Accepted author's manuscript. Published in final edited form as: Clinical Nutrition 2021 (in press). Publisher DOI: 10.1016/j.clnu.2021.03.013

Admission kidney function is a strong predictor for the response to nutritional support in patients at nutritional risk: *Secondary analysis of a prospective randomized trial*

[1,9]Annika Bargetzi, MD*, [9]Nora Emmenegger*, [9]Simone Wildisen*, [1,14]Manuela Nickler, MD, [1,9]Laura Bargetzi, MD, [1,9]Lara Hersberger, MD, [14]Stephan Segerer, Prof., [1]Nina Kaegi-Braun, MD, [1,2]Pascal Tribolet, RD, [1,13]Filomena Gomes, PhD, [3]Claus Hoess, MD, [3]Vojtech Pavlicek, MD, [4]Stefan Bilz, MD, [4]Sarah Sigrist, MD, [4]Michael Brändle, Prof., [5]Christoph Henzen, Prof., [6]Robert Thomann, MD, [7]Jonas Rutishauser, Prof., [8]Drahomir Aujesky, Prof., [8,11]Nicolas Rodondi, Prof., [8,12]Jacques Donzé, Prof., [10]Zeno Stanga, Prof., [1,9]Beat Mueller, Prof. and [1,9]Philipp Schuetz, Prof.

**equally contributing first authors*

[1] Medical University Department, Division of General Internal and Emergency Medicine, Kantonsspital Aarau, Aarau, Switzerland;

[2]Department of Health Professions, Bern University of Applied Sciences, Bern, Switzerland;

[3] Internal Medicine, Kantonsspital Muensterlingen, Switzerland;

[4] Internal Medicine & Endocrinology/Diabetes, Kantonsspital St.Gallen, Switzerland;

[5] Internal Medicine, Kantonsspital Luzern, Switzerland;

[6] Internal Medicine, Buergerspital Solothurn, Switzerland;

[7] Internal Medicine, Kantonsspital Baselland, Switzerland;

[8] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland;

[9] Medical Faculty of the University of Basel, Switzerland

[10] Division of Diabetes, Endocrinology, Nutritional Medicine & Metabolism, Inselspital, Bern University Hospital, University of Bern, Switzerland

[11]Institute of Primary Health Care (BIHAM), University of Bern, Switzerland;

[12]Division of General Internal Medicine, Brigham and Women's Hospital, Boston, MA, USA.

[13] The New York Academy of Sciences, New York City, NY, USA

[14] Division of Nephrology, Kantonsspital Aarau, Aarau, Switzerland

Keywords: kidney function, chronic kidney disease, malnutrition, nutritional support, clinical outcomes

Correspondence and reprint requests:
Prof. Dr. med. Philipp Schuetz, MD, MPH
University Department of Medicine
Kantonsspital Aarau
Tellstrasse
CH-5001 Aarau, Switzerland
Tel: +41 62 838 41 41(phone)
Fax: +41 62 838 41 00
E-mail: schuetzph@gmail.com

Abstract

Background: Patients with chronic kidney disease (CKD) are at substantial risk of malnutrition, which negatively affects clinical outcomes. We investigated the association of kidney function assessed at hospital admission and effectiveness of nutritional support in hospitalized medical patients at risk of malnutrition.

Methods: This is a secondary analysis of an investigator-initiated, randomized-controlled, Swiss multicenter trial (EFFORT) that compared individualised nutritional support with usual hospital food on clinical outcomes. We compared effects of nutritional support on mortality in subgroups of patients stratified according to kidney function at the time of hospital admission (estimated glomerular filtration rates [eGFR] <15, 15-29, 30-59, 60-89 and ≥90 ml/min/1.73m^2).

Results: We included 1,943 of 2,028 patients (96%) from the original trial with known admission creatinine levels. Admission eGFR was a strong predictor for the beneficial effects of nutritional support in regard to lowering of 30-day mortality. Patients with an eGFR <15, 15-29 and 30-59 had the strongest mortality benefit (odds ratios [95%CI] of 0.24 [0.05 to 1.25], 0.37 [0.14 to 0.95] and 0.39 [0.21 to 0.75], respectively), while patients with less severe impairment in kidney function had a less pronounced mortality benefits (p for interaction 0.001). A similar stepwise association of kidney function and response to nutritional support was found also for other secondary outcomes.

Conclusion: In medical inpatients at nutritional risk, admission kidney function was a strong predictor for the response to nutritional therapy. Initial kidney function thus may help to individualize nutritional support in the future by identification of patients with most clinical benefit.

Clinical trial registration: Registered under ClinicalTrials.gov Identifier no. NCT02517476

Keywords: malnutrition, nutritional support, outcome, randomized trial, chronic kidney disease, renal function

Introduction

The kidneys play a key role in maintaining fluid and electrolyte homeostasis, excretion of metabolic waste products, and regulation of various hormonal and metabolic pathways.[1] Patients with chronic kidney disease (CKD) display a variety of metabolic and nutritional abnormalities including protein-energy wasting. As a consequence, malnutrition is highly prevalent in the population of CKD patients [2-4]. Several factors put CKD patients at high risk of developing malnutrition including accumulation of nitrogen-containing compounds from dietary and intrinsic protein catabolism, which negatively affects appetite and taste, uremia that changes the microbiome, and disturbance of intestinal epithelia which reduces gastrointestinal nutrient absorption. Side effects of medication, as well as recommendations to follow a low protein diet are additional risk factors [2, 3, 5-8].

Importantly, patients with CKD admitted to hospital are often at risk for malnutrition or already malnourished, and their nutritional status further deteriorate during the hospital stay. Malnutrition is known to be strongly associated with increased mortality and morbidity, prolonged hospital stays, and functional decline [9]. There is currently strong evidence from clinical trials and meta-analyses of such trials demonstrating that nutritional support reduces risks associated with malnutrition in the medical inpatient population [3, 5, 10, 11]. Among these trials, the EFFORT (Effect of Early Nutritional Support on Frailty, Functional Outcomes and Recovery of Malnourished Medical Inpatients) trial showed a mortality benefit in medical inpatients at risk for malnutrition receiving nutritional support compared to usual care hospital nutrition. Interestingly, the most pronounced benefit of nutritional support was observed in the subgroup of patients with CKD [12]. While the importance of nutritional support in the population of CKD patients has been discussed for a long time, there has been an important lack of interventional data proving such a causal relationship [3, 6, 10, 11]. Previously, the importance of protein-restricted diets to delay the onset of renal replacement therapy has long been a key consideration in the nutritional management of CKD patients [13-16]. Yet, the results of different studies including the ‘Modification of Diet in Renal Disease’ (MDRD) study, failed to find a consistent beneficial effect of protein restriction for patients with CKD [14, 17, 18]. Some studies even found an increase in the risk for malnutrition along with low protein diet [15]. A 2018 Cochrane meta-analysis, found that very low protein diets probably reduce the

number of people with CKD 4 or 5, who progress to end-stage kidney disease, but low or very low protein diets probably do not influence death.[19] Still, older guidelines from 2002 recommended the application of low protein diet in early to moderate renal failure, but there is no general agreement on the level of GFR below which dietary protein intake should be reduced [3]. Similarly, the 2020 clinical practice guideline for nutrition in CKD recommended for adults with CKD stages 3-5 who are metabolically stable a protein restriction with or without keto acid analogs, to reduce risk for end-stage kidney disease (ESKD)/death and improve quality of life [1].

