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Published in:
Journal of Critical Care

DOI:
10.1016/j.jcrc.2020.09.017

Publication date:
2021

Journal of Critical Care 63 (2021) 161–166

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Time courses of urinary creatinine excretion, measured creatinine clearance and estimated glomerular filtration rate over 30 days of ICU admission

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ARTICLE INFO

Keywords:
Urinary creatinine excretion
Creatinine
Glomerular filtration rate
Creatinine clearance
Muscle mass
Muscle wasting
Sarcopenia
Urinary urea excretion
Urea:Creatinine ratio

ABSTRACT

Purpose: Baseline urinary creatinine excretion (UCE) is associated with ICU outcome, but its time course is not known.
Materials and methods: We determined changes in UCE, plasma creatinine, measured creatinine clearance (mCC) and estimated glomerular filtration (eGFR) in patients with an ICU-stay ≥30d without acute kidney injury stage 3. The Cockcroft-Gault, MDRD (modification of diet in renal disease) and CKD-EPI (chronic kidney disease epidemiology collaboration) equations were used.
Results: In 248 patients with 5143 UCEs hospital mortality was 24%. Over 30d, UCE absolutely decreased in male survivors and non-survivors and female survivors and nonsurvivors by 0.19, 0.16, 0.10 and 0.05 mmol/d/d (all $P < 0.001$). Relative decreases in UCE were similar in all four groups: 1.3, 1.4, 1.2 and 0.9%/d respectively. Over 30d, mCC remained unchanged, but eGFR rose by 31% (CKD-EPI) and 73% (MDRD) and creatinine clearance estimated by Cockcroft-Gault by 59% (all $P < 0.001$).
Conclusions: Over 1 month of ICU stay, UCE declined by ≥1%/d which may correspond to an equivalent decline in muscle mass. These rates of UCE decrease were similar in survivors, non-survivors, males and females underscoring the intransigent nature of this process. In contrast to measured creatinine clearance, estimates of eGFR progressively rose during ICU stay.

1. Introduction

ICU patients typically display considerable muscle loss during critical illness, and lower muscle mass is associated with an increased mortality and morbidity [1-3]. However, the time course of muscle mass loss during ICU admission remains poorly explored.

Urinary creatinine excretion (UCE) is a non-invasive and low-cost method to estimate muscle mass. Recently, baseline UCE, as a marker for muscle mass, was demonstrated to be strongly associated with mortality in a large cohort of ICU patients [4]. Additionally a decreased UCE at ICU discharge in patients with a prolonged ICU admission has been reported [5]. However, the time course of UCE and related parameters during ICU admission has not been described.

UCE measurements are routinely performed in our ICU to determine measured creatinine clearance (mCC), because this may be a more accurate indicator of renal function than creatinine alone or formulas that estimate the glomerular filtration rate (eGFR) [5-7]. Moreover, the assessment of renal function with eGFR could be confounded during prolonged critical illness as loss of muscle mass can lead to decreases in plasma creatinine [5,6,8]. Consequently, the use of eGFR equations in patients with a prolonged ICU stay might result in both overestimation and underestimation of renal function and so-called augmented renal clearance [9,10], possibly leading to inadequate drug dosing [11].

The objective of this study was to describe the time course of UCE in critically ill patients with an ICU stay of at least 30 days. We also compared the changes of mCC with estimated creatinine clearance according to Cockcroft-Gault and eGFR to identify potential underestimation or overestimation of renal function.

Abbreviations: AKI, acute kidney injury; APACHE, acute physiology and chronic health evaluation; BSA, body surface area; CI, confidence interval; CKD-EPI, chronic kidney disease – epidemiology collaboration; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; mCC, measured creatinine clearance; MDRD, modification of diet in renal disease; UCE, urinary creatinine excretion; UUE, urinary urea excretion.

