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Original article

Urea-to-creatinine ratio as a biomarker for clinical outcome and response to nutritional support in non-critically ill patients: A secondary analysis of a randomized controlled trial

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SUMMARY

Background: Assessing a patient's catabolism in clinical practice is challenging but could help guide nutritional interventions. The urea-to-creatinine ratio (UCR) reflects muscle breakdown and protein metabolism and has been associated with risk for overfeeding and adverse outcomes in the critical care setting. We validated this concept in a well-characterized population of medical ward patients from a previous nutritional trial.

Methods: This secondary analysis of the Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial (EFFORT) examined baseline UCR and changes during follow-up in medical inpatients at risk for malnutrition. A catabolic state was defined as a high baseline UCR or an increase in UCR over 7 days. The primary endpoint was mortality at 30 days.

Results: We included 1595 of 2028 EFFORT patients with baseline UCR measurements and 870 who also had UCR measurements on day 7. A high baseline UCR, as well as an increase in UCR over 7 days, were associated with increased mortality (adjusted HR for 30-day mortality 2.05 (1.47–2.87) $p < 0.001$ and 2.02 (1.34–3.06) $p = 0.001$). There was no difference in treatment response when stratifying patients based on baseline or follow-up UCR.

Conclusion: Assessment of catabolism through UCR measurement at baseline and changes during follow-up was associated with increased mortality and adverse outcomes in medical inpatients at nutritional risk. However, this stratification was not associated with response to nutritional therapy in our sample. Further studies into the dynamic changes in UCR are needed to better understand the clinical implications for medical ward patients.

Clinical Trial Registration: Clinicaltrials.gov as NCT02517476 (registered 7 August 2015)

1. Introduction

Malnutrition is a multifactorial caused syndrome that occurs when there is an insufficient intake or absorption of essential nutrients, leading to changes in body composition, such as reduced muscle mass and body cell mass. This condition results in decreased physical and mental function and negatively impacts clinical outcomes in acutely ill patients [1,2]. These patients often experience

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malnutrition due to both inadequate nutritional intake and disease-related factors [3]. Randomized controlled trials (RCTs) have demonstrated that nutritional therapy improves morbidity and mortality in medical inpatients [4–6]. In contrast, this positive effect could not be replicated in patients in intensive care units (ICUs), where early initiation of full nutritional support was associated with neutral or even worse outcomes [7–9]. Regardless of the underlying cause of critical illness, the stress imposed on the body during this medical condition triggers catabolism that cannot be reversed by exogenous nutrition [10], making these patients particularly vulnerable to overfeeding [11]. Besides ICU patients, there are also subgroups among medical patients—such as those with high inflammation or advanced cancer—who display a similar malnutrition phenotype that does not seem to respond to nutritional therapy [12,13]. Overfeeding occurs when the exogenous intake together with the endogenous energy production exceeds demand. Yet, determining a patient's current metabolic state remains a challenge in clinical practice, as there are currently no standardized and validated measures for endogenous energy production and, consequently, for assessing catabolism [14].

Recent studies suggest that the urea-to-creatinine ratio (UCR) could be a potential surrogate marker for estimating catabolism and muscle wasting, and thus helpful for guiding nutritional treatment in ICU patients [2,15]. Catabolism and muscle wasting are linked to increased urea production and decreased creatinine production, resulting in a higher UCR [2,16]. Specifically, protein and amino acids, whether originating from the body or external sources, that are not taken up by skeletal muscles for protein synthesis undergo deamination and are metabolized to urea in the liver [9,17]. Consequently, both external amino acid intake and muscle breakdown contribute to elevated urea production during illness, indicating impaired protein metabolism [2]. Creatinine is a byproduct of creatine metabolism in muscles and serves as a marker for total muscle mass, with low creatinine indicating low muscle mass [18–20]. Accordingly, the UCR may be useful in distinguishing catabolic from anabolic states [2,16].

To date, investigations regarding the use of UCR have mainly been conducted in the ICU setting. Herein, in a secondary analysis of the large, randomized *Effect of early nutritional* support *on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial (EFFORT*), we investigated the UCR as a potential surrogate marker for assessing the metabolic state and its prognostic implications in medical inpatients at nutritional risk.