Herein, we performed a preplanned secondary analysis of a randomized multicenter trial in Switzerland [12] to investigate the association of kidney function as assessed by admission creatinine levels and the effects of nutritional support during the hospitalization on mortality and other clinical outcomes in patients with different stages of renal impairment.

Methods

Study design and setting

This is a secondary analysis of an investigator-initiated, prospective randomised controlled multicenter trial (EFFORT) [12]. The trial compared early individual nutritional support versus no nutritional support (usual care hospital nutrition) on different outcomes for in-hospital patients at nutritional risk. A total of eight secondary and tertiary care hospitals in Switzerland participated. The trial protocol [20] and the main results, as well as different secondary analyses, have been published previously[12, 21-25]. The ethics committee of northwest / central Switzerland (EKNZ) approved the study protocol in January 2014 (EKNZ; 2014_001).

Patient population

To assess inpatients at nutritional risk, the Nutritional Risk Screening 2002 (NRS-2002), a validated tool to determine risk of malnutrition, was used. This screening tool is composed of the severity of the underlying disease (which attributes 0-3 points); as well as weight loss, body mass index, food intake (0-3 points) and age over 70 years (1 point) with a higher score indicating higher risk for malnutrition. The original study included patients with a total score $\geq$ 3 points and an expected length

of stay > 4 days. Patients initially treated in an intensive care unit or surgical unit; unable to tolerate oral nutrition intake; with a terminal condition; treated for anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, stem cell transplantation or gastric bypass surgery; or existing contraindications for nutritional support were excluded.

For this secondary analysis, the study population was divided into five groups based on the estimated glomerular filtration rate (eGFR) at hospital admission (**Appendix, Supplemental Figure 1**). The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula [26]. Patients with missing creatinine level at hospital admission were excluded. An impaired renal function was defined as eGFR <90 ml/min/1.73m^2 Categorization was based on CKD stages as proposed by the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines [27]. For convenience we will refer to them as CKD stages 1 to 5. Patients on dialysis were assigned to CKD stage 5 (eGFR <15 ml/min/1.73m^2).

For the subgroup analysis regarding etiology of kidney failure, we stratified patients based on the comorbidities including diabetes, cardiovascular disease and hypertension. Macrovascular disease was defined as either suffering from peripheral arterial disease or coronary heart disease.

Study intervention

Patients randomized to the intervention group received personalized nutritional support within 48 hours after hospitalization and randomization. A trained registered dietitian developed an individual nutritional plan. The daily protein target was set at 1.2 – 1.5 g/kg of bodyweight (0.8 g/kg of bodyweight for patients with renal failure [eGFR <30]) and the Harris-Benedict equation was used to establish caloric requirements. The plan started with oral nutritional support. If less than 75% of caloric and protein targets were reached within 5 days, an escalation in nutritional support to enteral tube feeding or parenteral feeding was performed. Every 24 – 48 hours, the nutritional intake was re-assessed. Patients randomized to the control group received standard hospital food without nutritional consultation and implementation.

Endpoints

We investigated the association between admission kidney function and the effect of nutritional support on mortality within 30 days (primary endpoint). Secondary endpoints were grouped into clinical outcomes including all-cause mortality within 180 days, adverse outcome within 30 days (all-cause mortality, admission to an intensive care unit, non-elective hospital re-admission after discharge and major complications), major complication (nosocomial infection, respiratory failure, major cardiovascular event, acute renal failure and gastrointestinal failure) and the composite endpoint kidney failure (an increase of 1.5 times of serum creatinine level, decline in glomerular filtration rate of 25% and developing an eGFR of <15ml/min/m2); economically relevant outcomes within 30 days including admission to an intensive care unit, non-elective hospital re-admission and length of hospital stay (LOS); and functional outcomes (decline in functional status of 10% or more, functional impairment measured by the Barthel's Index and quality of life assessed with the European Quality of Life 5 Dimensions Index (including the visual-analogue scale EQ-5D VAS)).

Barthel's index ranges from 0 to 100 points, the European Quality of Life 5 Dimensions index (EQ-5D) ranges from 0 to 1 and EQ-5D VAS (including visual-analogue scale) ranges from 0 to 100 points, respectively. Higher scores indicate better performance of activities of daily living, better quality of life or better health status, respectively

Follow-up interviews, via phone calls, at day 30 and 180 were accomplished by study nurses who were blinded to group assignment. Mortality during follow-up was verified by family members or the patient's family physician.

Statistical analyses

The aim of this secondary analysis was to examine differences in the clinical response to nutritional support between patients with different eGFR stages at hospital admission. Second, we analyzed the prognostic implications of NRS 2002 in patients with renal impairment (eGFR <90ml/min/1.73m^2).

For the NRS 2002 analyses, we used regression models adjusted for study center, Barthel's Index and eGFR at admission. We calculated Cox regression models for time-to-event analyses with recorded hazard ratios (HR). A Kaplan Meier estimates was used for graphical display of the probability of all-cause mortality within 180 days.

We used regression models to explore an association between individual nutritional support and primary and secondary outcomes. We adjusted all models for predefined covariates including study centre, baseline nutritional risk (based on NRS 2002) and baseline Barthel's Index. We calculated logistic regression for binary outcomes with reporting of odds ratios (ORs) and linear regression models for continuous outcomes with reporting of coefficients. Kaplan Meier estimates were used to illustrate the primary endpoint. We performed subgroup analyses for etiology of renal impairment and admission diagnosis regarding 30-day mortality.

All statistical analyses were performed with STATA 15.1 (Stata Corp, College Station, TX, USA). A *P* value <0.05 (for a 2-sided test) was considered to indicate statistical significance.

Results

Out of 2'028 patients included in the original trial, we used data of 1'943 patients (96%) with available admission serum creatinine levels (see flow chart in **Appendix, Supplemental Figure 1**). **Table 1** shows baseline characteristics according to severity of impaired kidney function based on admission eGFR rates. While the overall burden of comorbidities was high in the overall cohort, patients with higher stages of CKD were older and had higher frequencies of comorbidities, particularly regarding diabetes, macrovascular disease and hypertension (**Table 1**). Groups were well balanced regarding randomization within the different CKD groups.

There was an increase in the average daily intake of calories and protein in intervention group patients compared to control group patients (see details in **Appendix, Supplemental Table 1**).

Prognostic significance of malnutrition risk in patients with impaired renal function

First, we performed an analysis to investigate whether nutritional risk as assessed by the NRS score is predictive for mortality in patients with an impaired renal function (eGFR <90 ml/min/1.73m^2). **Figure 1** shows the time to event analysis with a higher likelihood for 180-day mortality in patients stratified according to admission NRS of 3, 4 or ≥5 points (adjusted HR of 1.39 per increase in NRS (95% CI 1.21 to 1.59), p<0.001). Similar associations were found between NRS and impairment of activities of daily living and impairment in quality of life. No significant associations between

NRS and other endpoints were found, including length of hospital stay (LOS) or admission to an intensive care unit (**Table 2**).

