(8):1216-1223.
12. Landi F, Cruz-Jentoft AJ, Liperoti R, et al. Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from ilSIRENTE study. *Age and ageing.* 2013;42(2):203-209.
13. van den Ham EC, Kooman JP, Schols AM, et al. Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* 2005;5(8):1957-1965.
14. Clark BC, Manini TM. Sarcopenia ≠ Dynapenia. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2008;63(8):829-834.
15. Newman AB, Kupelian V, Visser M, et al. Strength, But Not Muscle Mass, Is Associated With Mortality in the Health, Aging and Body Composition Study Cohort. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2006;61(1):72-77.
16. Isoyama N, Qureshi AR, Avesani CM, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. *Clinical journal of the American Society of Nephrology : CJASN.* 2014;9(10):1720-1728.
17. Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet (London, England).* 2015;386(9990):266-273.
18. Wang AY, Sea MM, Ho ZS, Lui SF, Li PK, Woo J. Evaluation of handgrip strength as a nutritional marker and prognostic indicator in peritoneal dialysis patients. *The American journal of clinical nutrition.* 2005;81(1):79-86.
19. Ling CHY, Taekema D, de Craen AJM, Gussekloo J, Westendorp RGJ, Maier AB. Handgrip strength and mortality in the oldest old population: the Leiden 85-plus study. *CMAJ : Canadian Medical Association Journal.* 2010;182(5):429-435.
20. Strand BH, Cooper R, Bergland A, et al. The association of grip strength from midlife onwards with all-cause and cause-specific mortality over 17 years of follow-up in the Tromsø Study. *Journal of Epidemiology and Community Health.* 2016;70(12):1214-1221.
21. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *BMJ : British Medical Journal.* 2008;337(7661):92-95.
22. Ozkayar N, Altun B, Halil M, et al. Evaluation of sarcopenia in renal transplant recipients. *Nephro-urology monthly.* 2014;6(4):e20055.
23. Oterdoom LH, van Ree RM, de Vries AP, et al. Urinary creatinine excretion reflecting muscle mass is a predictor of mortality and graft loss in renal transplant recipients. *Transplantation.* 2008;86(3):391-398.
24. El Haggan W, Vendrely B, Chauveau P, et al. Early evolution of nutritional status and body composition after kidney transplantation. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2002;40(3):629-637.
25. Chan W, Bosch JA, Jones D, McTernan PG, Phillips AC, Borrows R. Obesity in kidney transplantation. *Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation.* 2014;24(1):1-12.
26. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity - definition, etiology and consequences. *Current opinion in clinical nutrition and metabolic care.* 2008;11(6):693-700.
27. Honda H, Qureshi AR, Axelsson J, et al. Obese sarcopenia in patients with end-stage renal disease is associated with inflammation and increased mortality. *The American journal of clinical nutrition.* 2007;86(3):633-638.
28. Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *Journal of applied physiology (Bethesda, Md : 1985).* 2003;95(5):1851-1860.

29. Wieskotten S, Moissl U, Chamney P, Wabel P. Reference Ranges for Human Body Composition and Fluid Overload. http://www.bcm-fresenius.com/mediafiles/information_on_reference_ranges.pdf.
30. World-Health-Organisation. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation. *Geneva, 8-11 December 2008.*
31. Miskulin DC, Athienites NV, Yan G, et al. Comorbidity assessment using the Index of Coexistent Diseases in a multicenter clinical trial. *Kidney international.* 2001;60(4):1498-1510.
32. National Collaborating Centre for Nursing and Supportive Care (UK). Appendix J, The General Practice Physical Activity Questionnaire (GPPAQ), Available from: https://www.ncbi.nlm.nih.gov/books/NBK51962/. *Irritable Bowel Syndrome in Adults: Diagnosis and Management of Irritable Bowel Syndrome in Primary Care [Internet].* 2008 Feb. (NICE Clinical Guidelines, No. 61.);London: Royal College of Nursing (UK).
33. Leal VO, Stockler-Pinto MB, Farage NE, et al. Handgrip strength and its dialysis determinants in hemodialysis patients. *Nutrition (Burbank, Los Angeles County, Calif).* 2011;27(11-12):1125-1129.
34. Wabel P, Chamney P, Moissl U, Jirka T. Importance of Whole-Body Bioimpedance Spectroscopy for the Management of Fluid Balance. *Blood Purification.* 2009;27(1):75-80.
35. Schlundt DG. Accuracy and Reliability of Nutrient Intake Estimates. *The Journal of nutrition.* 1988;118(12):1432-1435.
36. Gómez-Besteiro MI, Santiago-Pérez MI, Alonso-Hernández Á, Valdés-Cañedo F, Rebollo-Álvarez P. Validity and Reliability of the SF-36 Questionnaire in Patients on the Waiting List for a Kidney Transplant and Transplant Patients. *Am J Nephrol* 2004;24(3):346–351
37. Wang CW, Feng S, Covinsky KE, et al. A Comparison of Muscle Function, Mass, and Quality in Liver Transplant Candidates: Results from the Functional Assessment in Liver Transplantation (FrAILT) Study. *Transplantation.* 2016;100(8):1692-1698.
38. McGregor RA, Cameron-Smith D, Poppitt SD. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. *Longevity & healthspan.* 2014;3(1):9.
39. Wilson FP, Xie D, Anderson AH, et al. Urinary Creatinine Excretion, Bioelectrical Impedance Analysis, and Clinical Outcomes in Patients with CKD: The CRIC Study. *Clinical Journal of the American Society of Nephrology.* 2014;9(12):2095-2103.
40. Pedersen BK. The diseasome of physical inactivity--and the role of myokines in muscle--fat cross talk. *The Journal of physiology.* 2009;587(23):5559-5568.
41. Pedersen L, Hojman P. Muscle-to-organ cross talk mediated by myokines. *Adipocyte.* 2012;1(3):164-167.
42. Whitham M, Febbraio MA. The ever-expanding myokinome: discovery challenges and therapeutic implications. *Nature reviews Drug discovery.* 2016;15(10):719-729.
43. Cheema BS, Chan D, Fahey P, Atlantis E. Effect of progressive resistance training on measures of skeletal muscle hypertrophy, muscular strength and health-related quality of life in patients with chronic kidney disease: a systematic review and meta-analysis. *Sports medicine (Auckland, NZ).* 2014;44(8):1125-1138.
44. Greenwood SA, Koufaki P, Mercer TH, et al. Aerobic or Resistance Training and Pulse Wave Velocity in Kidney Transplant Recipients: A 12-Week Pilot Randomized Controlled Trial (the Exercise in Renal Transplant [ExeRT] Trial). *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2015;66(4):689-698.
45. Artero EG, Lee D-c, Lavie CJ, et al. Effects of Muscular Strength on Cardiovascular Risk Factors and Prognosis. *Journal of cardiopulmonary rehabilitation and prevention.* 2012;32(6):351-358.
46. Grygiel-Gorniak B, Puszczewicz M. A review on irisin, a new protagonist that mediates muscle-adipose-bone-neuron connectivity. *European review for medical and pharmacological sciences.* 2017;21(20):4687-4693.