2. Material and methods

2.1. Study design

This is a secondary analysis of the EFFORT trial, a pragmatic, investigator-initiated, non-commercial, randomized controlled trial (RCT), conducted in 8 Swiss medical centers [4]. Data collection was performed between 2014 and 2018. The results, follow-up and several secondary analyses of the EFFORT trial have been published previously [21–23]. EFFORT investigated the effect of individualized nutritional support compared to standard of care in medical inpatients at nutritional risk on clinical outcomes. More details on the study design are available elsewhere [24]. The Ethics Committee of Northwest and Central Switzerland (EKNZ) approved the study protocol in January 2014 (registration ID 2014_001).

2.2. Patient population

To be included in EFFORT, patients had to have a Nutritional Risk Screening 2002 (NRS) total score of at least 3 points, an expected hospital stay of at least 5 days and written informed consent. Exclusions included ICU or surgical admission, prior nutritional support, inability to ingest orally, previous trial participation, terminal illness or contraindications to nutritional support. Details are stated in the original publication [24]. For this secondary analysis, only patients with available blood urea and creatinine measurements were eligible. Patients from one participating center were excluded due to unsystematic errors in laboratory data. In addition, observations with extreme laboratory values (creatinine <20 μmol/l or urea >50 mmol/l) without possible verification were excluded.

2.3. Nutritional intervention

Patients were randomized with an interactive web-response system, with variable block sizes, and patients were stratified according to site and the severity of malnutrition. For the intervention group, individualized nutritional therapy was initiated within 48 h of hospital admission and therapy was guided by trained registered dietitians based on international guidelines for hospitalized polymorbid patients [25]. Nutritional management was changed to enteral, and then parenteral nutrition, if oral intake failed to meet at least 75 % of daily energy and protein needs for 5 consecutive days. More details of the nutritional algorithms have been published previously [24]. Patients in the control group received standard hospital food without nutritional counselling.

2.4. Patient management throughout the trial

Adult patients were screened for nutritional risk using the NRS [26]. Each patient received medical and nutritional assessment by a study dietician, including socio-demographic and anthropometric data, baseline muscle strength and functional status. Daily reassessments of nutritional intake were performed during hospital stay, and nutritional strategies were adapted if targets were not met. Blood samples were collected in the morning at study inclusion and after 7 days for the measurement of study blood markers [24]. Data collection and management was conducted using the secuTrial© software.

2.5. Endpoints

The primary endpoint was 30-day all-cause mortality. Secondary endpoints included all-cause mortality at 180 days, 1 year, and 5 years, adverse events within 30 days, and a decline in functional status of more than 10 % (measured by Barthel Index [27]). Endpoints were obtained by trained and blinded study nurses through telephone interviews at 30 days, 180 days, 1 year and annually after trial inclusion.

2.6. Calculation of urea to creatinine ratio and patient stratification

Blood samples were taken systematically in the morning (i.e. 6-7 am) upon inclusion to the study and within 48 h of admission. Creatinine and urea were measured photometrically. UCR was calculated by dividing the blood urea concentration by the serum creatinine concentration. This analysis measured urea in mmol/l and creatinine in μmol/l, yielding the formula: UCR = (urea in mmol/l/creatinine in μmol/l)/1000. UCR was calculated at two distinct time points: upon admission and day 7. If a patient was discharged earlier than on day 7, the discharge value was used. The change in UCR was determined by comparing values from admission to day 7. A threshold for admission UCR was calculated using the Liu method [28]. An anabolic metabolic state was defined for patients who showed a decrease in UCR from baseline to day 7 or a low baseline UCR, consistent with previous studies [16,29].

Conversely, an increasing UCR over time or a high baseline UCR was considered indicative of catabolic processes.

2.7. Statistical analysis

In descriptive statistics, continuous variables are presented as mean ± standard deviation (SD), while binary and categorical variables are expressed as counts and percentages. Statistical significance was evaluated using 95 % confidence intervals (CI), with a significance threshold set at a p-value of 0.05. Baseline characteristics of included patients were compared based on baseline UCR and change in UCR. Continuous, normally distributed, variables were compared using a 2-sample t-test. We used qnorm plots to check for visual normality. Categorical and binary variables were compared using Pearson's chi-squared test. Multivariate regression analysis was conducted to explore predictions and account for potential confounding factors and random imbalances, as UCR may be affected by various clinical variables [30]. Included variables were sex, age, NRS, nutritional intervention, primary admission diagnoses, and comorbidities. The threshold for baseline UCR was statistically determined using a receiver operating characteristic (ROC) analysis and Youden's J statistic defining a threshold for UCR at 83 [31].