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https://doi.org/10.1016/j.jcrc.2020.09.017
0883-9441/

2. Patients and methods

2.1. Study setting, patient selection and outcome

This study was a sub-analysis of a recently published study in 6151 patients admitted for ≥24 h to our ICU between 2002 and 2016 [4]. From these patients, we selected those with an ICU-stay of ≥30 days and for whom sufficient 24 h urine samples were available. Sufficient was defined as having at least 4 UCE measurements of which the first measurement was performed at ICU day 1–3 and the last measurement in the final week of ICU admission. Patients with acute kidney injury (KDIGO-AKI) stage 3 (i.e. an increase of plasma creatinine to >300% from baseline, or ≥ 354 μmol/L or requiring RRT [12]) during the first 30 days were excluded. UCE was calculated by multiplying the urinary creatinine concentration in the 24 h urine with the 24 h urine volume. In case of missing UCEs, values were linearly interpolated over a maximum of 4 missing UCEs. Plasma creatinine values were not interpolated. As males are known to have a considerably higher UCE than females, we separately examined the UCE time courses for the two sexes. For comparison we also recorded plasma urea and urinary urea excretion (UUE).

2.2. Formulas

The mCC was calculated as 694.44·UCE/(plasma creatinine) mL/min (694.44 equals 1000·1000/1440 to convert mmol to μmol, L to mL and days to minutes respectively). We also used the Cockcroft-Gault formula to estimate creatinine clearance, with sex, age and weight as input variables [13]. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula and according to the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula [14,16] which both use plasma creatinine, sex, and age as input variables.

Body surface area (BSA) was calculated as $0.007184 \cdot (\text{weight}^{0.425} \cdot \text{height}^{0.725})$.

Augmented renal clearance was defined as an mCC ≥130 mL/min/1.73m^2. As we analyzed UCE in 24 h urine collections, we expressed the changes in UCE per day as changes in mmol per day per day (mmol/d/d).

2.3. Statistical analysis

Normally distributed data is expressed as mean (SD) and skewed data as median (IQR). A chi-square test for categorical variables, *t*-test for normally distributed continuous variables or a Mann-Whitney *U* test for skewed distributed continuous variables was performed to determine differences between two groups. When more groups were compared, a one-way ANOVA was performed where appropriate.

The time course of UCE and renal function was estimated by a linear regression model. In particular to obtain more accurate estimates of the initial values at ICU day 0 and subsequent other days, not the actual mean of measured values but the linear regression function was used to estimate the baseline and subsequent changes in of UCE, glomerular filtration and creatinine clearance.

Additionally, changes in UCE and UUE over the first 90 days of ICU admission were studied. As not all patients had an ICU stay of more than 90 days, not all patients fully contributed to the 90 days. Further subgroup analyses were performed in patients who developed AKI, in patients who did not develop AKI and for the incidence of augmented renal clearance. Also patients admitted to the ICU directly from home were compared with those who were first admitted at the ward. We also conducted analyses in which we analyzed UCE per kg body weight.

P-values were considered to be significant when they were less than 0.05. Data was analyzed with *R* version 3.5.1. (*R* Foundation for Statistical Computing, Vienna, Austria). Differences between parameters of linear regressions were compared with the *emmeans* package in *R*.

3. Results

Of a total of 6151 patients, 5823 patients (Supplementary SFig. 1) were excluded because of an ICU admission shorter than 30 days, subsequently 66 patients were excluded because of insufficient UCEs and finally 14 patients were excluded because of AKI stage 3 during the first 30 ICU days. In the remaining 248 patients (Table 1), a total of 6641 UCEs were used, of which 1498 (23%) were interpolated. 7170 plasma creatinine values (28.9 per patient) were used for the same period. In addition, another 1026 UCE values were measured between day 30 and 90.

The median age was 60 (47–70) years and 87 (35%) patients were female. The median ICU LOS was 41 (35–54) days and the hospital LOS was 63 (48–83) days, with a hospital mortality of 24%. 85 (34%) patients were admitted to another hospital before transfer to our hospital. The median time that the hospital non-survivors died after ICU admission was 50 (39–74) days, with a range of 30–222 days.