Association of kidney function and effect of nutritional support on mortality

Second, we investigated effects of nutritional support on mortality stratified according to the kidney function of patients (**Table 3**). Admission eGFR was a strong predictor for the beneficial effects of nutritional support in regard to lowering of 30-day mortality, with patients with an eGFR <15, 15-29 and 30-59 showing the strongest benefit (adjusted OR 0.24 [95%CI 0.05 to 1.25], 0.37 [95%CI 0.14 to 0.95] and 0.39 [95%CI 0.21 to 0.75], respectively), while patients with less severe impairment in kidney function had a less pronounced mortality benefit (p for interaction 0.001). Results were similar for mortality at 180 days, with the greatest benefit observed on those with more severe kidney function impairment, although the overall effect was less pronounced. **Figure 2** shows Kaplan Meier survival estimates for the different groups regarding 30-day mortality.

Associations of admission eGFR and secondary endpoints

Third, we investigated effects of nutritional support on other secondary endpoints stratified according to the kidney function of patients (**Table 3**). Similar to the primary endpoint, we found an association between kidney function and effects of nutritional support on several secondary endpoints with evidence for effect modification, including mortality at 180 days (p for interaction 0.002), decline in functional status (p for interaction 0.006), and quality of life measures (p for interaction 0.001 and 0.014).

Subgroup analysis for 30- and 180-day mortality

Finally, we performed a subgroup analyses, to better understand whether the association between kidney function and effect of nutritional support would also be influenced by illnesses with relevant impact on kidney function. We observed a greater benefit of nutritional support in patients with impaired kidney function and macrovascular disease than in patients suffering from diabetes or hypertension regarding 30-day mortality (**Figure 3**). No significant difference was observed regarding 180-day mortality (**Figure 4**).

289
290
291

Discussion

The main finding of this secondary analysis of a multicenter randomized trial is that kidney function is a strong predictor for treatment response to nutritional support in regard to mortality and other outcomes in medical inpatients at nutritional risk. While malnutrition has for long been identified as an important prognostic factor in patients with CKD, the notion that these patients show a strong benefit from nutritional support is novel and has important clinical implications. There are several findings of this analysis worth discussing in more detail.

First, our data show that malnutrition risk, as assessed by the NRS 2002, in patients with impaired renal function is strongly associated with adverse clinical outcomes. Specifically, patients with a NRS 2002 score of ≥5 points had a doubling in the risk for mortality over 180 days compared to patients with a NRS 2002 score of 3 points (16.9% vs. 32.5%). This association was true also at short term follow up, and even more pronounced for long-term mortality. Results were also similar regarding functional outcome and quality of life measures and remained significant in the multivariate analysis. These results are in line with previous studies showing that nutritional risk has a major impact on outcomes of medical patients [9, 24, 28], and specifically also for CKD patients [3, 6, 13].

Second, our data show that patients with nutritional risk and impaired kidney function show strong benefit from individualized nutritional support, as compared to usual hospital food. Specifically, when stratifying patients based on the admission eGFR, we found a stepwise increase in effect size from our intervention. While guidelines recommend nutritional monitoring in CKD patients [3, 29, 30], there is currently insufficient evidence from randomized trials supporting a more widespread use of nutritional support in these patients. In some of the larger nutritional trials, including the NOURISH trial, patients with advanced kidney failure were excluded due to possible harm associated with higher protein contents of oral supplements [31]. Unlike these trials, we included patients with different severities of renal impairment and recommended lower protein goals of 0.8g/kg bodyweight per day for patients with renal failure. Whether higher targets would have produced similar results, however, remains unclear from our trial.

Third, functional ability including quality of life or activities of daily living have been found to be significantly impaired in CKD patients [32, 33]. Previous research found functional disability to aggravate along with worsening of the kidney function [34]. Previous studies also showed a positive association of nutritional status and functional ability in general patient populations [24, 35]. In addition, an Australian trial also found an association between quality of life and nutritional status in pre-dialysis patients, and more importantly an improvement in quality of life through providing personalized nutritional counselling in comparison with standard nutritional care [36]. In line with these results, our data show a strong improvement in quality of life and functional status through the provision of nutritional support in hospitalized patients with impaired admission renal function.

Forth, when looking into subgroup analyses based on different comorbidities as presumed etiological factors of kidney failure, we did not find significant interactions except for patients with impaired kidney function and macrovascular disease regarding 30-day mortality. In most patients, however, the etiology of CKD was not proven by kidney biopsy but relied on clinical parameters including past history of diabetes or hypertension – the most common risk factors for CKD [29, 37-39]. Based on the ESPEN Guidelines, particularly for patients with diabetic nephropathy, a restriction of dietary protein is advised [3, 40-43], as previous research found an improvement in kidney function through low-protein diet in this patient population [41, 43]. However, other studies could not replicate these findings of a low-protein diet [17, 18]. Investigating the modification of hypertension through nutritional support and its influence on CKD [44-47], sodium restriction appeared to be an important factor to treat hypertension and therefore delay renal failure [46, 47]. A meta-analysis including six studies and data of 566’156 individual patients investigated the association of adherence to the DASH diet (Dietary Approaches to Stop Hypertension) and clinical outcomes. Based on their results, the DASH diet was inversely associated with the incidence of CKD and protective against a rapid decline in eGFR [45]. While a specific dietary pattern (DASH diet) seems to have a protective role in the etiology of CKD, once the disease is established and places the patient at risk of malnutrition, the benefit from nutritional support seem to be clear.

To the best of our knowledge this is the first study to investigate clinical and functional benefits of nutritional support in patients according to different CKD stages. There are still limitations to this analysis including the non-blinding of patients and dieticians, the lack of follow-up information regarding kidney function during follow-up, and the use of different protein targets to validate the protein target used in the protocol (0.8 g protein/kg bodyweight and day). Furthermore, about 20% of patients in the intervention group did not achieve their protein and caloric goals according to the nutritional protocol. Also, we conducted our analysis based on the creatinine level at hospital admission and did not have baseline creatinine of each patient at hand. We could therefore not stratify our analysis based on acute or chronic kidney failure.

In conclusion, our trial data indicate that (1) admission kidney function was a strong predictor for the response to nutritional therapy in medical inpatients at nutritional risk, and (b) nutritional risk is a strong prognostic indicator in patients with CKD. Initial kidney function thus may help to individualize nutritional support in the future by identification of patients that show most benefit from this intervention.

ACKNOWLEDGMENTS

We thank all patients and hospital staff for support of the EFFORT trial.

DISCLOSURES

The study was investigator-initiated and supported by a grant from the Swiss National Foundation to P.Schuetz (SNSF Professorship, PP00P3_150531) and the Forschungsrat of the Kantonsspital Aarau (1410.000.058 and 1410.000.044). The Institution of P.Schuetz has previously received unrestricted grant money unrelated to this project from Neste Health Science and Abbott Nutrition. The institution of Z.Stanga received speaking honoraria and research support from Neste Health Science, Abbott Nutrition and Fresenius Kabi. Mr. St. Segerer was supported by a grant of the Fundação Pesquisa e Desenvolvimento Humanitario. All other authors report no conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract form.