47. O'Connor PJ, Herring MP, Caravalho A. Mental Health Benefits of Strength Training in Adults. *American Journal of Lifestyle Medicine.* 2010;4(5):377-396.
48. Mayer F, Scharhag-Rosenberger F, Carlsohn A, Cassel M, Müller S, Scharhag J. The Intensity and Effects of Strength Training in the Elderly. *Deutsches Ärzteblatt International.* 2011;108(21):359-364.
49. Pasiakos SM, McLellan TM, Lieberman HR. The effects of protein supplements on muscle mass, strength, and aerobic and anaerobic power in healthy adults: a systematic review. *Sports medicine (Auckland, NZ).* 2015;45(1):111-131.
50. Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2011;22(3):859-871.
51. Gordon PL, Sakkas GK, Doyle JW, Shubert T, Johansen KL. The Relationship between Vitamin D and Muscle Size and Strength in Patients on Hemodialysis. *Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation.* 2007;17(6):397-407.
52. Ceglia L. Vitamin D and Its Role in Skeletal Muscle. *Current opinion in clinical nutrition and metabolic care.* 2009;12(6):628-633.
53. Cesari M, Penninx BW, Lauretani F, et al. Hemoglobin levels and skeletal muscle: results from the InCHIANTI study. *The journals of gerontology Series A, Biological sciences and medical sciences.* 2004;59(3):249-254.
54. Lentine KL, Delos Santos R, Axelrod D, Schnitzler MA, Brennan DC, Tuttle-Newhall JE. Obesity and kidney transplant candidates: how big is too big for transplantation? *Am J Nephrol.* 2012;36(6):575-586.
55. Linda O, Kirsty A, Merrilyn B, David J, Nikky I, Ingrid H. Central obesity is common in renal transplant recipients and is associated with increased prevalence of cardiovascular risk factors. *Nutrition & Dietetics.* 2007;64(3):200-206.
56. Kovesdy CP, Czira ME, Rudas A, et al. Body mass index, waist circumference and mortality in kidney transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* 2010;10(12):2644-2651.

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Table 1: Baseline Population Characteristics

	All KTRs (n = 128)	KTRs with Normal Muscle Strength (n = 46)	KTRs with Low Muscle Strength (n = 82)	*p-value
Demographic & Lifestyle Parameters				
†Mean age (years)	49 ± 15	45 ± 14	52 ± 15	0.008
Gender (male, %)	56	48	62	0.15
[a]Ethnicity (%): Caucasian Non-Caucasian (Afro-Caribbean, Asian, and others)	 78 22	 80 20	 77 23	 0.83 0.83
‡Median time post-transplantation (years)	5 (2 – 11)	3 (1 – 7)	6 (2 – 14)	0.005
Smoking status (%): Non-smoker Ex-smoker Current smoker	 63 28 9	 70 22 8	 59 32 9	 0.26 0.23 0.98
‡Median alcohol intake (units/week)	3 (2 – 5)	3 (2 – 5)	3 (2 – 6)	0.95
†Mean physical activity level (hours/week)	14 ± 5	16 ± 6	13 ± 4	0.04
Clinical Parameters				
Pre-emptive transplantation (%)	22	28	18	0.20
‡Median Dialysis vintage (years)	2 (1 – 4)	1 (1 – 3)	2 (1 – 5)	0.04
‡Median ICED score	2 (2 – 2)	2 (2 – 2)	2 (2 – 2)	0.37
Presence of diabetes (%): Pre-transplantation DM NODAT Non-diabetic	 9 15 75	 4 16 78	 13 14 73	 0.13 0.80 0.68
Previous acute rejection episodes (%)	9	12	8	0.54
Statin usage (%)	55	56	54	0.98
Immunosuppressive medication usage (%): Prednisolone CNI Adjunctive antiproliferative agent	 78 91 88	 69 94 84	 92 88 90	 0.002 0.36 0.41
Dosage of immunosuppressive medications (mg/day): ‡Median dose of Prednisolone ‡Median dose of Tacrolimus ‡Median dose of Cyclosporin ‡Median dose of Mycophenolate Mofetil ‡Median dose of Azathioprine	 5 (5 – 5) 4.0 (2.5 – 7.4) 150 (150 – 200) 1000 (1000 – 1500) 100 (50 – 100)	 5 (5 – 5) 3.8 (2.0 – 5.5) 150 (140 – 200) 1000 (735 – 1220) 75 (50 – 100)	 5 (5 – 5) 5.0 (3.0 – 8.0) 150 (150 – 200) 1000 (1000 – 1500) 100 (50 – 100)	 0.44 0.20 0.62 0.35 0.71
Laboratory Parameters				
†Mean eGFR (mL/min/1.73m^2)	45 ± 18	47 ± 18	44 ± 18	0.47
‡Median hsCRP (mg/L)	2.47 (1.00 – 4.89)	2.00 (0.79 – 5.50)	2.67 (1.10 – 4.48)	0.42
†Mean Hb (g/dL)	12.7 ± 1.6	13.0 ± 1.7	12.5 ± 1.4	0.04
‡Median 25-hydroxyvitamin D (nmol/L)	40 (22 – 64)	60 (29 – 82)	35 (20 – 53)	0.001
Anthropometry, Nutritional Status & Body Composition Parameters				
†Mean BMI (kg/m^2)	28.1 ± 5.7	27.6 ± 5.5	28.4 ± 5.9	0.46
‡Median SGA score	7 (7 – 7)	7 (7 – 7)	7 (6 – 7)	0.10
†Mean waist circumference (cm)	98 ± 17	95 ± 17	100 ± 16	0.09
†Mean HGS (kg)	24.4 ± 9.3	30.3 ± 9.6	20.7 ± 6.8	<0.001

Bio-impedance measurements (kg/m^2): †Mean LTI (kg/m^2) †Mean FTI (kg/m^2)	 14.1 ± 2.9 13.8 ± 6.3	 15.1 ± 3.0 12.4 ± 5.6	 13.4 ± 2.7 14.7 ± 6.5	 0.002 0.04
Dietary Intake Parameters				
†Mean protein intake (g/kg/day) †Mean energy intake (kcal/kg/day)	1.10 ± 0.16 34 ± 8	1.25 ± 0.17 36 ± 9	1.01 ± 0.16 33 ± 7	0.04 0.20

*****Comparison between KTRs with normal and low muscle strength.

†Normally distributed data, results expressed as mean ± standard deviation.
‡Non-normally distributed data, results expressed as median with interquartile range.

[a]For the purpose of statistical analysis, the ethnicity of patients classified as Afro-Caribbean (5 %), Asian (15 %), and others (2 %) was grouped as "Non-Caucasian" (22 %).