3.1. Time course of UCE

The mean UCE estimated with linear regression at admission was 11.6 (95%CI 11.3–11.8) compared to an estimated UCE of 7.1 mmol/d at day 30 (6.9–7.3), $P < 0.001$). Based on linear regression, the estimated mean UCE at baseline was 57% higher in males compared to females: 13.6 (95%CI 13.3–13.8) vs 7.7 (7.4–8.0) mmol/d ($P < 0.001$) as was the estimated UCE at day 30: 8.1 (95%CI 7.9–8.4) vs. 5.0 (4.7–5.3) mmol/d ($P < 0.001$).

Linear regression analysis showed that UCE decreased by 0.18 (95% CI 0.17–0.19) in males and by 0.09 (0.07–0.11) mmol/d/d in females, respectively ($P < 0.001$), equivalent to an 1.2–1.3%/d decrease of UCE for both sexes.

Linear regression also showed that survivors had higher initial UCEs than non-survivors. UCE decreased in survivors by 0.16 (95%CI

Table 1
Patient characteristics and outcome.

	Survivors	Non-survivors	*P*-value
N	189	59	
Sex, female	70 (37%)	17 (29%)	0.318
Age, years	58 [42, 68]	65 [53.5, 74]	0.003
Reason for admission (%)			0.042
Medical	24 (13%)	7 (11%)	
Abdominal/vascular surgery	46 (24%)	13 (22%)	
Neurosurgery	4 (2%)	1 (2%)	
Transplant	8 (4%)	2 (3%)	
Cardiothoracic surgery	19 (10%)	7 (12%)	
Trauma	33 (18%)	1 (2%)	
Miscellaneous	55 (29%)	28 (48%)	
Location before current hospital admission			0.35
Hospital admission			
Home	121 (64%)	42 (71%)	
Other institution	68 (36%)	17 (29%)	
LOS before ICU, days	0 [0,1]	1 [0, 3.5]	0.006
ICU LOS, days	41 [35, 53]	43 [35, 65]	0.155
Hospital LOS, days	64 [52, 83]	56 [40, 76]	0.039
APACHE-IV	65 [52, 77]	83 [63, 96]	0.006
Length, cm	175 [170, 182]	178 [170, 185]	0.616
Weight, kg	80 [70, 90]	76 [65, 90]	0.169
BMI kg/m^2	26.1 [23.1, 29.4]	23.9 [22.1, 27.7]	0.038
BSA m^2	1.97 [1.82, 2.14]	1.92 [1.75, 2.11]	0.379
Acute kidney injury[a]			0.414
No AKI	89 (47%)	22 (37%)	
Stage 1	61 (32%)	23 (39%)	
Stage 2	39 (21%)	14 (24%)	
Stage 3	0	0	

[a] Acute kidney injury was determined for the whole study period (i.e. the first 30 days of ICU admission) All patients with AKI stage 3 were excluded from analysis. Mean (SD), medians [IQR] or numbers (%) are presented.

0.14–0.17) and in non-survivors by 0.13 (0.10–0.16) mmol/d/d ($P = 0.07$), equivalent to a 1.3%/d decrease in both groups.

The change in UCE in survivors and non-survivors was also separately studied in males and females (Fig. 1). Admission UCE estimated by linear regression was higher in surviving female patients 8.3 (95% CI 7.9–8.6) vs. 5.5 (4.8–6.3) mmol/d respectively ($P < 0.001$). UCE at day 30 remained different with a mean UCE of 5.2 (95%CI 4.9–5.5) mmol/d for female survivors and a mean UCE of 4.0 (95%CI 3.3–4.7) mmol/d for female non-survivors ($P = 0.003$). In female survivors, UCE showed a linear decrease of 0.10 (95%CI 0.08–0.12), whereas in female non-survivors, UCE showed a decrease of 0.05 (0.01–0.09) mmol/d/d ($P = 0.033$).