The potential prognostic value of the UCR was examined by assessing its association with clinical outcomes using Cox regression for all time-to-event analyses. Additionally, logistic and linear regression models were fitted to explore the association between UCR and further secondary endpoints, with odds ratios (OR) and coefficients reported, respectively. To determine whether the response to nutritional support was different according to UCR stratifications, we compared mortality hazards between the intervention and control groups, presenting HRs and Kaplan–Meier curves. Additionally, a forest plot on short-term mortality stratified by baseline UCR, change in UCR and inflammation was created. Another forest plot was generated and further stratified for protein target achievement and baseline estimated glomerular filtration rate (eGFR) to account for potential confounders and known predictors.

We also performed sensitivity analyses because certain medical conditions can affect the biochemical markers used to calculate UCR. Therefore, we reanalyzed the data, excluding patients with conditions known to alter blood urea or creatinine levels [20,32,33]. We excluded patients with gastrointestinal bleeding, as it raises blood urea, and those with acute kidney injury, chronic kidney disease stage 4 or higher, or on dialysis, due to reduced creatinine elimination.

All analyses adhered to the intention-to-treat principle. Statistical analyses were conducted using Stata version 17.0 (StataCorp).

3. Results

3.1. Patient population

Of the 2028 patients in the main trial, 1595 had a baseline UCR measurement (Supplementary Fig. 1) and were eligible for this secondary analysis, with 870 also having a UCR measurement on day 7. Table 1 presents baseline characteristics of all patients and stratified by anabolic and catabolic change in UCR from admission to day 7. There were small differences in the distribution of baseline characteristics between patients with anabolic and catabolic changes in UCR, particularly concerning gastrointestinal disease and congestive heart failure. The risk of malnutrition, estimated by the NRS total score, was evenly distributed between both UCR groups.

3.2. Association of baseline nutritional and medical parameters and UCR

We assessed the relationship between various baseline characteristics and both baseline UCR and its change over time to identify potential influencing factors. While nutritional parameters were not associated with either baseline or change in UCR over 7 days, some comorbidities were significantly associated with baseline UCR (Supplementary Table 1). Congestive heart failure and diabetes were associated with higher baseline UCR in a multivariate model. However, no characteristics were found to significantly impact the change in UCR over time.

3.3. Association of baseline and change in UCR, and clinical outcomes

A higher baseline UCR and a catabolic change in UCR were both associated with increased risk of mortality at any follow-up time point (Table 2). Specifically, a higher baseline UCR and a catabolic change in UCR were associated with a doubling in the risk of 30-day mortality (adjusted HR of 2.05 [1.47 to 2.87]; $p < 0.001$ and 2.02 [1.34 to 3.06]; $p = 0.001$). Supplementary Fig. 2 shows HR for each quartile of baseline UCR and demonstrates a stepwise increase in risk with higher quartiles. Kaplan–Meier curves (Fig. 1) show the probability of mortality by anabolic versus catabolic UCR change over 3 years. An anabolic UCR change was associated with higher 30-day survival, regardless of randomization group. Although the intervention group showed better overall survival, anabolic patients had a survival advantage within each group (Fig. 2).

Additionally, higher baseline UCR was significantly associated with an increased risk of adverse events within 30 days of admission in an adjusted model with a HR of 1.45 [1.14 to 1.84]; $p = 0.002$. It was also linked to a decline in functional status of more than 10 %, with an adjusted HR of 1.79 [1.32 to 2.42]; $p < 0.001$.

3.4. Association of baseline UCR and change in UCR with the response to nutritional support

We further examined whether the effect of nutritional therapy would differ in subgroups stratified by UCR. We found that nutritional intervention was generally associated with higher overall 30-day survival, as displayed in the forest plot (Fig. 3), independent of baseline UCR or change in UCR. However, when patients were further stratified according to their levels of inflammation, we found that patients with high inflammation tended to benefit less from nutritional therapy regardless of the baseline UCR or UCR change.

Additionally, we found that patients with an eGFR below 29 at admission had a more pronounced survival benefit from nutrition intervention with HRs ranging from 0.30 to 0.43, which was independent of baseline or change in UCR. Patients with an eGFR of 30–90 showed a similar treatment response with HRs of 0.14–0.63, while patients with an eGFR above 90 did not show a positive response (HRs of 1.22–1.44). Again, both effects were independent of baseline or change in UCR. Another stratification to distinguish patients who met their protein targets during hospitalization, i.e. a protein intake of at least 75 % of calculated needs, did not increase predictive capacity of the UCR (Supplementary Fig. 3).

3.5. Sensitivity analysis

In a sensitivity analysis, excluding patients with certain conditions that could affect blood urea and/or creatinine levels where possible, we found similar effects (shown in Supplementary Tables 2 and 3, Supplementary Figs. 4 and 5).