Author contributions

AB, NE, SW and PS were responsible for the data analysis and interpretation of this secondary analysis. AB, NE, SW and PS drafted the final manuscript with all authors contributing to critical revision of the manuscript. PS was responsible for obtaining funding. MN, LB, LH, StS, NK, PT were involved in data collection and approved the final version of the manuscript.

FG, CH, VP, SB, SS, MB, CH, RT, JR, DA, NR, JD were involved in drafting the trial protocol, supervision of study sites, drafting of the final manuscript and approving the final version of the manuscript of the original EFFORT trial.

ZS and BM were involved in obtaining funding, drafting the trial protocol, supervision of study sites, drafting of the final manuscript of the original EFFORT trial and approved the final version of the current manuscript. The corresponding authors had full access to all the data used and had a shared final responsibility for the accuracy of the analysed data.

The data underlying this article cannot be shared publicly due to the privacy of patients who participated in this trial. The data will be shared on reasonable request to the corresponding author once all secondary analyses are finalized.

References

[1] Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. Am J Kidney Dis. 2020;76:S1-S107.

[2] Iorember FM. Malnutrition in Chronic Kidney Disease. Front Pediatr. 2018;6:161.

[3] Toigo G, Aparicio M, Attman PO, Cano N, Cianciaruso B, Engel B, et al. Expert Working Group report on nutrition in adult patients with renal insufficiency (part 1 of 2). Clin Nutr. 2000;19:197-207.

[4] Garg AX, Blake PG, Clark WF, Clase CM, Haynes RB, Moist LM. Association between renal insufficiency and malnutrition in older adults: results from the NHANES III. Kidney Int. 2001;60:1867-74.

[5] Kalantar-Zadeh K, Fouque D. Nutritional Management of Chronic Kidney Disease. N Engl J Med. 2017;377:1765-76.

[6] Kalantar-Zadeh K, Fouque D. Nutritional Management of Chronic Kidney Disease. N Engl J Med. 2018;378:584-5.

[7] Carrero JJ, Thomas F, Nagy K, Arogundade F, Avesani CM, Chan M, et al. Global Prevalence of Protein-Energy Wasting in Kidney Disease: A Meta-analysis of Contemporary Observational Studies From the International Society of Renal Nutrition and Metabolism. J Ren Nutr. 2018;28:380-92.

[8] Aggarwal HK, Jain D, Chauda R, Bhatia S, Sehgal R. Assessment of Malnutrition Inflammation Score in Different Stages of Chronic Kidney Disease. Pril (Makedon Akad Nauk Umet Odd Med Nauki). 2018;39:51-61.

[9] Felder S, Lechtenboehmer C, Bally M, Fehr R, Deiss M, Faessler L, et al. Association of nutritional risk and adverse medical outcomes across different medical inpatient populations. Nutrition. 2015;31:1385-93.

[10] Toigo G, Aparicio M, Attman PO, Cano N, Cianciaruso B, Engel B, et al. Expert working group report on nutrition in adult patients with renal insufficiency (Part 2 of 2). Clin Nutr. 2000;19:281-91.

[11] Cano N, Fiaccadori E, Tesinsky P, Toigo G, Druml W, Dgem, et al. ESPEN Guidelines on Enteral Nutrition: Adult renal failure. Clin Nutr. 2006;25:295-310.

[12] Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet. 2019;393:2312-21.

[13] Yan B, Su X, Xu B, Qiao X, Wang L. Effect of diet protein restriction on progression of chronic kidney disease: A systematic review and meta-analysis. PLoS One. 2018;13:e0206134.

[14] Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med. 1994;330:877-84.

[15] Yue H, Zhou P, Xu Z, Liu L, Zong A, Qiu B, et al. Effect of low-protein diet on kidney function and nutrition in nephropathy: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr. 2020;39:2675-85.

[16] Rhee CM, Ahmadi SF, Kovesdy CP, Kalantar-Zadeh K. Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. J Cachexia Sarcopenia Muscle. 2018;9:235-45.

[17] Rughooputh MS, Zeng R, Yao Y. Protein Diet Restriction Slows Chronic Kidney Disease Progression in Non-Diabetic and in Type 1 Diabetic Patients, but Not in Type 2

462 Diabetic Patients: A Meta-Analysis of Randomized Controlled Trials Using Glomerular
463 Filtration Rate as a Surrogate. PLoS One. 2015;10:e0145505.
464 [18] Pan Y, Guo LL, Jin HM. Low-protein diet for diabetic nephropathy: a meta-analysis
465 of randomized controlled trials. Am J Clin Nutr. 2008;88:660-6.
466 [19] Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with
467 chronic kidney disease. Cochrane Database Syst Rev. 2018;10:CD001892.
468 [20] Schuetz P, Fehr R, Baechli V, Geiser M, Gomes F, Kutz A, et al. Design and rationale of
469 the effect of early nutritional therapy on frailty, functional outcomes and recovery of
470 malnourished medical inpatients (EFFORT): a pragmatic, multicenter, randomized-
471 controlled trial-Protocol. International Journal of Clinical Trials. 2018;5:142-50.
472 [21] Schuetz P, Sulo S, Walzer S, Vollmer L, Stanga Z, Gomes F, et al. Economic evaluation
473 of individualized nutritional support in medical inpatients: Secondary analysis of the
474 EFFORT trial. Clin Nutr. 2020;39:3361-8.
475 [22] Merker M, Felder M, Gueissaz L, Bolliger R, Tribolet P, Kagi-Braun N, et al.
476 Association of Baseline Inflammation With Effectiveness of Nutritional Support Among
477 Patients With Disease-Related Malnutrition: A Secondary Analysis of a Randomized
478 Clinical Trial. JAMA Netw Open. 2020;3:e200663.
479 [23] Kaegi-Braun N, Tribolet P, Gomes F, Fehr R, Baechli V, Geiser M, et al. Six-month
480 outcomes after individualized nutritional support during the hospital stay in medical
481 patients at nutritional risk: Secondary analysis of a prospective randomized trial. Clin
482 Nutr. 2020.
483 [24] Hersberger L, Bargetzi L, Bargetzi A, Tribolet P, Fehr R, Baechli V, et al. Nutritional
484 risk screening (NRS 2002) is a strong and modifiable predictor risk score for short-term
485 and long-term clinical outcomes: secondary analysis of a prospective randomised trial.
486 Clin Nutr. 2020;39:2720-9.
487 [25] Friedli N, Baumann J, Hummel R, Kloter M, Odermatt J, Fehr R, et al. Refeeding
488 syndrome is associated with increased mortality in malnourished medical inpatients:
489 Secondary analysis of a randomized trial. Medicine (Baltimore). 2020;99:e18506.
490 [26] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new
491 equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-12.
492 [27] Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney
493 Disease Guideline Development Work Group M. Evaluation and management of chronic
494 kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical
495 practice guideline. Ann Intern Med. 2013;158:825-30.
496 [28] Sanson G, Sadiraj M, Barbin I, Confezione C, De Matteis D, Boscutti G, et al.
497 Prediction of early- and long-term mortality in adult patients acutely admitted to
498 internal medicine: NRS-2002 and beyond. Clin Nutr. 2020;39:1092-100.
499 [29] Brown RO, Compher C, American Society for P, Enteral Nutrition Board of D.
500 A.S.P.E.N. clinical guidelines: nutrition support in adult acute and chronic renal failure.
501 JPEN J Parenter Enteral Nutr. 2010;34:366-77.
502 [30] Harada K, Suzuki S, Ishii H, Hirayama K, Aoki T, Shibata Y, et al. Nutrition Status
503 Predicts Severity of Vascular Calcification in Non-Dialyzed Chronic Kidney Disease. Circ
504 J. 2017;81:316-21.
505 [31] Deutz NE, Matheson EM, Matarese LE, Luo M, Baggs GE, Nelson JL, et al.
506 Readmission and mortality in malnourished, older, hospitalized adults treated with a
507 specialized oral nutritional supplement: A randomized clinical trial. Clin Nutr.
508 2016;35:18-26.
509 [32] Wyld MLR, Morton RL, Aouad L, Magliano D, Polkinghorne KR, Chadban S. The
510 impact of comorbid chronic kidney disease and diabetes on health-related quality-of-
511 life: a 12-year community cohort study. Nephrol Dial Transplant. 2020.