Also in male patients, admission UCE estimated by linear regression was higher in survivors: 14.3 (95%CI 14.0–14.5) vs. 11.4 (11.0–11.9) mmol/d respectively ($P < 0.001$). At day 30, the difference in UCE between male survivors and non-survivors remained: 8.7 (95%CI 8.4–9.0) compared to 6.5 (6.0–6.9) mmol/d ($P < 0.001$). UCE showed a decrease of 0.19 (95%CI 0.17–0.20) in male survivors and of 0.17 (0.14–0.19) mmol/d/d in male non-survivors ($P = 0.19$).

The relative decreases in UCE were similar for male survivors, male non-survivors, female survivors and female non-survivors:1.3, 1.5, 1.2 and 0.9%/d, respectively ($P = 0.42$).

3.2. Measures of renal function during 30 ICU days

To assess potential overestimation of kidney function, we examined various methods of kidney function assessment (Fig. 2). Over the course of 30 days, measured creatinine clearance (mCC) remained similar with a rate of change of +0.01 mL/min/d (95% CI −0.22 to +0.20; $P = 0.20$). In contrast the kidney function estimates all showed pronounced time-dependent changes. Plasma creatinine showed a decrease of −1.17 μmol/L/d (95%CI −1.36 to −0.97). eGFR according to CKD-EPI showed an increase of +0.86 mL/min/1.73m^2/d (95%CI +0.66 to +1.06). Creatinine clearance predicted according to the Cockcroft-Gault formula displayed a stronger increase of +2.08 mL/min/d (95% CI +1.88 to +2.28). When the MDRD eGFR was determined, the observed increase was even more pronounced at +2.23 mL/min/1.73m^2/d (95%CI +2.03 to +2.42). All slopes except that for mCC differed significantly from 0 (STable 1; $P < 0.001$). Mutual comparisons between mCC, Cockroft-Gault, MDRD and CKD-EPI showed that the slopes significantly differed from each other $P < 0.001$).

3.3. Additional analyses and sensitivity analyses

Fig. 3 demonstrates the course of UCE and UUE over the first 12 weeks of ICU admission of the included ICU patients. As some ICU patients had shorter ICU stays, not all 248 patients fully contributed to the 90 days. Note that on a molar basis UUE is approximately one or two orders of a magnitude higher than UCE. Except that UUE was relatively lower in the first week, UCE and UUE showed a similar steady decrease that became less pronounced after the first ICU month.

SFig. 2 shows that the decrease in UCE in patients with no AKI, AKI-1 and AKI-2 was similar during the first 30 ICU days. SFig. 3 shows the