Abbreviations: BMI = Body Mass Index; **CNI** = Calcineurin Inhibitor; **eGFR** = estimated Glomerular Filtration Rate; **FTI** = Fat Tissue Index; **Hb** = haemoglobin; **HGS** = Handgrip Strength; **hsCRP** = high-sensitivity C-Reactive Protein; **ICED** = Index of Coexistent Disease; **LTI** = Lean Tissue Index; **NODAT** = New Onset Diabetes After Transplantation; **Pre-transplantation DM** = Pre-transplantation Diabetes Mellitus; **KTRs** = Kidney Transplant Recipients; **SGA** = Subjective Global Assessment.

Table 2: Adjusted Associations of Muscular, Adiposity, and Composite Indices with the Risk of Mortality and Acute Hospitalisation

	*Model 1		**Model 2		***Model 3	
	Multivariate Cox Regression		Multivariate Cox Regression		Multivariate Cox Regression	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Muscular & Adiposity Indices (Continuous Scale)						
HGS (kg)	0.93 (0.90, 0.97)	<0.001	0.92 (0.89, 0.97)	<0.001	0.95 (0.90, 0.99)	0.03
LTI (kg/m^2)	0.89 (0.80, 0.99)	0.03	0.87 (0.75, 0.99)	0.04	0.88 (0.74, 1.02)	0.12
BMI (kg/m^2)	1.02 (0.98, 1.07)	0.36	1.01 (0.96, 1.07)	0.66	1.01 (0.92, 1.09)	0.65
FTI (kg/m^2)	1.03 (0.99, 1.08)	0.15	1.04 (0.99, 1.09)	0.16	1.02 (0.96, 1.08)	0.55
Waist Circumference (cm)	1.01 (0.99, 1.02)	0.51	1.01 (0.99, 1.02)	0.74	1.00 (0.97, 1.03)	0.97
Categorical and Composite Indices (Categorical Scale)						
[a]Low Muscle Strength	3.63 (2.16, 6.21)	<0.001	3.07 (1.71, 5.51)	<0.001	2.45 (1.30, 4.64)	0.006
[b]Low Muscle Mass	2.09 (1.10, 4.12)	0.02	1.78 (0.98, 3.67)	0.08	1.01 (0.62, 1.85)	0.19
[c]Sarcopenia	1.94 (1.10, 3.42)	0.02	1.76 (0.89, 3.48)	0.10	1.58 (0.69, 3.60)	0.28
[d]Obesity	1.31 (0.83, 2.06)	0.25	1.14 (0.69, 1.88)	0.35	1.15 (0.70, 1.80)	0.44
[e]Sarcopenic Obesity	2.36 (1.20, 4.63)	0.02	2.24 (0.99, 4.96)	0.08	1.89 (0.67, 5.37)	0.23

***Model 1:** Adjusted for age, gender, ethnicity, smoking status, and alcohol consumption.
****Model 2:** Adjusted for variables in model 1 plus ICED, diabetes status (non-diabetic or pre-transplantation DM or NODAT), eGFR, dialysis vintage, pre-emptive transplantation, time post transplantation, acute rejection episodes, use of statin, and use of CNI or adjunctive antiproliferative agent or prednisolone.
*****Model 3:** Adjusted for variables in models 1 and 2 plus SGA score, physical activity level, vitamin D, Hb, hsCRP, and dietary intakes of protein and energy.

[a]Low Muscle Strength, defined as HGS < Reference Cut-offs.
[b]Low Muscle Mass, defined as LTI < Reference Cut-offs.
[c]Sarcopenia, defined as both HGS and LTI < Reference Cut-offs.
[d]Obesity, defined as fulfillment of ≥ 2 out of 3 criteria from BMI ≥ $30kg/m^2$, FTI > Reference Cut-offs, and Waist Circumference > WHO Cut-offs.
[e]Sarcopenic Obesity, defined as a combination of sarcopenia and obesity.

Abbreviations: **BMI** = Body Mass Index; **CI** = Confidence Interval; **CNI** = calcineurin inhibitor; **eGFR** = estimated Glomerular Filtration Rate; **FTI** = Fat Tissue Index; **Hb** = Haemoglobin; **HR** = Hazard Ratio; **HGS** = Handgrip Strength; **hsCRP** = high-sensitivity C-Reactive Protein; **ICED** = Index of Coexistent Disease; **LTI** = Lean Tissue Index; **NODAT** = New Onset Diabetes After Transplantation; **Pre-transplantation DM** = Pre-transplantation Diabetes Mellitus; **SGA** = Subjective Global Assessment; **WHO** = World Health Organisation.

Table 3a: Adjusted Associations of Muscular, Adiposity, and Composite Indices with Physical Health-related Quality of Life

	*Model 1		**Model 2		***Model 3	
	Linear Regression		Linear Regression		Linear Regression	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Muscular & Adiposity Indices						
HGS (kg)	1.7 (1.2, 2.3)	0.001	1.6 (1.1, 2.3)	0.001	1.6 (0.9, 2.4)	0.001
LTI (kg/m^2)	1.2 (0.5, 1.9)	0.001	1.2 (0.5, 1.9)	0.005	1.1 (0.4, 1.8)	0.03
BMI (kg/m^2)	-0.2 (-0.9, 0.6)	0.69	-0.3 (-1.2, 0.6)	0.67	-0.4 (-1.6, 0.9)	0.66
FTI (kg/m^2)	-0.3 (-1.1, 0.4)	0.41	-0.1 (-0.8, 0.7)	0.48	-0.7 (-1.7, 0.4)	0.51
Waist Circumference (cm)	-0.1 (-3.0, 3.1)	0.39	-0.1 (-2.9, 3.2)	0.42	-0.2 (-0.6, 0.2)	0.58
Categorical and Composite Indices						
[a]Low Muscle Strength	-17.9 (-27.1, -8.7)	0.001	-16.5 (-26.2, -6.7)	0.001	-12.2 (-23.6, -0.8)	0.04
[b]Low Muscle Mass	-11.5 (-20.5, -2.4)	0.01	-10.3 (-18.2, -2.3)	0.03	-8.8 (-16.9, -0.8)	0.04
[c]Sarcopenia	-18.8 (-31.4, -6.2)	0.004	-14.1 (-23.6, -4.6)	0.004	-14.7 (-27.2, -2.5)	0.03
[d]Obesity	-3.9 (-12.2, 4.4)	0.36	-1.2 (-10.2, 7.7)	0.48	-0.9 (-11.3, 12.5)	0.41
[e]Sarcopenic Obesity	-12.9 (-26.1, 0.3)	0.06	-11.7 (-27.8, 4.5)	0.15	-5.7 (-26.9, 15.4)	0.59

***Model 1:** Adjusted for age, gender, ethnicity, smoking status, and alcohol consumption.
****Model 2:** Adjusted for variables in model 1 plus ICED, diabetes status (non-diabetic or pre-transplantation DM or NODAT), eGFR, dialysis vintage, pre-emptive transplantation, time post transplantation, acute rejection episodes, use of statin, and use of CNI or adjunctive antiproliferative agent or prednisolone.
*****Model 3:** Adjusted for variables in models 1 and 2 plus SGA score, physical activity level, vitamin D, Hb, hsCRP, and dietary intakes of protein and energy.