[33] Thancharoen O, Waleekhachonloet O, Limwattananon C, Anutrakulchai S. Cognitive impairment, quality of life and healthcare utilization in patients with chronic kidney disease stages 3 to 5. Nephrology (Carlton). 2020;25:625-33.
[34] Mandelli S, Riva E, Tettamanti M, Detoma P, Giacomin A, Lucca U. Association of renal function with cognition, functional ability and mood in the oldest-old: The 'Health and Anemia study'. Nephrology (Carlton). 2020;25:48-54.
[35] Vearing R, Casey S, Zaremba C, Bowden S, Ferguson A, Goodisson C, et al. Evaluation of the impact of a post-hospital discharge Transitional Aged Care Service on frailty, malnutrition and functional ability. Nutr Diet. 2019;76:472-9.
[36] Campbell KL, Ash S, Bauer JD. The impact of nutrition intervention on quality of life in pre-dialysis chronic kidney disease patients. Clin Nutr. 2008;27:537-44.
[37] Yu Z, Rebholz CM, Wong E, Chen Y, Matsushita K, Coresh J, et al. Association Between Hypertension and Kidney Function Decline: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis. 2019;74:310-9.
[38] Wang M, Li J, Li Y, Yao S, Zhao M, Wang C, et al. The effects of hypertension and diabetes on new-onset chronic kidney disease: A prospective cohort study. J Clin Hypertens (Greenwich). 2020;22:39-46.
[39] Tomiyama C, Higa A, Dalboni MA, Cendoroglo M, Draibe SA, Cuppari L, et al. The impact of traditional and non-traditional risk factors on coronary calcification in pre-dialysis patients. Nephrol Dial Transplant. 2006;21:2464-71.
[40] Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. Ann Intern Med. 1996;124:627-32.
[41] Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med. 1991;324:78-84.
[42] Giordano M, Ciarambino T, Castellino P, Cataliotti A, Malatino L, Ferrara N, et al. Long-term effects of moderate protein diet on renal function and low-grade inflammation in older adults with type 2 diabetes and chronic kidney disease. Nutrition. 2014;30:1045-9.
[43] Nezu U, Kamiyama H, Kondo Y, Sakuma M, Morimoto T, Ueda S. Effect of low-protein diet on kidney function in diabetic nephropathy: meta-analysis of randomised controlled trials. BMJ Open. 2013;3.
[44] Raphael KL. The Dietary Approaches to Stop Hypertension (DASH) diet in chronic kidney disease: should we embrace it? Kidney Int. 2019;95:1296-8.
[45] Taghavi M, Sadeghi A, Maleki V, Nasiri M, Khodadost M, Pirouzi A, et al. Adherence to the dietary approaches to stop hypertension-style diet is inversely associated with chronic kidney disease: a systematic review and meta-analysis of prospective cohort studies. Nutr Res. 2019;72:46-56.
[46] Mallamaci F, Pisano A, Tripepi G. Hypertension management in chronic kidney disease. Nephrol Dial Transplant. 2020.
[47] Yuzbashian E, Asghari G, Mirmiran P, Amouzegar-Bahambari P, Azizi F. Adherence to low-sodium Dietary Approaches to Stop Hypertension-style diet may decrease the risk of incident chronic kidney disease among high-risk patients: a secondary prevention in prospective cohort study. Nephrol Dial Transplant. 2018;33:1159-68.

Tables and Figure Legend

Table 1. Patient baseline characteristics

Figure 1. Effect of nutritional status on 180-day mortality in patients with impaired renal function [print: bw; suppl.: colour]

Table 2. Association between NRS-2002 and outcomes in patients with impaired renal function

Table 3. Effect of nutritional support on outcomes, stratified by admission estimated glomerular filtration rate (eGFR)

Figure 2. Kaplan Meier estimates of 30-day all-cause mortality [print: bw; suppl.: colour]

Figure 3. Association between nutritional support and 30-day mortality in pre-specified subgroups

Figure 4. Association between nutritional support and 180-day mortality in pre-specified subgroups