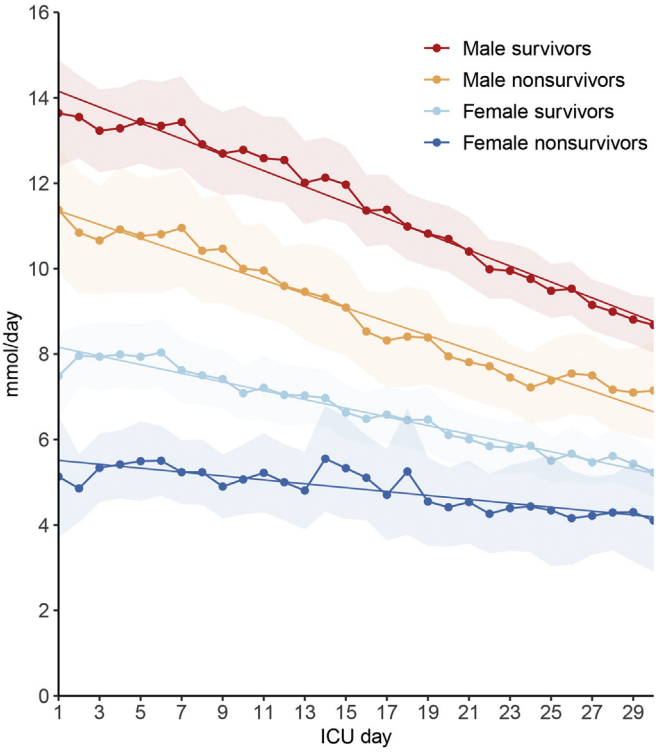

Fig. 1. Course of UCE in surviving and non-surviving males and females during the first 30 days of ICU stay. Males are depicted in blue and females in red. The dots represent the mean values, whereas the light shaded errors bars represent the 95%CI. The respective regression formulas are: male survivors: UCE = −0.19 (95%CI −0.20 to −0.17) ICUday +14.34(95%CI 14.01 to 14.67), male non survivors: UCE = −0.16(95%CI −0.19 to −0.14) ICUday +11.52(95%CI 11.10 to 11.94), female survivors: UCE = −0.10 (95%CI −0.11 to −0.09) ICUday +8.26 (95%CI 8.01 to 8.52), female nonsurvivors: UCE = −0.05 (95%CI −0.07 to −0.02) ICUday +5.56(95%CI 5.18 to 5.93).

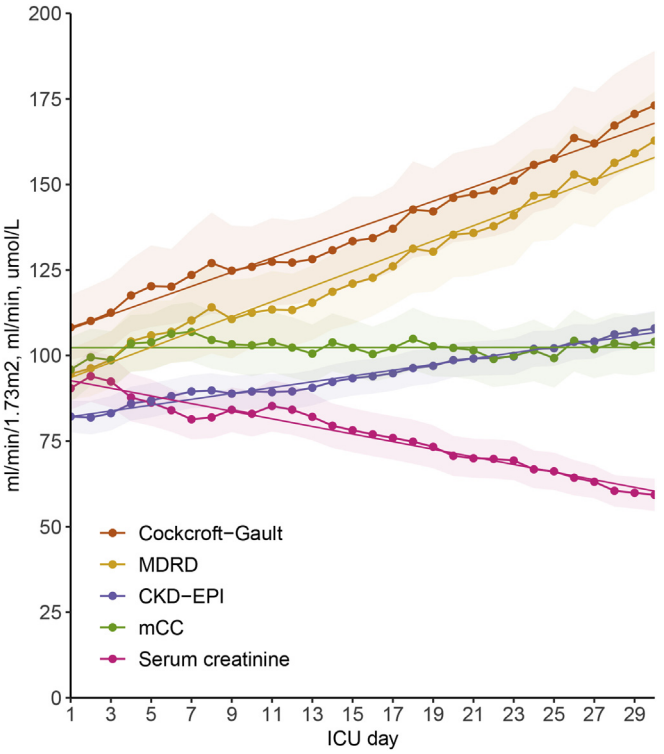

Fig. 2. Different measures of kidney function over the course of 30 ICU days. eGFR according to the CKD-EPI and MDRD formula are depicted in mL/min/1.73m^2. Measured creatinine clearance (mCC) and creatinine clearance according to the Cockcroft-Gault formula are depicted in mL/min. Information on weight was not available for the whole study cohort, this figure depicts the renal function of 196 (79%) patients with available information on weight. The dots represent the mean values, whereas the light shaded errors bars represent the 95%CI. The respective regression formulas are: Cockcroft-Gault = 2.07(95%CI 1.80 to 2.35) ICUday+105.71 (95%CI 100.85–110.56) (mL/min), MDRD = 2.22 (95%CI 1.97 to 2.47) ICU day +91.3 (95%CI 86.9 to 95.7) (mL/min/1.73m^2), CKD = 0.85 (95%CI 0.74 to 0.95) ICU day +81.3 (95%CI 79.4 to 83.2) (mL/min/1.73m^2), mCC = 0.004 (95%CI −0.18 to +0.19) ICU day +102.3 (95%CI 99.0 to 105.5) (mL/min), plasma creatinine = −1.11 (95%CI −1.24 to −0.98) ICU day +93.8 (95%CI 91.5 to 96.1) (μmol/L).