[a]Low Muscle Strength, defined as HGS < Reference Cut-offs.
[b]Low Muscle Mass, defined as LTI < Reference Cut-offs.
[c]Sarcopenia, defined as both HGS and LTI < Reference Cut-offs.
[d]Obesity, defined as fulfillment of ≥ 2 out of 3 criteria from BMI ≥ 30kg/m^2, FTI > Reference Cut-offs, and Waist Circumference > WHO Cut-offs.
[e]Sarcopenic Obesity, defined as a combination of sarcopenia and obesity.

Abbreviations: **β** = beta coefficient; **BMI** = Body Mass Index; **CI** = Confidence Interval; **CNI** = calcineurin inhibitor; **eGFR** = estimated Glomerular Filtration Rate; **FTI** = Fat Tissue Index; **Hb** = Haemoglobin; **HGS** = Handgrip Strength; **hsCRP** = high-sensitivity C-Reactive Protein; **ICED** = Index of Coexistent Disease; **LTI** = Lean Tissue Index; **NODAT** = New Onset Diabetes After Transplantation; **Pre-transplantation DM** = Pre-transplantation Diabetes Mellitus; **SGA** = Subjective Global Assessment; **WHO** = World Health Organisation.

Table 3b: Adjusted Associations of Muscular, Adiposity, and Composite Indices with Mental Health-related Quality of Life

	*Model 1		**Model 2		***Model 3	
	Linear Regression		Linear Regression		Linear Regression	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Muscular & Adiposity Indices						
HGS (kg)	1.2 (0.7, 1.6)	0.001	1.1 (0.5, 1.6)	0.001	0.8 (0.2, 1.5)	0.01
LTI (kg/m^2)	1.5 (1.0, 2.1)	0.002	1.1 (0.7, 1.6)	0.02	0.8 (-0.1, 1.8)	0.08
BMI (kg/m^2)	0.4 (-0.3, 1.1)	0.06	0.8 (-0.1, 1.7)	0.10	0.1 (-1.1, 1.1)	0.68
FTI (kg/m^2)	0.2 (-0.4, 0.8)	0.63	0.4 (-0.3, 1.1)	0.66	-0.3 (-1.2, 0.6)	0.68
Waist Circumference (cm)	0.2 (-0.1, 0.4)	0.18	0.2 (-0.1, 0.5)	0.19	-0.1 (-0.5, 0.3)	0.63
Categorical and Composite Indices						
[a]Low Muscle Strength	-11.1 (-19.7, -2.6)	0.01	-10.6 (-18.7, -2.5)	0.01	-9.9 (-19.6, -0.3)	0.04
[b]Low Muscle Mass	-10.3 (-18.1, -2.6)	0.01	-8.2 (-15.7, -0.5)	0.04	-1.1 (-11.2, 8.9)	0.21
[c]Sarcopenia	-13.2 (-23.2, -3.2)	0.02	-12.6 (-23.6, -1.6)	0.03	-7.4 (-20.6, 5.8)	0.26
[d]Obesity	-6.1 (-15.6, 3.5)	0.21	-1.8 (-9.5. 5.9)	0.64	-0.1 (-7.2, 6.9)	0.72
[e]Sarcopenic Obesity	-7.9 (-20.9, 5.1)	0.23	-4.3 (-18.2, 9.7)	0.54	-2.2 (-20.1. 15.5)	0.68

***Model 1:** Adjusted for age, gender, ethnicity, smoking status, and alcohol consumption.
****Model 2:** Adjusted for variables in model 1 plus ICED, diabetes status (non-diabetic or pre-transplantation DM or NODAT), eGFR, dialysis vintage, pre-emptive transplantation, time post transplantation, acute rejection episodes, use of statin, and use of CNI or adjunctive antiproliferative agent or prednisolone.
*****Model 3:** Adjusted for variables in models 1 and 2 plus SGA score, physical activity level, vitamin D, Hb, hsCRP, and dietary intakes of protein and energy.

[a]Low Muscle Strength, defined as HGS < Reference Cut-offs.
[b]Low Muscle Mass, defined as LTI < Reference Cut-offs.
[c]Sarcopenia, defined as both HGS and LTI < Reference Cut-offs.
[d]Obesity, defined as fulfillment of ≥ 2 out of 3 criteria from BMI ≥ 30kg/m^2, FTI > Reference Cut-offs, and Waist Circumference > WHO Cut-offs.
[e]Sarcopenic Obesity, defined as a combination of sarcopenia and obesity.

Abbreviations: β = beta coefficient; **BMI** = Body Mass Index; **CI** = Confidence Interval; **CNI** = calcineurin inhibitor; **eGFR** = estimated Glomerular Filtration Rate; **FTI** = Fat Tissue Index; **Hb** = Haemoglobin; **HGS** = Handgrip Strength; **hsCRP** = high-sensitivity C-Reactive Protein; **ICED** = Index of Coexistent Disease; **LTI** = Lean Tissue Index; **NODAT** = New Onset Diabetes After Transplantation; **Pre-transplantation DM** = Pre-transplantation Diabetes Mellitus; **SGA** = Subjective Global Assessment; **WHO** = World Health Organisation.

Table 4: Predictors of Muscle Strength (Handgrip Strength) in Kidney Transplant Recipients