Appendix

Supplemental Figure 1. Trial profile

Supplemental Table 1. Amount of protein and calories reached

583 **TABLES LEGENDS**

584 **Table 1. Patient baseline characteristics**

Factor	eGFR ≥ 90			eGFR 60-89			eGFR 30-59			eGFR 15-29			eGFR <15		
Randomization	Control	Intervention	p-value	Control	Intervention	p-value	Control	Intervention	p-value	Control	Intervention	p-value	Control	Intervention	p-value
N	235	206		303	332		288	281		101	112		42	43	
Sociodemographics															
Male sex (%)	132 (56.2%)	114 (55.3%)	0.86	155 (51.2%)	178 (53.6%)	0.54	146 (50.7%)	135 (48.0%)	0.53	52 (51.5%)	55 (49.1%)	0.73	32 (76%)	25 (58%)	0.077
Mean age (years) (SD)	58.3 (14.9)	56.7 (14.5)	0.24	74.5 (10.6)	74.4 (11.0)	0.9	79.3 (8.8)	78.2 (9.5)	0.16	80.5 (8.5)	80.8 (10.2)	0.8	77.6 (9.1)	72.6 (12.8)	0.042
Age group (%)															
< 65 years	119 (50.6%)	114 (55.3%)	0.16	36 (11.9%)	38 (11.4%)	0.91	11 (3.8%)	10 (3.6%)	0.65	2 (2.0%)	5 (4.5%)	0.57	1 (2%)	5 (10%)	0.12
65 - 75 years	89 (37.9%)	79 (38.3%)		110 (36.3%)	126 (38.0%)		79 (27.4%)	87 (31.0%)		22 (21.8%)	22 (19.6%)		15 (36%)	19 (44%)	
>75 years	27 (11.5%)	13 (6.3%)		157 (51.8%)	168 (50.6%)		198 (68.8%)	184 (65.5%)		77 (76.2%)	85 (75.9%)		26 (62%)	19 (44%)	
Nutritional assessment															
Mean BMI (kg/m2) (SD)	23.3 (4.8)	23.1 (4.8)	0.59	24.5 (5.3)	24.9 (5.4)	0.43	25.7 (5.1)	25.7 (5.4)	0.91	25.1 (5.2)	26.0 (5.1)	0.17	25.2 (5.3)	25.2 (5.6)	1
Mean bodyweight (kg) (SD)	67.6 (16.7)	66.2 (15.4)	0.44	71.3 (16.0)	71.8 (17.1)	0.71	72.3 (16.3)	73.7 (17.6)	0.39	71.4 (15.1)	72.8 (15.5)	0.57	72.7 (16.0)	67.2 (15.8)	0.16
NRS 2002 score (%)															
3 points	91 (38.7%)	79 (38.3%)	0.52	94 (31.0%)	100 (30.1%)	0.87	73 (25.3%)	82 (29.2%)	0.5	27 (26.7%)	31 (27.7%)	0.8	11 (26%)	8 (19%)	0.13
4 points	90 (38.3%)	87 (42.2%)		112 (37.0%)	125 (37.7%)		116 (40.3%)	98 (34.9%)		40 (39.6%)	46 (41.1%)		12 (29%)	23 (53%)	
5 points	46 (19.6%)	37 (18.0%)		83 (27.4%)	87 (26.2%)		80 (27.8%)	85 (30.2%)		25 (24.8%)	29 (25.9%)		15 (36%)	9 (21%)	
6 points	8 (3.4%)	3 (1.5%)		14 (4.6%)	20 (6.0%)		19 (6.6%)	16 (5.7%)		9 (8.9%)	6 (5.4%)		4 (10%)	3 (7%)	
Weight loss - no. (%)															
≤5% in 3 months	110 (46.8%)	92 (44.7%)	0.91	160 (52.8%)	170 (51.2%)	0.27	163 (56.6%)	155 (55.2%)	0.93	60 (59.4%)	65 (58.0%)	0.85	26 (62%)	15 (35%)	0.068
>5% in 3 months	33 (14.0%)	30 (14.6%)		49 (16.2%)	47 (14.2%)		35 (12.2%)	39 (13.9%)		17 (16.8%)	16 (14.3%)		3 (7%)	8 (19%)	
>5% in 2 months	29 (12.3%)	30 (14.6%)		46 (15.2%)	43 (13.0%)		39 (13.5%)	36 (12.8%)		7 (6.9%)	11 (9.8%)		2 (5%)	5 (12%)	
>5% in 1 months	63 (26.8%)	54 (26.2%)		48 (15.8%)	72 (21.7%)		51 (17.7%)	51 (18.1%)		17 (16.8%)	20 (17.9%)		11 (26%)	15 (35%)	
Loss of appetite - no. (%)															
No	37 (15.7%)	29 (14.1%)	0.62	40 (13.2%)	40 (12.0%)	0.66	25 (8.7%)	25 (8.9%)	0.93	5 (5.0%)	10 (8.9%)	0.26	5 (12%)	4 (9%)	0.7
Yes	198 (84.3%)	177 (85.9%)		263 (86.8%)	292 (88.0%)		263 (91.3%)	256 (91.1%)		96 (95.0%)	102 (91.1%)		37 (88%)	39 (91%)	
Normal required food intake preceding week - no. (%)															
>75%	32 (13.6%)	23 (11.2%)		43 (14.2%)	36 (10.8%)	0.3	22 (7.6%)	27 (9.6%)	0.83	2 (2.0%)	4 (3.6%)	0.35	4 (10%)	3 (7%)	0.39
50-75%	50 (21.3%)	56 (27.2%)		90 (29.7%)	116 (34.9%)		104 (36.1%)	95 (33.8%)		32 (31.7%)	47 (42.0%)		10 (24%)	12 (28%)	
25-50%	99 (42.1%)	89 (43.2%)		129 (42.6%)	129 (38.9%)		115 (39.9%)	114 (40.6%)		48 (47.5%)	45 (40.2%)		20 (48%)	14 (33%)	
<25%	54 (23.0%)	38 (18.4%)		41 (13.5%)	51 (15.4%)		47 (16.3%)	45 (16.0%)		19 (18.8%)	16 (14.3%)		8 (19%)	14 (33%)	
Severity of illness - no. (%)															
Very Mild	7 (3.0%)	8 (3.9%)	0.37	11 (3.6%)	11 (3.3%)	0.5	5 (1.7%)	5 (1.8%)	0.88	2 (2.0%)	1 (0.9%)	0.49	0 (0%)	0 (0%)	0.082