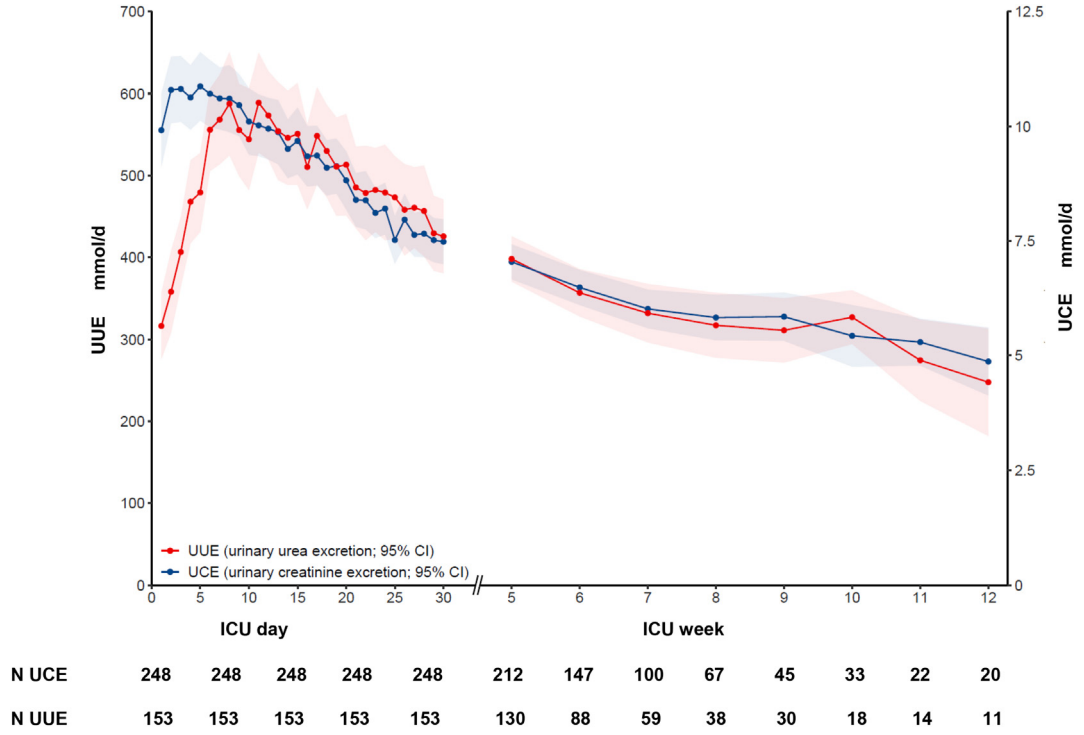

Fig. 3. Course of UCE and UUE over the first 90 days of ICU admission. There appears to be a rapid decline in UCE in the first weeks with later a gradual diminishment of this rate of decline. After the first week the time course of UUE is similar to that of UCE. Week 5 consists of day 32–day 38, etc. Note that as UUE is more than an order of magnitude higher than UCE, units are separately shown on two Y-axes. Also note that the number of UUE measurements is lower than UCE measurements and that the number of patients contributing to these data rapidly decreases after the first 4 ICU weeks.

overall differences between males and females in the time course of UCE when corrected for weight. Here also, females showed a considerably lower UCE/kg than males.

According to the definition of augmented renal clearance (ARC) of mCC > 130 mL/min/1.73m^2, 21% of the patients had ARC after admission, and 21% had ARC as well at day 30 ($P = 0.747$). Not surprisingly, ARC was most prevalent in patients with no AKI (SFig. 4).

We also examined the time course of the plasma urea: creatinine ratio (UCR) which is associated with active catabolism and muscle wasting in trauma patients [17]. In our patients UCR showed rapid rise without any decrease during the first 30 days (SFig. 5), underscoring a sustained catabolic state.