	Univariate Linear Regression Analysis		Multivariate Linear Regression Analysis*	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**
Muscular and Adiposity Indices				
LTI (kg/m^2)	2.3 (1.9, 2.7)	<0.001	1.9 (1.4, 2.5)	<0.001
FTI (kg/m^2)	-0.2 (-0.5, 0.1)	0.07		
Waist circumference (cm)	0.2 (-0.3, 0.8)	0.10		
BMI (kg/m^2)	0.3 (0.1, 0.6)	0.04		
Demographic and Lifestyle Parameters				
†Age (years)	-1.2 (-2.2, -0.1)	0.01	-0.7 (-1.3, -0.1)	0.03
Gender (Male)	11.0 (8.4, 13.6)	<0.001	3.8 (1.0, 6.6)	0.009
§**Ethnicity** Caucasian Non-Caucasian	 0 -3.3 (-7.2, 0.6)	 0.10		
Smoking status Non-smoker Ex-smoker Current smoker	 0 -2.5 (-6.1, 1.1) -2.9 (-8.7, 2.8)	 0.31		
Alcohol consumption (units/week)	0.4 (-0.2, 0.9)	0.27		
Clinical Parameters				
ICED	0.1 (-4.7, 4.9)	0.96		
Diabetes status Non-diabetic NODAT Pre-transplantation DM	 0 -0.2 (-4.8, 4.4) -3.5 (-9.1, 2.0)	 0.21		
†Dialysis vintage (years)	-0.2 (-4.4, 4.1)	0.22		
Pre-emptive transplantation	1.7 (-2.2, 5.6)	0.20		
†Time post transplantation (years)	-2.4 (-4.7, -0.1)	0.04		
Acute rejection episodes	1.0 (-4.6, 6.6)	0.73		
Immunosuppressive medication Prednisolone CNI Adjunctive antiproliferative agent	 -5.9 (-11.4, -0.4) -3.2 (-7.1, 0.7) 1.5 (-3.4, 6.4)	 0.04 0.21 0.55		
Use of statin	1.3 (-2.0, 4.6)	0.43		
Laboratory Parameters				
†eGFR (mL/min/1.73m^2)	0.4 (-0.5, 1.3)	0.40		
†hsCRP (mg/L)	-0.4 (-2.7, 1.9)	0.76		
Hb (g/dL)	2.3 (1.3, 3.3)	<0.001	1.1 (0.2, 1.9)	0.001
†Vitamin D (nmol/L)	1.1 (0.6, 1.6)	<0.001	0.6 (0.2, 0.9)	0.005
Nutritional Status, Physical Activity Level, and Dietary Intake Parameters				
SGA score	3.4 (1.4, 5.3)	0.001		
Physical activity level (hours/week)	1.0 (0.5, 1.5)	<0.001	0.5 (0.2, 0.9)	0.003
†Protein intake (g/day)	1.7 (1.2, 2.3)	0.01	1.0 (0.5, 1.6)	0.04
‡Energy intake (kcal/day)	0.4 (0.1, 0.7)	0.04		
			Adjusted R^2	63%

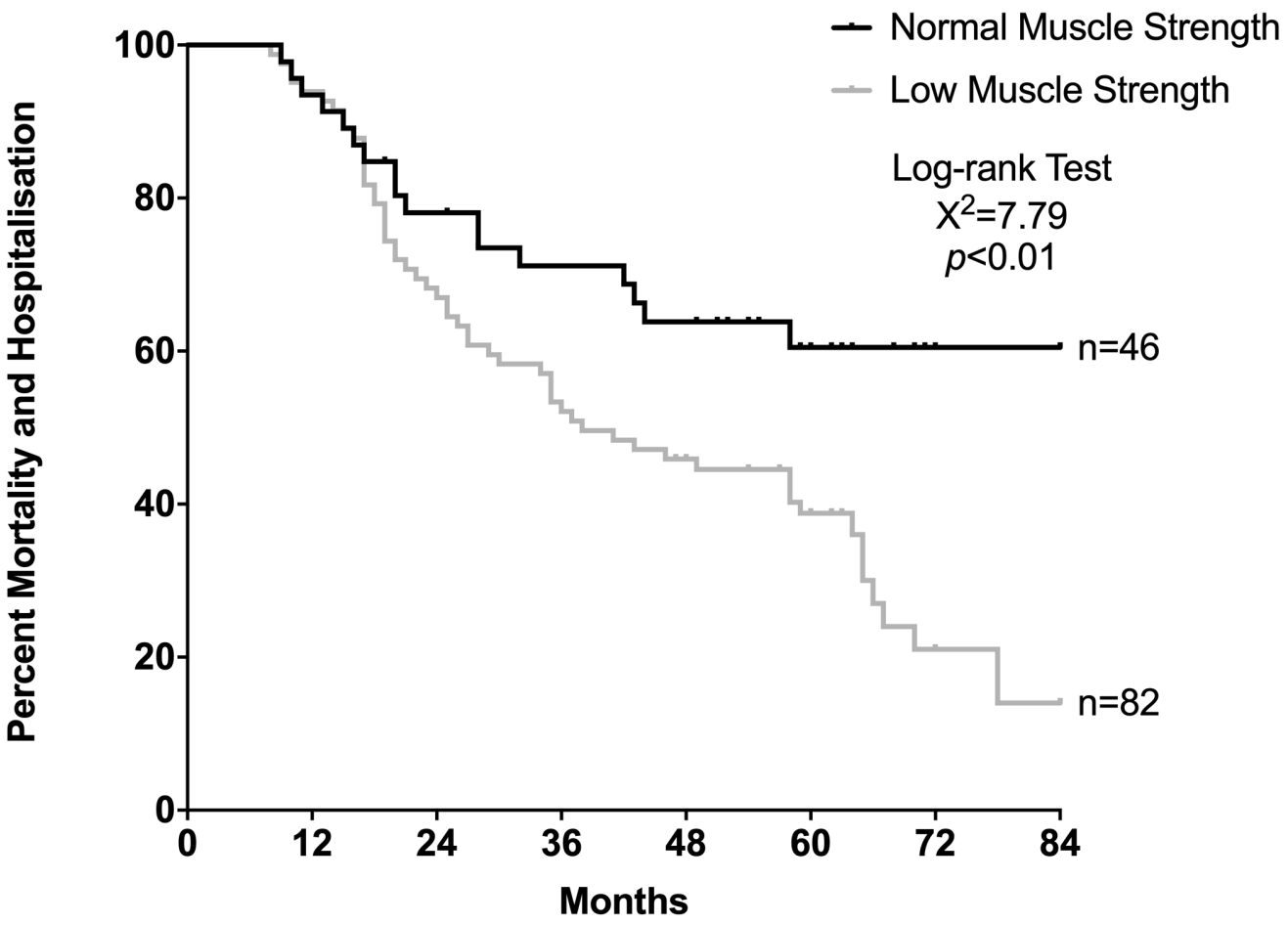
*****Results in the final multivariate linear regression model were presented.

§For the purpose of statistical analysis, the ethnicity of patients classified as "Afro-Caribbean", "Asian", and "others" was grouped as "Non-Caucasian"; 78 % "Caucasian" verses 22 % "Non-Caucasian".

†β reported for a 10-unit increase in explanatory variable. ‡β reported for a 100-unit increase in explanatory variable.