Mild	141 (60.0%)	129 (62.6%)		186 (61.4%)	219 (66.0%)		192 (66.7%)	180 (64.1%)		77 (76.2%)	77 (68.8%)		26 (62%)	34 (79%)	
Moderate	84 (35.7%)	69 (33.5%)		103 (34.0%)	101 (30.4%)		86 (29.9%)	89 (31.7%)		21 (20.8%)	33 (29.5%)		16 (38%)	9 (21%)	
Severe	3 (1.3%)	0 (0.0%)		3 (1.0%)	1 (0.3%)		5 (1.7%)	7 (2.5%)		1 (1.0%)	1 (0.9%)		0 (0%)	0 (0%)	
Etiology of kidney failure															
Diabetes	NA	NA		60 (19.8%)	69 (20.8%)	0.76	86 (29.9%)	71 (25.3%)	0.22	36 (35.6%)	38 (33.9%)	0.79	14 (33%)	17 (40%)	0.5
Macrovascular Disease	NA	NA		93 (30.7%)	100 (30.1%)	0.88	113 (39.2%)	115 (40.9%)	0.68	57 (56.4%)	56 (50.0%)	0.35	20 (48%)	18 (42%)	0.59
Hypertension	NA	NA		156 (51.5%)	182 (54.8%)	0.4	198 (68.8%)	191 (68.0%)	0.84	73 (72.3%)	73 (65.2%)	0.27	25 (60%)	26 (60%)	0.93
Glomerulonephritis	NA	NA		0 (0.0%)	3 (0.9%)		1 (0.3%)	4 (1.4%)		5 (5.3%)	1 (1.0%)		4 (8.2%)	5 (9.8%)	
Dialysis															
Hemodialysis	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		8 (19%)	7 (16%)	0.59
Peritoneal Dialysis	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0%)	1 (2%)	
Comorbidities															
Diabetes	28 (11.9%)	24 (11.7%)	0.93	53 (17.5%)	64 (19.3%)	0.56	78 (27.1%)	68 (24.2%)	0.43	31 (30.7%)	35 (31.2%)	0.93	14 (33%)	16 (37%)	0.71
Hypertension	74 (31.5%)	60 (29.1%)	0.59	156 (51.5%)	182 (54.8%)	0.4	198 (68.8%)	191 (68.0%)	0.84	73 (72.3%)	73 (65.2%)	0.27	25 (60%)	26 (60%)	0.93
Coronary heart disease	18 (7.7%)	17 (8.3%)	0.82	81 (26.7%)	90 (27.1%)	0.92	98 (34.0%)	103 (36.7%)	0.51	52 (51.5%)	48 (42.9%)	0.21	16 (38%)	15 (35%)	0.76
Peripheral artery disease	14 (6.0%)	7 (3.4%)	0.21	20 (6.6%)	19 (5.7%)	0.65	35 (12.2%)	31 (11.0%)	0.68	19 (18.8%)	14 (12.5%)	0.2	10 (24%)	7 (16%)	0.39
Chronic heart failure	15 (6.4%)	7 (3.4%)	0.15	45 (14.9%)	40 (12.0%)	0.3	67 (23.3%)	68 (24.2%)	0.79	32 (31.7%)	44 (39.3%)	0.25	9 (21%)	9 (21%)	0.96
Tumor	72 (30.6%)	77 (37.4%)	0.14	106 (35.0%)	118 (35.5%)	0.88	100 (34.7%)	93 (33.1%)	0.68	26 (25.7%)	28 (25.0%)	0.9	13 (31%)	9 (21%)	0.29
Chronic obstructive pulmonary disease	41 (17.4%)	27 (13.1%)	0.21	43 (14.2%)	52 (15.7%)	0.6	42 (14.6%)	45 (16.0%)	0.64	18 (17.8%)	10 (8.9%)	0.055	4 (10%)	5 (12%)	0.75
Stroke	14 (6.0%)	8 (3.9%)	0.32	33 (10.9%)	18 (5.4%)	0.011	23 (8.0%)	32 (11.4%)	0.17	11 (10.9%)	12 (10.7%)	0.97	4 (10%)	3 (7%)	0.67
Dementia	4 (1.7%)	1 (0.5%)	0.23	10 (3.3%)	11 (3.3%)	0.99	15 (5.2%)	18 (6.4%)	0.54	2 (2.0%)	5 (4.5%)	0.31	3 (7%)	3 (7%)	0.98
Mean GFR (SD)															
Day 1	103 (12)	105 (12)	0.14	77 (9)	77 (9)	0.74	45 (8)	46 (8)	0.1	23 (4)	23 (4)	0.8	10 (3)	9 (3)	0.066
Day 7/Discharge	103 (15)	105 (16)	0.24	79 (13)	79 (13)	0.78	54 (17)	56 (16)	0.22	35 (16)	34 (15)	0.98	25 (28)	21 (21)	0.49
Mean Kreatinine (SD)															
Day 1	58 (14)	57 (13)	0.63	76 (14)	77 (14)	0.82	120 (25)	117 (24)	0.2	210 (45)	209 (44)	0.88	466 (170)	550 (246)	0.08
Day 7/Discharge	58 (15)	57 (15)	0.73	74 (18)	74 (17)	0.93	107 (36)	104 (34)	0.31	165 (61)	165 (68)	0.95	303 (164)	340 (201)	0.4
Mean Phosphat (SD)															
Day 1	0.88 (0.26)	0.85 (0.23)	0.49	0.87 (0.24)	0.87 (0.23)	0.97	1.00 (0.31)	0.98 (0.37)	0.68	1.17 (0.41)	1.15 (0.27)	0.73	1.71 (0.56)	1.64 (0.58)	0.62
Day 7/Discharge	0.93 (0.26)	0.96 (0.23)	0.52	0.92 (0.26)	0.98 (0.36)	0.14	1.01 (0.31)	0.97 (0.24)	0.2	1.02 (0.36)	1.03 (0.34)	0.86	1.20 (0.46)	1.12 (0.44)	0.49

Groups based on the estimated glomerular filtration rate (eGFR) at hospital admission. Continuous values as median and IQR, categorial/binary values as absolute number and percentage. BMI = Body Mass Index, NRS = Nutritional Risk Screening

585

586

Table 2. Association between NRS-2002 and outcomes in patients with impaired renal function

	NRS 3 points (N=426)	**NRS 4 points** (N=572)	**NRS ≥5 points** (N=504)	**p-value**	**Hazard Ratio (HR), Odds Ratio (OR), Coefficient**	**Regression analysis** (adjusted) (95% CI and p-value)
Primary outcome						
All-cause mortality within 30 days	28 (6.6%)	52 (9.1%)	57 (11.3%)	0.044	HR	1.19 (0.95 to 1.48), p=0.130
Secondary outcomes						
Clinical outcome						
All-cause mortality within 180 days	72 (16.9%)	136 (23.8%)	164 (32.5%)	<0.001	HR	1.39 (1.21 to 1.59), p<0.001
Adverse Outcome within 30 days	97 (22.8%)	143 (25.0%)	142 (28.2%)	0.160	OR	1.12 (0.96 to 1.31), p=0.145
Kidney Failure Event	22 (5.2%)	20 (3.5%)	28 (5.6%)	0.240	OR	0.94 (0.68 to 1.30), p=0.711
Non-elective hospital readmission within 30 days	37 (8.7%)	45 (7.9%)	46 (9.1%)	0.750	HR	1.07 (0.86 to 1.35), p=0.537
Mean length of stay (days)	8.9 (6.0)	9.9 (6.6)	9.7 (6.6)	0.054	Coefficient	0.36 (-0.06 to 0.77), p=0.091
Functional outcome						
Decline of functional status of >10%	46 (10.8%)	70 (12.2%)	77 (15.3%)	0.110	OR	1.19 (0.97 to 1.46), p=0.088
Mean Barthel score (points) within 30 days	95.09 (9.41)	94.86 (9.40)	94.22 (10.50)	0.350	Coefficient	-0.14 (-0.76 to 0.48), p=0.655
Mean EQ-5D index (points)	0.77 (0.30)	0.73 (0.34)	0.69 (0.35)	0.004	Coefficient	-0.02 (-0.04 to 0.00), p=0.033
Mean EQ-5D VAS index (points)	61 (25)	57 (27)	54 (29)	0.005	Coefficient	-1.96 (-3.88 to -0.05), p=0.044

Data are number of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for study centre, Barthel's Index and eGFR at admission. Continuous values are median and IQR, categorial/ binary values as absolute number and percentage

HR = Hazard Ratio, OR = Odds Ratio, EQ-5D = Euroquol-5 Dimensions, VAS = Visual Analogue Scale

591 **Table 3. Effect of nutritional support on outcomes, stratified by admission eGFR**