When the potential impact of pre-ICU hospital time on baseline UCE as defined in [4] was examined (STable 1) we found a 14–20% ($P = 0.022$ and $P = 0.017$) lower UCE at ICU-admission in patients who had already been in the our hospital or another hospital before ICU admission.

4. Discussion

This study shows that urinary creatinine excretion (UCE) - as an indicator of muscle mass - steadily decreased over the first 30 days of prolonged ICU admission. The observed relative decrease in UCE of ≥1% per day was similar in survivors, non-survivors, males and females, although estimated baseline UCE was clearly different between these groups. Since creatinine levels also decreased over this period, this resulted in progressively higher estimates of renal function by the Cockcroft-Gault, MDRD and CKD-EPI equations. In contrast to these estimates, the measured creatinine clearance remained stable.

Our current study is the first to detail the time course of UCE during prolonged ICU admission. The absolute rate of change in UCE appeared to be primarily dependent on the absolute baseline value, as reflected by the stronger absolute decline in males compared to females and a stronger decline in survivors than non-survivors. Apparently, those with more muscle mass have more potential to lose muscle mass. When the relative decrease in UCE was computed, the mean value varied between 0.9 and 1.4%/d between the four mentioned groups ($P = 0.39$). In a long-term follow-up study of patients with chronic kidney disease stage 3 and 4, UCE also steadily decreased at a fixed - albeit much slower - relative rate [20]. In this study UCE was independently related to kidney failure and mortality and patients showed an approximate decline in UCE of 1.5% per year [20]. Other studies in critically ill patients, most of which measured muscle mass by ultrasonography, reported a decrease in muscle mass between 1 and 3%/d [1,21-24].

The rate of decrease in UCE in patients who were still in the ICU after 30 days appeared to diminish although it did not stabilize during the first 12 ICU weeks (Fig. 3). Such a plateau phase or even an increase of the UCE might appear earlier in patients with only a brief ICU stay and clear clinical recovery afterwards, but this assumption should be verified in further studies. Except for the first 2 weeks, the time course of urinary urea excretion (UUE) mirrored that of UCE. The time course of the plasma urea: creatinine ratio (UCR) is a known marker of muscle catabolism in trauma patients [17]. UCR also showed elevated and rising levels in our patients during the first 30 ICU days (SFig. 5), compatible with pronounced catabolism.

Apparently, ongoing loss of muscle mass is difficult to inhibit or even modify during critical illness [26]. We also performed a sub-analysis where we compared 'direct' admissions from home through the emergency department to the ICU with 'indirect' admissions from patients who had been longer in the hospital before ICU admission. Indirect admissions had a 18% lower UCE (STable 1), compatible with muscle loss that occurred preceding ICU admission. Although muscle wasting obviously is strongly related with outcome, our results do not point to a novel clinical intervention strategy. Unfortunately we currently do not possess the tools to inhibit muscle wasting despite our best efforts to optimally feed the patients [2,27-30]. If future interventions would be able to decrease muscle wasting, UCE would be a useful surrogate parameter to quantify such an effect. On the other hand, UCE could help

to quantify the effect of specific interventions that are known to increase muscle loss, such as prolonged muscular paralysis.

Probably because it reflects muscle mass [31], UCE shows a strong association with mortality in both critically ill and non-critically ill patient groups [4,32,33]. More direct methods to measure muscle mass have been used in ICU patients [34]. Bioelectrical impedance represents a non-invasive method, but is not very suitable in ICU patients due to its requirement for fluid homeostasis [35]. ^{40}K scintigraphy, the golden standard to measure body cell mass, could also be an accurate method to assess muscle mass and thus muscle wasting [31,37]. Repeated ultrasonography can detect muscle wasting [21-24], but because of the lack of a common protocol, interpretation remains difficult [36]. Future studies in which changes in UCE are compared with ultrasonography in a larger study population would be interesting.