Table 1
Baseline characteristics stratified by change in UCR from admission to cohort day 7.

	Overall	Cohort day 7[a]	Change in UCR[b]		P-value
			Anabolic	Catabolic	
N	1595	870	460	410	
Sociodemographic					
Male sex	835 (52.4 %)	457 (52.5 %)	245 (53.3 %)	212 (51.7 %)	0.65
Age years, mean (SD)	73.2 (13.5)	73.8 (12.9)	73.9 (12.3)	73.6 (13.6)	0.78
Nutritional assessment					
BMI kg/m2, mean (SD)	24.8 (5.3)	24.9 (5.5)	25.1 (5.4)	24.8 (5.5)	0.44
Weight at admission kg, mean (SD)	71.0 (16.6)	71.4 (16.8)	72.5 (17.3)	70.3 (16.1)	0.09
NRS total score					
3	507 (31.8 %)	254 (29.2 %)	124 (27.0 %)	130 (31.7 %)	0.39
4	618 (38.7 %)	351 (40.3 %)	190 (41.3 %)	161 (39.3 %)	
5	388 (24.3 %)	215 (24.7 %)	116 (25.2 %)	99 (24.1 %)	
6	82 (5.1 %)	50 (5.7 %)	30 (6.5 %)	20 (4.9 %)	
Admission diagnosis					
Infection	491 (30.8 %)	263 (30.2 %)	141 (30.7 %)	122 (29.8 %)	0.77
Tumor	287 (18.0 %)	172 (19.8 %)	85 (18.5 %)	87 (21.2 %)	0.31
Cardiovascular disease	171 (10.7 %)	99 (11.4 %)	44 (9.6 %)	55 (13.4 %)	0.07
Frailty	158 (9.9 %)	74 (8.5 %)	39 (8.5 %)	35 (8.5 %)	0.98
Lung disease	99 (6.2 %)	47 (5.4 %)	25 (5.4 %)	22 (5.4 %)	0.96
Gastrointestinal disease	126 (7.9 %)	75 (8.6 %)	50 (10.9 %)	25 (6.1 %)	0.01
Renal disease	50 (3.1 %)	36 (4.1 %)	16 (3.5 %)	20 (4.9 %)	0.30
Comorbidities					
Hypertension	875 (54.9 %)	507 (58.3 %)	270 (58.7 %)	237 (57.8 %)	0.79
Malignant disease	514 (32.2 %)	301 (34.6 %)	156 (33.9 %)	145 (35.4 %)	0.65
Chronic kidney disease	526 (33.0 %)	325 (37.4 %)	173 (37.6 %)	152 (37.1 %)	0.87
Coronary heart disease	453 (28.4 %)	243 (27.9 %)	125 (27.2 %)	118 (28.8 %)	0.60
Diabetes	345 (21.6 %)	204 (23.4 %)	115 (25.0 %)	89 (21.7 %)	0.25
Congestive heart failure	287 (18.0 %)	158 (18.2 %)	70 (15.2 %)	88 (21.5 %)	0.02
Chronic obstructive pulmonary dis.	241 (15.1 %)	119 (13.7 %)	56 (12.2 %)	63 (15.4 %)	0.17
Peripheral arterial disease	150 (9.4 %)	87 (10.0 %)	42 (9.1 %)	45 (11.0 %)	0.37
Lab analysis at admission					
Urea (mmol/l), mean (SD)	9.3 (7.32)	10.4 (8.12)	11.0 (7.55)	9.6 (8.66)	0.01
Creatinine (μmol/l), mean (SD)	117.2 (96.75)	128.3 (112.19)	121.4 (87.56)	136.0 (134.25)	0.056
UCR, mean (SD)	81.3 (33.23)	83.5 (34.52)	92.9 (35.31)	73.0 (30.36)	<0.001
CRP (mg/l), mean (SD)	72.60 (85.96)	78.63 (86.39)	83.46 (92.31)	73.22 (79.01)	0.08

BMI: Body Mass Index, NRS: Nutritional Risk Screening 2002, CRP: C-reactive protein, UCR: Urea-to-creatinine Ratio.
[a] Individuals with available measurements used for calculation of UCR on admission and day 7.
[b] The metabolic state was assumed based on changes in UCR. A decline in UCR over time suggests an anabolic metabolic state, a rise in UCR over time indicates a catabolic metabolic state.