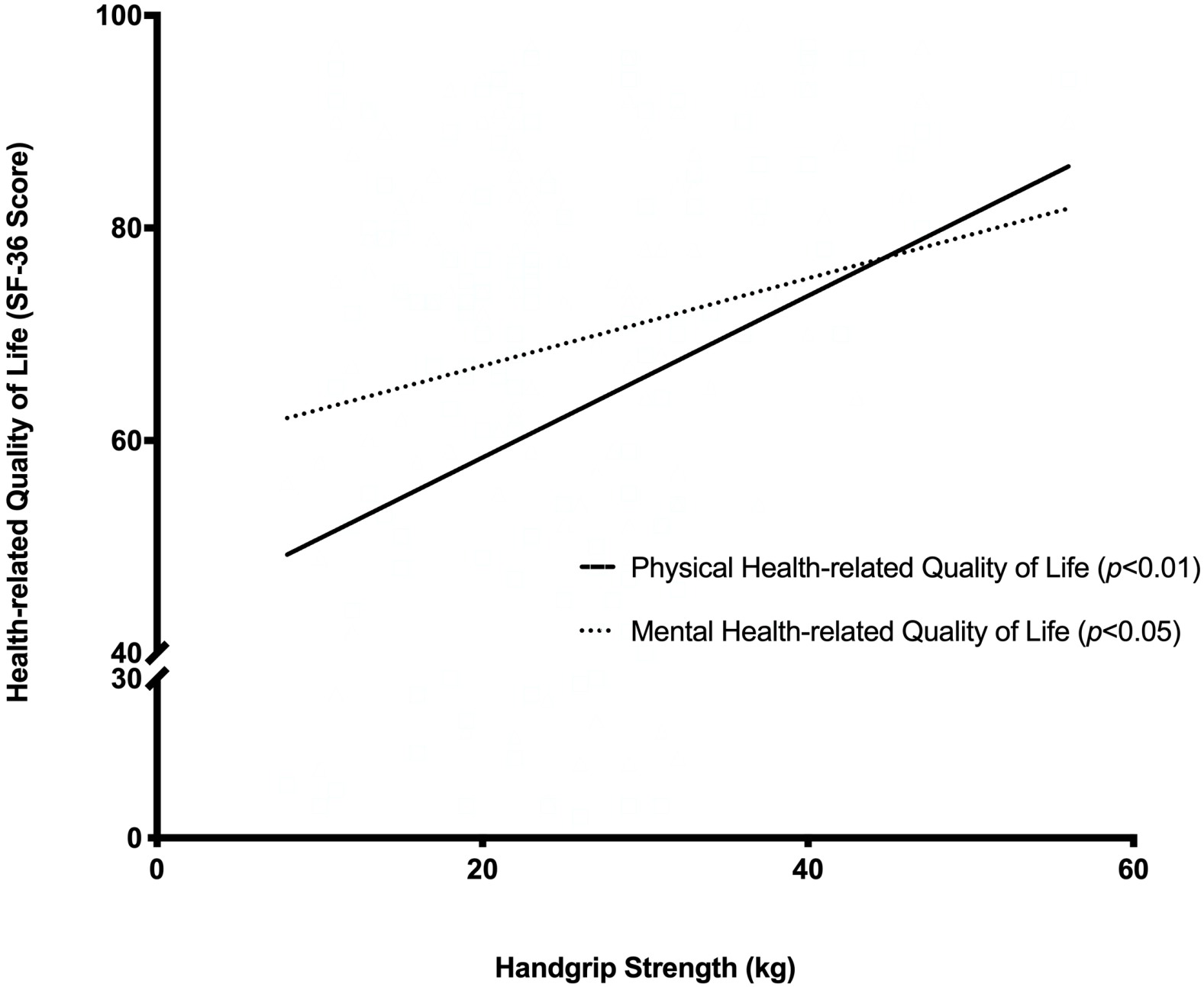
Abbreviations: β = beta coefficient**; BMI** = Body Mass Index; **CI** = Confidence Interval; **CNI** = Calcineurin Inhibitor; **eGFR** = estimated Glomerular Filtration Rate; **FTI** = Fat Tissue Index; **Hb** = Haemoglobin; **hsCRP** = high-sensitivity C-Reactive Protein; **ICED** = Index of Coexistent Disease; **LTI** = Lean Tissue Index; **NODAT** = New Onset Diabetes After Transplantation; **Pre-DM** = Pre-transplantation Diabetes Mellitus; **SGA** = Subjective Global Assessment.

Figure 1: Time to Composite Endpoint of All-Cause Mortality and Acute Hospitalisation in Kidney Transplant Recipients with Normal and Low Muscle Strength



Number at Risk	Months							
	0	12	24	36	48	60	72	84
Normal Muscle Strength	17	14	7	4	1	0	0	0
Low Muscle Strength	56	51	29	17	12	7	1	0

Figure 2: Association between Handgrip Strength and Health-related Quality of Life in Kidney Transplant Recipients



Supplementary Material, Table 1a: Correlations between Muscular and Adiposity Indices

Muscular and/or Obesity Indices	**HGS**			
LTI	$\tau = 0.73$ $p < 0.001$	**LTI**		
FTI	$\tau = -0.16$ $p = 0.07$	$\tau = -0.40$ $p < 0.001$	**FTI**	
BMI	$\tau = 0.19$ $p = 0.11$	$\tau = 0.06$ $p = 0.50$	$\tau = 0.89$ $p < 0.001$	**BMI**
Waist Circumference	$\tau = -0.31$ $p = 0.09$	$\tau = -0.16$ $p = 0.18$	$\tau = 0.71$ $p < 0.001$	$\tau = 0.87$ $p < 0.001$

Abbreviations: BMI = Body Mass Index, **FTI** = Fat Tissue Index, **HGS** = Handgrip Strength; **LTI** = Lean Tissue Index.

Supplementary Material, Table 1b: Correlations between Muscular Derangement Entities, Obesity, and Sarcopenic Obesity

Categorical or Composite Indices	*Low Muscle Strength	**Low Muscle Mass	***Sarcopenia	†Obesity
**Low Muscle Mass	$r = 0.25$ $p < 0.01$			
***Sarcopenia	$r = 0.67$ $p < 0.001$	$r = 0.59$ $p < 0.001$		
†Obesity	$r = 0.06$ $p = 0.53$	$r = 0.31$ $p < 0.01$	$r = 0.16$ $p = 0.07$	
††Sarcopenic Obesity	$r = 0.47$ $p < 0.001$	$r = 0.43$ $p < 0.001$	$r = 0.73$ $p < 0.001$	$r = 0.40$ $p < 0.001$

*Low Muscle Strength, defined as HGS < Reference Cut-offs.
** Low Muscle Mass, defined as LTI < Reference Cut-offs.
***Sarcopenia, defined as both HGS and LTI < Reference Cut-offs.
†Obesity, defined as fulfillment of ≥ 2 out of 3 criteria from BMI ≥ 30kg/m^2, FTI > Reference Cut-offs, and Waist Circumference > WHO Cut-offs.
††Sarcopenic Obesity, defined as a combination of sarcopenia and obesity.

Abbreviations: **BMI** = Body Mass Index, **HGS** = Handgrip Strength; **LTI** = Lean Tissue Index; **FTI** = Fat Tissue Index; **WHO** = World Health Organisation.