In contrast to measured creatinine clearance (mCC) which utilizes UCE and plasma creatinine, estimates that are only based on plasma or serum creatinine are still used far more often. The Cockcroft-Gault equation was developed to predict creatinine clearance without laboratory determination of urinary creatinine excretion [13]. The MDRD study equation was developed for the assessment of GFR in CKD patients [14]. This was followed by the design of the CKD-EPI equation, which was meant to be an improved method for the assessment of GFR in patients with and without CKD, since the earlier developed MDRD study formula tended to underestimate measured GFRs at higher levels [16]. In our patients, the estimated GFR and estimated creatinine clearance equations falsely indicated an incremental rise in GFR which was most prominent for the Cockroft-Gault and MDRD equations (Fig. 2). The Cockroft-Gault formula was developed in 1976 when obesity was not as prevalent as today [25]. Although the inaccuracy of estimated renal function has long been known [5,7,26], our data underscore that the estimates of GFR markedly increase during prolonged ICU admission that is accompanied by decreasing muscle mass and creatinine production. Whereas Cockroft-Gault and MDRD progressively overestimated the mCC over time, CKD-EPI instead *under*estimated the mCC initially with the difference becoming smaller over time (Fig. 2). The overall incidence of augmented renal clearance as assessed by mCC corrected for BSA was 21% and did not change during ICU stay (SFig. 4).

Our study confirms that glomerular filtration equations should not be used in critically ill patients. Although the MDRD and CKD-EPI eGFR formulas are still frequently used in ICU patients they were not designed for evaluating renal function in such patients [14,16]. They do not only falsely suggest progressive renal recovery, but may also put patients at risk for drug dosing errors [5]. Measured creatinine clearance through UCE in the 24 h urine is thus the most reliable method to assess renal function in this patient group. To our knowledge, only few ICUs routinely measure UCE.

Routine UCE measurement is an easy, non-invasive and inexpensive method that once correctly implemented does not entail a significant additional workload.

A limitation of our study is its post hoc design. Also, we chose to select a specific and small subset of patients from a much larger cohort [4]. However, we believe that patients with a prolonged ICU stay of 30 days or more were best suited to clearly demonstrate the time course of UCE and plasma creatinine. Information on comorbidities such as sepsis, heart disease or liver disease was not available. Another potential limitation are the common changes in glomerular filtration rate in ICU patients which influence UCE [10,38]. UCE might also increase as a consequence of augmented renal clearance, but the persistent linear decrease we observed in UCE did not indicate this. Frequently prescribed drugs, such as diuretics and vasopressors may alter glomerular filtration rate [39,40]. Because UCE cannot be assessed in anuric patients, we excluded patients with AKI stage 3. Estimated GFR values were compared to measured creatinine clearance, which is not the golden standard for GFR assessment but is reliable in ICU patients when overestimation caused by possible increased tubular creatinine excretion is taken into account [7]. Measurement of UCE requires a complete 24 h urine collection. Because a large majority of ICU patients have urine catheters and our ICU nurses collect 24 h urine in all patients on a daily basis, the risk of collecting errors is low. Creatinine levels can be increased by meat intake. However, this was not a potential confounding factor in our study, since all our patients received enteral or parenteral feeding without any meat or added creatine.

In conclusion, UCE steadily decreases during the first month of ICU admission. During this period males, females, survivors and non-survivors showed the same relative decrease in UCE, underscoring the difficulty in reducing catabolism during ICU treatment. Decreased endogenous creatinine production, related to muscle loss, leads to progressively higher estimates of creatinine clearance or GFR when compared to the actually measured creatinine clearance. We believe that use of the UCE may improve the assessment of muscle mass and that mCC constitutes a superior tool to monitor renal function.

Ethics approval and consent to participate

This study was approved by our hospital's medical ethical committee and since it concerned an analysis of anonymized laboratory and clinical data, all collected during standard clinical care, informed consent was not required (METc 2011/132).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

There was no external funding for this work.

Authors' contributions

LH, RP and MN analyzed the data. MV, LH and MN interpreted the data. All authors contributed in writing the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.09.017.

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