Table 2
Association of baseline UCR and change in UCR with mortality and secondary clinical outcomes.

	n. of event (%)		Adj. HR (95%CI) p-value
	Anabolic	Catabolic	
30-day all-cause mortality			
Baseline UCR[a]	60/954 (6.3 %)	86/641 (13.4 %)	2.05 (1.47–2.87) p < 0.001
Change in UCR[b]	36/460 (7.8 %)	61/410 (14.9 %)	2.02 (1.34–3.06) p = 0.001
180-day all-cause mortality			
Baseline UCR[a]	190/954 (19.9 %)	194/641 (30.3 %)	1.51 (1.23–1.85) p < 0.001
Change in UCR[b]	98/460 (21.3 %)	139/410 (33.9 %)	1.73 (1.34–2.24) p < 0.001
1-year all-cause mortality	Baseline UCR[a]		
Baseline UCR[a]	267/883 (30.2 %)	246/598 (41.1 %)	1.40 (1.17–1.67) p < 0.001
Change in UCR[b]	134/430 (31.1 %)	165/381 (43.3 %)	1.54 (1.23–1.94) p < 0.001
5-year all-cause mortality			
Baseline UCR[a]	435/883 (49.3 %)	383/598 (64.0 %)	1.38 (1.20–1.59) p < 0.001
Change in UCR[b]	240/430 (55.8 %)	246/381 (64.6 %)	1.37 (1.15–1.64) p < 0.001
			Adj. OR (95%CI) p-value
Adverse outcome within 30 days			
Baseline UCR[a]	214/954 (22.4 %)	195/641 (30.4 %)	1.45 (1.14–1.84) p = 0.002
Change in UCR[b]	116/460 (25.2 %)	122/410 (29.8 %)	1.28 (0.94–1.73) p = 0.116
Decline in functional status of more than 10 %			
Baseline UCR[a]	95/954 (10.0 %)	113/641 (17.6 %)	1.79 (1.32–2.42) p < 0.001
Change in UCR[b]	58/460 (12.6 %)	69/410 (16.8 %)	1.44 (0.97–2.12) p = 0.068

Calculation was adjusted by sex, age, received nutritional support, Nutritional Risk Screening (NRS), infection as admission diagnosis, tumor as admission diagnosis, hypertension, kidney impairment. UCR: Urea-to-creatinine Ratio, adj.: adjusted, HR: hazard ratio, adj.: adjusted, HR: hazard ratio, OR: odds ratio.
[a] At admission, a threshold for UCR was statistically determined at 83.22. A ratio lower than the threshold proposed as an anabolic metabolic state, a ratio above the threshold proposed as a catabolic metabolic state.
[b] The metabolic state was assumed based on changes in UCR. A decline in UCR over time suggests an anabolic metabolic state, while a rise in UCR over time indicates a catabolic metabolic state.

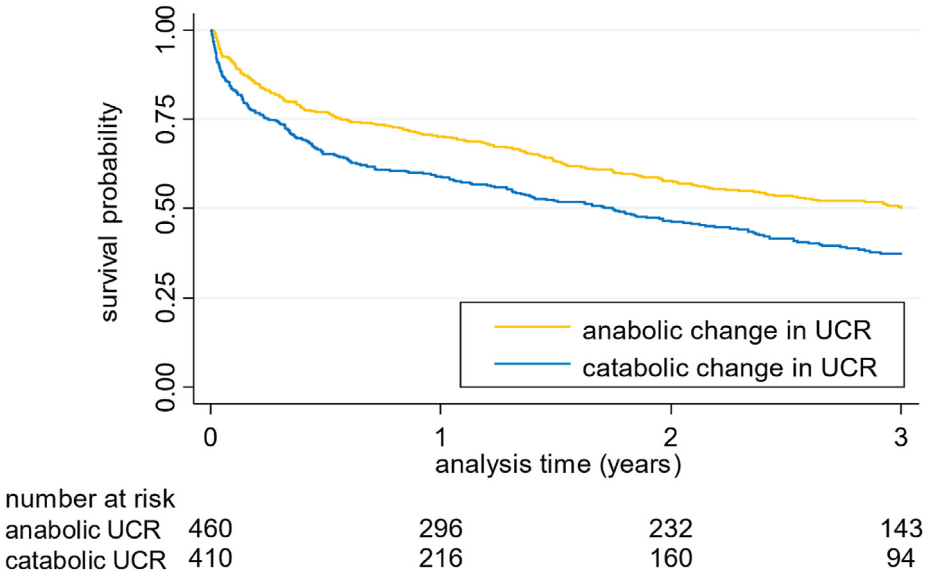

Fig. 1. Kaplan–Meier estimate for time to death comparing change in UCR. Metabolic change in UCR was determined between admission and cohort day 7. A decline in UCR suggests an anabolic metabolic state, and a rise in UCR over time indicates a catabolic metabolic state. The 3-year follow-up was based on categorization into anabolic or catabolic change in UCR done on cohort day 7. UCR: Urea-to-creatinine ratio.