Supplementary Material, Table 2a: Univariate Associations of Muscular, Adiposity, and Composite Indices with the Risk of Mortality and Acute Hospitalisation

	Univariate Cox Regression	
	HR (95% CI)	**p-value**
Muscular & Adiposity Indices		
HGS (kg)	0.95 (0.92, 0.97)	<0.001
LTI (kg/m^2)	0.92 (0.85, 0.99)	0.03
BMI (kg/m^2)	1.01 (0.97, 1.06)	0.26
FTI (kg/m^2)	1.03 (0.99, 1.07)	0.11
Waist Circumference (cm)	1.00 (0.99, 1.02)	0.42
Categorical and Composite Indices		
[a]Low Muscle Strength	3.81 (2.37, 6.11)	<0.001
[b]Low Muscle Mass	1.06 (0.66, 1.71)	0.81
[c]Sarcopenia	2.39 (1.41, 4.03)	0.001
[d]Obesity	1.21 (0.79, 1.85)	0.17
[e]Sarcopenic Obesity	2.67 (1.42, 5.02)	0.002

[a]Low Muscle Strength, defined as HGS < Reference Cut-offs.
[b]Low Muscle Mass, defined as LTI < Reference Cut-offs.
[c]Sarcopenia, defined as both HGS and LTI < Reference Cut-offs.
[d]Obesity, defined as fulfillment of ≥ 2 out of 3 criteria from BMI ≥ 30kg/m^2, FTI > Reference Cut-offs, and Waist Circumference > WHO Cut-offs.
[e]Sarcopenic Obesity, defined as a combination of sarcopenia and obesity.

Abbreviations: **BMI** = Body Mass Index; **CI** = Confidence Interval; **FTI** = Fat Tissue Index; **HR** = Hazard Ratio; **HGS** = Handgrip Strength; **LTI** = Lean Tissue Index; **WHO** = World Health Organisation.

Supplementary Material, Table 2b: Univariate Associations between Covariates and the Risk of Mortality and Acute Hospitalisation

	Univariate Cox Regression	
	HR (95% CI)	**p-value**
Demographic and Social Parameters		
Age	1.05 (1.02, 1.09)	0.01
Gender (Male)	0.84 (0.53, 1.33)	0.45
Ethnicity: Caucasian Non-Caucasian (Asian, Afro-Caribbean, and Others)	 0.54 (0.34, 0.94) 1.77 (1.07, 2.92)	 0.03 0.03
Smoking status: Non-smoker Ex-smoker Current smoker	 1.00 1.29 (1.01, 1.71) 3.56 (1.80, 7.06)	 <0.001
Alcohol consumption (units/week)	0.95 (0.88, 1.04)	0.24
Clinical Parameters		
ICED	1.20 (1.09, 1.32)	0.04
Diabetes status: Non-diabetic NODAT Pre-transplantation DM	 1.00 1.31 (0.69, 2.50) 1.21 (0.60, 2.42)	 0.41
Dialysis vintage (years)	1.06 (1.01, 1.13)	0.03
Pre-emptive transplantation	0.82 (0.46, 1.48)	0.51
Time post transplantation (years)	1.10 (1.03, 1.19)	0.03
Acute rejection episodes	1.23 (0.59, 2.57)	0.59
Immunosuppressive medications: CNI Adjunctive antiproliferative agent Prednisolone	 1.06 (0.49, 2.31) 1.42 (0.68, 2.98) 1.32 (0.75, 2.33)	 0.89 0.35 0.34
Use of statin	1.21 (0.75, 1.95)	0.44
Laboratory Parameters		
eGFR (mL/min/1.73m^2)	0.99 (0.98, 1.01)	0.06
hsCRP	1.03 (1.01, 1.05)	0.04
Hb (g/dL)	0.81 (0.70, 0.93)	0.002
Vitamin D (nmol/L)	0.99 (0.98, 1.01)	0.11
Nutritional Status, Physical Activity Level, and Dietary Intake Parameters		
SGA score	0.77 (0.61, 0.98)	0.04
Physical activity level (hours/week)	1.01 (0.96, 1.04)	0.24
Protein intake (g/day)	0.99 (0.98, 1.01)	0.81
Energy intake (kcal/day)	0.99 (0.98, 1.01)	0.82

Abbreviations: CI = Confidence Interval; **CNI** = calcineurin inhibitor; **eGFR** = estimated Glomerular Filtration Rate; **Hb** = Haemoglobin; **HR** = Hazard Ratio; **hsCRP** = high-sensitivity C-Reactive Protein; **ICED** = Index of Coexistent Disease; **NODAT** = New Onset Diabetes After Transplantation; **Pre-transplantation DM** = Pre-transplantation Diabetes Mellitus; **SGA** = Subjective Global Assessment.

Supplementary Material, Table 3a: Univariate Associations of Muscular, Adiposity, and Composite Indices with Physical Health-related Quality of Life

	Univariate Linear Regression	
	β (95% CI)	**p-value**
Muscular & Adiposity Indices		
HGS (kg)	1.8 (1.3, 2.3)	<0.001
LTI (kg/m^2)	1.2 (0.6, 1.8)	<0.001
BMI (kg/m^2)	-0.1 (-0.9, 0.7)	0.67
FTI (kg/m^2)	-0.3 (-1.0, 0.5)	0.40
Waist Circumference (cm)	-0.1 (-0.4, 0.1)	0.29
Categorical and Composite Indices		
[a]Low Muscle Strength	-16.1 (-25.4, -6.9)	<0.001
[b]Low Muscle Mass	-10.9 (-20.1, -1.8)	0.01
[c]Sarcopenia	20.6 (-32.1, -9.2)	0.001
[d]Obesity	-5.8 (-13.7, 2.1)	0.15
[e]Sarcopenic Obesity	-14.3 (-29.4, 0.7)	0.06

[a]Low Muscle Strength, defined as HGS < Reference Cut-offs.
[b]Low Muscle Mass, defined as LTI < Reference Cut-offs.
[c]Sarcopenia, defined as both HGS and LTI < Reference Cut-offs
[d]Obesity, defined as fulfillment of ≥ 2 out of 3 criteria from BMI ≥ 30kg/m^2, FTI > Reference Cut-offs, and Waist Circumference > WHO Cut-offs.
[e]Sarcopenic Obesity, defined as a combination of sarcopenia and obesity.

Abbreviations: **β** = beta coefficient; **BMI** = Body Mass Index; **CI** = Confidence Interval; **FTI** = Fat Tissue Index; **HGS** = Handgrip Strength; **LTI** = Lean Tissue Index; **WHO** = World Health Organisation.