	Control	Intervention	p-value	Hazard Ratio (HR), Odds Ratio (OR), Coefficient	Regression analysis (adjusted) (95% CI and p-value)	P interaction
Primary outcome						
All-cause mortality within 30 days						
GFR ≥90	11/235 (4.7%)	17/206 (8.3%)	0.120	OR	1.78 (0.77 to 4.08), p=0.175	0.001
GFR 60-89	20/303 (6.6%)	24/332 (7.2%)	0.760	OR	1.06 (0.55 to 2.03), p=0.862	
GFR 30-59	36/288 (12.5%)	16/281 (5.7%)	0.005	OR	0.39 (0.21 to 0.75), p=0.004	
GFR 15-29	18/101 (17.8%)	9/112 (8.0%)	0.032	OR	0.37 (0.14 to 0.95), p=0.038	
GFR <15	10/42 (24%)	4/43 (9%)	0.071	OR	0.24 (0.05 to 1.25), p=0.090	
Secondary outcome						
Clinical Outcome						
All-cause mortality within 180 days						
GFR ≥90	40/235 (17.0%)	46/206 (22.3%)	0.160	OR	1.53 (0.90 to 2.58), p=0.116	0.002
GFR 60-89	68/303 (22.4%)	75/332 (22.6%)	0.960	OR	1.01 (0.68 to 1.50), p=0.974	
GFR 30-59	73/288 (25.3%)	64/281 (22.8%)	0.470	OR	0.91 (0.61 to 1.35), p=0.637	
GFR 15-29	38/101 (37.6%)	28/112 (25.0%)	0.047	OR	0.58 (0.31 to 1.09), p=0.089	
GFR <15	17/42 (40%)	9/43 (21%)	0.051	OR	0.19 (0.05 to 0.68), p=0.010	
Adverse Outcome within 30 days						
GFR ≥90	48/235 (20.4%)	50/206 (24.3%)	0.330	OR	1.20 (0.75 to 1.93), p=0.451	0.026
GFR 60-89	69/303 (22.8%)	66/332 (19.9%)	0.370	OR	0.83 (0.56 to 1.23), p=0.345	
GFR 30-59	91/288 (31.6%)	68/281 (24.2%)	0.049	OR	0.70 (0.48 to 1.02), p=0.063	
GFR 15-29	34/101 (33.7%)	28/112 (25.0%)	0.045	OR	0.42 (0.21 to 0.82), p=0.011	
GFR <15	14/42 (40%)	13/43 (30%)	0.320	OR	0.49 (0.15 to 1.63), p=0.245	
KidneyFailureEvent						
GFR ≥90	6/235 (2.6%)	4/206 (1.9%)	0.670	OR	0.80 (0.22 to 2.97), p=0.742	0.782
GFR 60-89	14/303 (4.6%)	13/332 (3.9%)	0.660	OR	0.80 (0.36 to 1.78), p=0.588	
GFR 30-59	17/288 (5.9%)	8/281 (2.8%)	0.075	OR	0.46 (0.19 to 1.10), p=0.080	
GFR 15-29	6/101 (5.9%)	7/112 (6.2%)	0.920	OR	0.98 (0.29 to 3.36), p=0.975	
GFR <15	2/42 (5%)	1/43 (2%)	0.540	OR	1.63 (0.05 to 48.35), p=0.774	
Non-elective hospital readmission within 30 days						
GFR ≥90	21/235 (8.9%)	21/206 (10.2%)	0.650	OR	1.16 (0.60 to 2.23), p=0.660	0.851
GFR 60-89	28/303 (9.2%)	25/332 (7.5%)	0.440	OR	0.84 (0.47 to 1.48), p=0.537	

GFR 30-59	26/288 (9.0%)	24/281 (8.5%)	0.840	OR	0.96 (0.53 to 1.74), p=0.890	
GFR 15-29	8/101 (8.9%)	9/112 (8.0%)	0.820	OR	0.55 (0.18 to 1.60), p=0.271	
GFR <15	2/42 (5%)	5/43 (12%)	0.250	OR	7.09 (0.19 to 272.05), p=0.292	
Mean length of stay (days)						
GFR ≥90	9.7 (6.6)	9.4 (7.2)	0.620	Coefficient	-0.38 (-1.65 to 0.88), p=0.550	0.782
GFR 60-89	9.1 (5.7)	9.0 (6.8)	0.800	Coefficient	-0.16 (-1.12 to 0.80), p=0.748	
GFR 30-59	9.5 (6.0)	9.8 (6.9)	0.650	Coefficient	0.22 (-0.82 to 1.26), p=0.673	
GFR 15-29	10.4 (5.6)	97 (6.3)	0.400	Coefficient	-0.46 (-2.14 to 1.21), p=0.586	
GFR <15	12.2 (7.7)	11.3 (7.7)	0.630	Coefficient	-0.62 (-4.29 to 3.05), p=0.737	
Functional Outcome						
Decline of functional status of >10%						
GFR ≥90	19/235 (8.1%)	24/206 (11.7%)	0.210	OR	1.51 (0.78 to 2.91), p=0.223	0.006
GFR 60-89	38/303 (12.5%)	34/332 (10.2%)	0.360	OR	0.83 (0.50 to 1.38), p=0.484	
GFR 30-59	52/288 (18.1%)	24/281 (8.5%)	<0.001	OR	0.44 (0.26 to 0.74), p=0.002	
GFR 15-29	18/101 (17.8%)	12/112 (10.7%)	0.140	OR	0.50 (0.22 to 1.16), p=0.105	
GFR <15	9/42 (21%)	6/43 (14%)	0.370	OR	0.34 (0.08 to 1.46), p=0.148	
Mean Barthel score (points) within 30 days						
GFR ≥90	96.21 (8.40)	95.75 (10.78)	0.620	Coefficient	-0.23 (-1.94 to 1.48), p=0.794	0.318
GFR 60-89	94.52 (10.76)	96.02 (8.29)	0.048	Coefficient	1.41 (-0.02 to 2.84), p=0.054	
GFR 30-59	94.50 (10.11)	93.52 (10.68)	0.260	Coefficient	-0.63 (-2.30 to 1.05), p=0.462	
GFR 15-29	95.30 (7.90)	94.87 (8.21)	0.700	Coefficient	-0.42 (-2.23 to 2.14), p=0.970	
GFR <15	94.76 (11.58)	93.26 (10.17)	0.530	Coefficient	-1.16 (-6.06 to 3.75), p=0.639	
Mean EQ-5D index (points)						
GFR ≥90	0.79 (0.28)	0.74 (0.34)	0.140	Coefficient	-0.04 (-0.09 to 0.02), p=0.175	0.001
GFR 60-89	0.76 (0.32)	0.76 (0.31)	0.860	Coefficient	0.00 (-0.05 to 0.04), p=0.867	
GFR 30-59	0.69 (0.36)	0.74 (0.30)	0.110	Coefficient	0.06 (0.00 to 0.11), p=0.037	
GFR 15-29	0.61 (0.39)	0.74 (0.32)	0.007	Coefficient	0.13 (0.03 to 0.23), p=0.008	
GFR <15	0.62 (0.41)	0.71 (0.34)	0.290	Coefficient	0.06 (-0.12 to 0.25), p=0.488	
Mean EQ-5D VAS index (points)						
GFR ≥90	61 (27)	57 (28)	0.230	Coefficient	-3.95 (-9.52 to 1.61), p=0.163	0.014
GFR 60-89	59 (26)	61 (26)	0.290	Coefficient	2.85 (-1.44 to 7.14), p=0.193	
GFR 30-59	55 (30)	61 (24)	0.016	Coefficient	6.71 (1.78 to 11.63), p=0.008	
GFR 15-29	49 (31)	55 (26)	0.140	Coefficient	6.15 (-2.70 to 15.00), p=0.172	
GFR <15	42 (33)	49 (25)	0.270	Coefficient	8.60 (-6.91 to 24.11), p=0.271	

Data are number of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for initial nutritional risk screening score, study centre and Barthel's index at admission. Continuous values are median and IQR, categorial/ binary values as

absolute number and percentage
HR = Hazard Ratio, OR = Odds Ratio, EQ-5D = Euroquol-5 Dimensions, VAS = Visual Analogue Scale

592
593