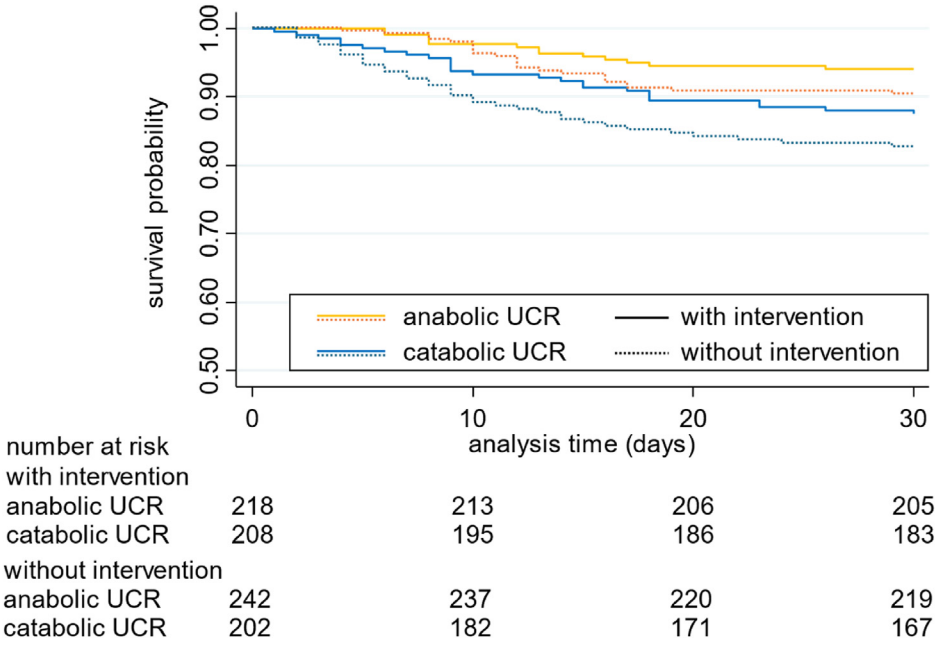

Fig. 2. Kaplan–Meier estimate for time to death comparing randomization group and anabolic versus catabolic change in UCR. Patients in the intervention group received nutritional support, and patients in the control group received standard hospital food. The metabolic state was assumed based on changes in UCR. A decline in UCR over time suggests an anabolic metabolic state, a rise in UCR over time indicates a catabolic metabolic state. UCR: Urea-to-creatinine ratio.

4. Discussion

Data from this large-scale cohort of non-critically ill medical inpatients from a previous nutritional trial indicated that a high baseline UCR or a catabolic change in UCR from admission to day 7 were independent risk factors for increased mortality and poor clinical outcomes. However, neither baseline UCR nor changes in UCR predicted which patients would benefit most from nutritional therapy, limiting its utility as a marker of therapy response. Although several disease-specific factors influenced UCR, sensitivity analysis showed robust results, supporting its broad applicability.

UCR has been suggested as a prognostic indicator in critical care settings and across various patient populations, including those with cardiogenic shock and infections [16,34–38]. Our results expand these findings and suggest that a high baseline UCR and a catabolic UCR dynamic during hospitalization are both independently associated with increased mortality among polymorbid medical ward patients with different illnesses that are at nutritional risk. Similar to our results, a secondary analysis of a large ICU trial comparing high to moderate protein intake (EFFORT Protein trial) also confirmed the association of UCR with mortality, which was independent of renal function and other confounding factors [43], as were our results. The authors of this trial concluded that the