Supplementary Material, Table 3b: Univariate Associations of Muscular, Adiposity, and Composite Indices with Mental Health-related Quality of Life

	Univariate Linear Regression	
	β (95% CI)	**p-value**
Muscular & Adiposity Indices		
HGS (kg)	1.4 (1.0, 1.8)	<0.001
LTI (kg/m^2)	1.7 (1.0, 2.5)	0.001
BMI (kg/m^2)	0.6 (0.1, 1.1)	0.04
FTI (kg/m^2)	0.2 (-0.4, 0.8)	0.50
Waist Circumference (cm)	0.1 (-0.2, 0.4)	0.19
Categorical and Composite Indices		
[a]Low Muscle Strength	-10.8 (-17.9, -2.6)	0.001
[b]Low Muscle Mass	-9.9 (-17.8, -2.1)	0.001
[c]Sarcopenia	-14.2 (-23.2, -4.9)	0.01
[d]Obesity	-6.2 (-15.8, 3.3)	0.18
[e]Sarcopenic Obesity	-7.9 (-18.7, 2.5)	0.16

[a]Low Muscle Strength, defined as HGS < Reference Cut-offs.
[b]Low Muscle Mass, defined as LTI < Reference Cut-offs.
[c]Sarcopenia, defined as both HGS and LTI < Reference Cut-offs.
[d]Obesity, defined as fulfillment of ≥ 2 out of 3 criteria from BMI ≥ 30kg/m^2, FTI > Reference Cut-offs, and Waist Circumference > WHO Cut-offs.
[e]Sarcopenic Obesity, defined as a combination of sarcopenia and obesity.

Abbreviations: **β** = beta coefficient; **BMI** = Body Mass Index; **CI** = Confidence Interval; **FTI** = Fat Tissue Index; **HGS** = Handgrip Strength; **LTI** = Lean Tissue Index; **WHO** = World Health Organisation.

Supplementary Material, Table 3c: Univariate Associations between Covariates and Physical Health-related Quality of Life

	Univariate Linear Regression	
	β (95% CI)	**p-value**
Demographic and Social Parameters		
Age	0.1 (-0.3, 0.4)	0.86
Gender (Male)	-9.5 (-18.3, -0.6)	<0.001
Ethnicity: Caucasian Non-Caucasian (Asian, Afro-Caribbean, and Others)	 0 -4.4 (15.1, 6.3)	 0.42
Smoking status: Non-smoker Ex-smoker Current smoker	 0 -8.0 (-17.8, 1.8) -5.6 (-14.8, 3.6)	 0.11
Alcohol consumption (units/week)	0.4 (-1.1, 1.8)	0.63
Clinical Parameters		
ICED	-6.4 (-19.3, 6.6)	0.33
Diabetes status: Non-diabetic NODAT Pre-transplantation DM	 0 -1.9 (-14.4, 10.5) -10.5 (-25.6, 4.6)	 0.17
Dialysis vintage (years)	-0.6 (-1.8. 0.6)	0.32
Pre-emptive transplantation	-3.0 (-13.9, 7.8)	0.58
Time post transplantation (years)	-0.8 (-1.4, -0.1)	0.02
Acute rejection episodes	4.3 (-10.9, 19.4)	0.58
Immunosuppressive medications: CNI Adjunctive antiproliferative agent Prednisolone	 7.1 (-8.0, 22.3) 1.4 (-12.0, 14.8) 9.7 (-0.9, 20.3)	 0.36 0.83 0.07
Use of statin	1.8 (-7.2, 10.8)	0.69
Laboratory Parameters		
eGFR (mL/min/1.73m^2)	0.1 (-0.1, 0.4)	0.33
hsCRP	-0.1 (-0.7, 0.6)	0.92
Hb (g/dL)	3.2 (0.4, 6.1)	0.03
Vitamin D (nmol/L)	1.8 (0.4, 3.3)	0.01
Nutritional Status, Physical Activity Level, and Dietary Intake Parameters		
SGA score	4.9 (-0.5, 10.2)	0.08
Physical activity level (hours/week)	1.2 (0.3, 2.1)	0.01
Protein intake (g/day)	0.8 (-16.7, 18.2)	0.93
Energy intake (kcal/day)	-0.2 (-1.1, 0.6)	0.61

Abbreviations: **β** = beta coefficient; **CI** = Confidence Interval; **CNI** = calcineurin inhibitor; **eGFR** = estimated Glomerular Filtration Rate; **Hb** = Haemoglobin; **hsCRP** = high-sensitivity C-Reactive Protein; **ICED** = Index of Coexistent Disease; **NODAT** = New Onset Diabetes After Transplantation; **Pre-transplantation DM** = Pre-transplantation Diabetes Mellitus; **SGA** = Subjective Global Assessment.

Supplementary Material, Table 3d: Univariate Associations between Covariates and Mental Health-related Quality of Life

	Univariate Linear Regression	
	β (95% CI)	**p-value**
Demographic and Social Parameters		
Age	0.1 (-0.2, 0.3)	0.65
Gender (Male)	-9.2 (-16.9, -1.7)	0.02
Ethnicity: Caucasian Non-Caucasian (Asian, Afro-Caribbean, and Others)	 0 -2.5 (-11.7, 6.8)	 0.60
Smoking status: Non-smoker Ex-smoker Current smoker	 0 -9.5 (-17.9, -1.1) -1.1 (-14.7, 12.6)	 0.03
Alcohol consumption (units/week)	-0.6 (-1.8, 0.6)	0.34
Clinical Parameters		
ICED	-4.8 (-15.9, 6.4)	0.40
Diabetes status: Non-diabetic NODAT Pre-transplantation DM	 0 -1.9 (-10.8, 6.9) -6.1 (-19.2, 7.0)	 0.67
Dialysis vintage (years)	-0.4 (-1.4, 0.6)	0.46
Pre-emptive transplantation	-0.3 (-9.7, 9.1)	0.94
Time post transplantation (years)	-0.4 (-1.0, 0.1)	0.13
Acute rejection episodes	3.9 (-9.1, 17.1)	0.55
Immunosuppressive medications: CNI Adjunctive antiproliferative agent Prednisolone	 5.1 (-7.9, 18.2) -1.0 (-12.6, 10.6) 8.3 (-0.8, 17.5)	 0.44 0.86 0.07
Use of statin	8.1 (1.2, 15.1)	0.02
Laboratory Parameters		
eGFR (mL/min/1.73m^2)	0.1 (-0.2, 0.2)	0.80
hsCRP	-0.1 (-0.7, 0.4)	0.70
Hb (g/dL)	2.1 (-0.3, 4.6)	0.09
Vitamin D (nmol/L)	1.3 (0.1, 2.5)	0.04
Nutritional Status, Physical Activity Level, and Dietary Intake Parameters		
SGA score	4.2 (-0.4, 8.8)	0.07
Physical activity level (hours/week)	0.8 (-0.1, 1.5)	0.06
Protein intake (g/day)	0.9 (-0.5, 2.4)	0.20
Energy intake (kcal/day)	0.1 (-0.7, 0.8)	0.82

Abbreviations: **β** = beta coefficient; **CI** = Confidence Interval; **CNI** = calcineurin inhibitor; **eGFR** = estimated Glomerular Filtration Rate; **Hb** = Haemoglobin; **hsCRP** = high-sensitivity C-Reactive Protein; **ICED** = Index of Coexistent Disease; **NODAT** = New Onset Diabetes After Transplantation; **Pre-transplantation DM** = Pre-transplantation Diabetes Mellitus; **SGA** = Subjective Global Assessment.