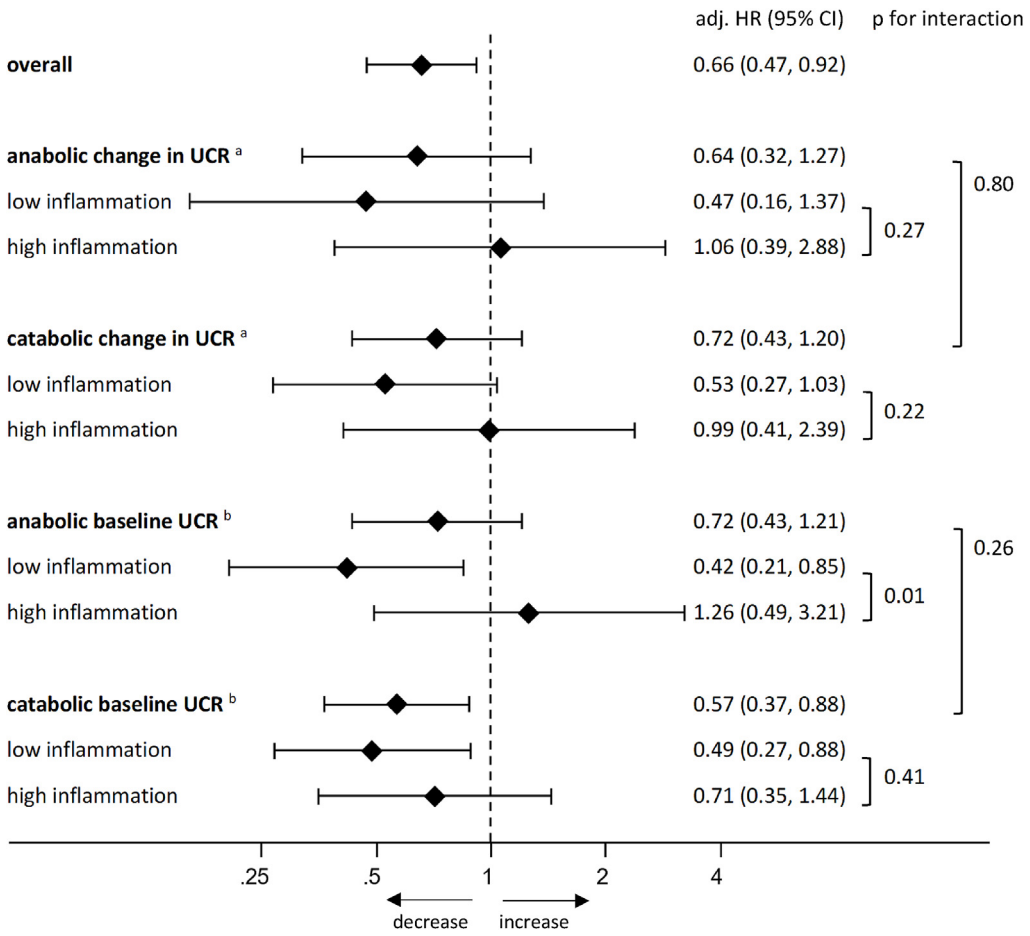

Fig. 3. Forest plot for the effect of nutritional support on 30-day mortality stratified by baseline UCR, change in UCR and co-factor inflammation.
[a] change in UCR was determined between baseline UCR and measurements on cohort day 7. A decline in UCR over time suggests an anabolic metabolic state, a rise in UCR over time indicates a catabolic metabolic state.
[b] at admission, a threshold for UCR was statistically determined at 83.22. A ratio lower than the threshold is proposed as an anabolic metabolic state, and a ratio above the threshold is proposed as a catabolic metabolic state.
In this study population, the threshold for high inflammation was defined as a CRP level of 100 mg/l. Levels above were defined as high inflammation, and values below were defined as low inflammation.
UCR: Urea-to-creatinine ratio, CRP: C-reactive protein.

indirect adverse effect of high-dose protein may have been mediated via ureagenesis. This suggests that impaired protein metabolism, rather than a specific nutritional intervention or protein dosage, is an independent risk factor for adverse clinical outcomes. Physiologically, this may be due to the accumulation of toxic intermediary metabolites, such as ammonia, from an overloaded urea cycle [39]. Thus, increasing protein intake for an anabolic effect is justified, but only within the limits of individual metabolic tolerance, as indicated by urea levels.

Despite these promising prognostic results, prospective studies are lacking to confirm that UCR-guided nutritional therapy would benefit patients. Herein, using data from our RCT, we assessed treatment response according to baseline and changes in UCR over 7 days. Our results, however, did not show that UCR could distinguish nutritional treatment responders from non-responders, as suggested in previous ICU trials [39] and a study involving patients with advanced cancer [13]. Several factors may explain this finding. First, our study included medical inpatients at nutritional risk who were acutely but not critically ill, so catabolic processes may have had a lesser impact on macronutrient metabolism. Second, we could not capture short-term dynamics with only two urea and creatinine measurements during the hospital stay. Third, protein intake in the intervention group was lower than in many ICU studies, particularly mean protein intake was 0.84 g (± 0.35) protein per kg bodyweight per day int the intervention group versus 0·70 g (± 0.34) protein per kg bodyweight per day in the control group [4], possibly causing an increase in urea that was less clinically meaningful. An additional stratification of patients that have reached at least 75 % of their protein requirements did not increase predictive capacity of the UCR. Lastly, the classification of anabolic and catabolic UCR values was based on a data-driven approach and clinical reasoning, as reliable reference values were unavailable, with reported means ranging from 14 [15] to 140 [40,41], depending on the condition.

Two other factor shown to be crucial for the response to treatment in medical inpatients are the extent of inflammation [12,42] and renal function at admission [21]. Our data support the hypothesis that the benefits of nutritional therapy diminish as inflammation increases. Regardless of their classification by UCR, patients with high inflammation showed fewer benefits from nutritional therapy than patients with moderate or low inflammation. These observed effect modifications may be explained by

the effects of inflammation on the metabolism, such as cytokine-induced anorexia and impaired gastrointestinal motility leading to gastroparesis and nausea [43]. In addition, the neuroendocrine and inflammatory responses cause the mobilization of energy stores, triggering lipolysis, glycolysis, glycogenolysis and gluconeogenesis in the liver, and the release of amino acids through muscle proteolysis. These metabolic changes cause hyperglycemia together with peripheral insulin resistance, which hinders the entry of glucose into cells [44,45] and increases overall catabolism [46]. Direct measurement of catabolism, specifically endogenous energy production, is currently unavailable [46], making surrogate biomarkers essential. While inflammation and admission eGFR support their high validity as a predictive marker, UCR has proven less reliable in our application for the reasons outlined above.

4.1. Strengths and limitations

The data of this study come from a well-characterized cohort included in a previous RCT, and all outcomes were prospectively assessed up to 5 years. We had consistent results in our sensitivity analysis, which strengthens the reliability. However, several limitations need to be mentioned. Not all laboratory tests were conducted on day 7 and were performed earlier, on days 5 or 6, due to early patient discharge, while others were missing follow-up laboratory tests for unknown reasons. This variability may have affected data consistency, particularly in classifying patients into anabolic or catabolic groups. Furthermore, missing data from early discharges may have introduced bias, as healthier patients were likely to be discharged earlier, thus underrepresenting this group in the final analysis. The threshold for defining baseline UCR as anabolic or catabolic was determined statistically using ROC and Youden's J statistic [31], as no standardized threshold level for UCR exists to date. Additionally, all patients included were at nutritional risk, with the result that metabolic disorders and catabolism occurred more frequently.

5. Conclusion

Assessment of catabolism through UCR measurement at baseline and changes during follow-up was associated with increased mortality and adverse outcomes in this cohort of medical inpatients at nutritional risk from a previous RCT. Although various comorbidities such as congestive heart failure, gastrointestinal issues, renal injury and inflammation may influence biochemical markers used for calculating UCR, we had consistent results in sensitivity analysis, strengthening the robustness of findings of UCR being a prognostic marker. However, the stratification of patients according to UCR was not associated with response to nutritional therapy in our sample. Further studies into the dynamic changes in UCR over time are needed to better understand the clinical implications for the medical ward patient. Finding validated markers of metabolic stress and feeding intolerance will be crucial to discovering a personalized nutritional approach that can improve outcomes in critically or acutely ill patients.

Author contributions

Julian Diethelm, Carla Wunderle and Philipp Schuetz: conceptualization, data curation, formal analysis, methodology, software, validation, visualization, writing - original draft, writing - review & editing. *Philipp Schuetz and the EFFORT Team*: investigation. *Philipp Schuetz*: resources, supervision, project administration, funding acquisition. *All authors* read and approved the final version of the manuscript. All authors confirm, they had full access to all data in this secondary analysis. All authors accept responsibility for the decision to submit for publication.

Ethics approval and consent to participate

The Ethics Committee of Northwestern Switzerland (EKNZ; 2014_001) approved the study protocol. All participants or their authorized representatives provided written informed consent. The trial was registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02517476).

Availability of data and materials

Our data will be made available to others with the publication of this manuscript, as already outlined in the primary EFFORT publication, on receipt of a letter of intention detailing the study hypothesis and statistical analysis plan. A signed data access agreement is required from all applicants. Please send requests to the principal investigator of this trial.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2025.03.042.

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