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Elevated urea-to-creatinine ratio provides a biochemical signature of muscle catabolism and persistent critical illness after major trauma

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Abstract

Purpose: Muscle wasting is common amongst patients with persistent critical illness and associated with increased urea production, but reduced creatinine production. We hypothesised that elevated urea:creatinine ratio would provide a biochemical signature of muscle catabolism and characterise prolonged intensive care (ICU) admissions after major trauma.

Methods: Using pre-specified hypotheses, we analysed two existing data sets of adults surviving ≥ 10 days following admission to ICU after major trauma. We analysed trauma-ICU admissions to the major trauma centre serving the North East London and Essex Trauma Network, with a verification cohort of trauma-ICU cases from the MIMIC-III database. We compared serum urea, creatinine, and urea:creatinine ratio (ratio of concentrations in mmol/L) between patients with persistent critical illness (defined as ICU stay of ≥ 10 days) and those discharged from ICU before day 10. In a sub-group undergoing sequential abdominal computerised tomography (CT), we measured change in cross-sectional muscle area (psoas muscle at L4 vertebral level and total muscle at L3 level) and assessed for relationships with urea:creatinine ratio and ICU stay. Results are provided as median [interquartile range].

Results: We included 1173 patients between February 1st, 2012 and May 1st, 2016. In patients with ICU stay ≥ 10 days, day 10 urea:creatinine ratio had increased by 133% [72–215], from 62 [46–78] to 141 [114–178], $p < 0.001$; this rise was larger ($p < 0.001$) than in patients discharged from ICU before day 10, 59% [11–122%], 61 [45–75] to 97 [67–128], $p < 0.001$. A similar separation in trajectory of urea:creatinine ratio was observed in 2876 trauma-ICU admissions from MIMIC-III. In 107 patients undergoing serial CTs, decrease in L4 psoas and L3 muscle cross-sectional areas between CTs significantly correlated with time elapsed ($R^2 = 0.64$ and $R^2 = 0.59$, respectively). Rate of muscle decrease was significantly greater ($p < 0.001$ for interaction terms) in 53/107 patients with the second CT during evolving, current or recent persistent critical illness. In this group, at the second CT urea:creatinine ratio negatively correlated with L4 psoas and L3 muscle cross-sectional areas (R^2 0.39, $p < 0.001$ and 0.44, $p < 0.001$).

Conclusion: Elevated urea:creatinine ratio accompanies skeletal muscle wasting representing a biochemical signature of persistent critical illness after major trauma. If prospectively confirmed, urea:creatinine ratio is a potential surrogate of catabolism to examine in epidemiological and interventional studies.

Keywords: Muscle wasting, Major trauma, Sarcopenia, Creatinine, Urea, Intensive care unit acquired weakness, Urea–creatinine ratio

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Introduction

Patients with prolonged ICU stay consume the majority of bed days have increased risk of late death and a lower chance of returning directly home at hospital discharge; however, this population has been poorly defined and characterised. Recently, a definition of "persistent critical illness" has been developed based on the point "beyond which diagnosis and severity of illness at admission are no more predictive of in-hospital mortality than are simple premorbid patient characteristics" [1]. This transition point occurs after 10 days from ICU admission [1, 2]. Persistent critical illness is described as a dynamic clinical state, with a 'cascade' of new clinical problems [3] and a propensity for development of new, late organ failures [4]. A similar sub-group of patients is now increasingly recognised after major trauma, associated with a secondary peak of "late deaths" as more patients survive their initial injuries [5, 6]. In contrast to settings such as sepsis, major polytrauma patients are often younger, with less comorbid disease and have a rapid onset of critical illness. Polytrauma thus represents a population, where phenotypes of prolonged ICU stay and persistent critical illness might be more easily explored, distinct from factors related to baseline frailty, and one where intervention might be particularly beneficial [7].

Postulated biological characteristics of prolonged critical illness include: a protein-catabolic state with muscle loss [8, 9], persistent inflammation [10], relative immunosuppression [6], and endocrine dysfunction [11]. However, such studies have generally examined small numbers of patients using investigations not routinely applied in clinical practice. Routinely collected clinical data may also reflect the altered biology of persistent critical illness providing large volumes of multi-dimensional data to explore characteristic biological signatures, Box 1. Furthermore, routinely collected laboratory and radiological data could help identify acquired muscle wasting and the presence of persistent catabolism [12], allowing future interventional strategies to be tailored to individual patient trajectories. Based on the previous pilot observations [13], we hypothesised that persistent critical illness after polytrauma would be associated with changes in urea:creatinine ratio and other routine biochemical markers reflecting catabolism and/or inflammation and that these changes would be accompanied by skeletal muscle wasting.

Take-home message

Urea-to-creatinine ratio is a simple, routinely available, preliminary marker of the catabolic state that characterises persistent critical illness after major trauma.

Box 1: Persistent critical illness: mapping of potential markers

Characteristic	Potential routine clinical data marker	Biological rationale
Persistent	Haemoglobin ↓	Suppression of erythropoiesis and blunted response to erythropoietin [5, 14]
Inflammation	C-reactive protein ↑	Discriminatory marker of acute phase of inflammation [15, 16]
	Neutrophil count ↑	Unchecked activation propagating inflammatory states [17]
Immunosuppression	Lymphocyte count ↓	Primarily described as dysfunction of adaptive immunity resulting in recurrent infection [9, 18]
	Neutrophil:lymphocyte ratio ↑	Putative marker of innate and adaptive immune responses [19]
Catabolism	Urea:creatinine ratio ↑	Metabolism of amino acids mobilised from muscle protein [11]
	Albumin ↓	Decreased protein turnover associated with mortality [20]
	Skeletal muscle mass ↓	Result of anabolic–catabolic imbalance [8]

Methods

Data sources

To test our hypothesis that alterations of urea, creatinine, and urea:creatinine might provide a metabolic signature of persistent critical illness, we analysed two existing data sets examining adults surviving ≥ 10 days following ICU admission for major trauma. In our main analysis, we studied trauma-ICU admissions to a Level 1 trauma centre serving the North East London and Essex trauma network (The Royal London Hospital). This trauma service covers a population of 3.5 million people from 12 hospital districts. This was a secondary analysis of a previously derived data set [21] approved by the Barts Health/

Queen Mary University of London Joint Research Office as a retrospective review of data collected as part of usual patient care with waiver of requirement for research ethics committee review. Data were obtained from ICU admission through to ICU discharge from hospital electronic records, and trauma and ICU audit databases. For comparison, we also analysed a trauma-ICU cohort from the Medical Information Mart for Intensive Care (MIMIC-III) database describing ICU admissions to the Beth Israel Hospital Boston MA, USA [22]. We used the STROBE recommendations for reporting of cohort studies [23].

Participants

The previously derived Royal London data set included all trauma admissions admitted to the adult ICU either directly or via the operating theatre between February 1st, 2012 to May 1st, 2016, excluding those with advanced kidney dysfunction at hospital admission (first serum creatinine value > 354 μmol/L or history of end-stage kidney disease) and any deaths within 24 h from ICU admission [21]. In our primary analysis of persistent critical illness, we further excluded patients who died before day 10 and those who received renal replacement therapy (RRT) in the ICU (as a confounder of the interpretation of changes in serum creatinine and urea).

Measurements

We assessed serum urea, creatinine, urea:creatinine (ratio of urea-to-creatinine concentrations in mmol/L), neutrophil count, lymphocyte count, neutrophil lymphocyte ratio, c-reactive protein (CRP), haemoglobin, and albumin. These parameters were pre-specified on the basis of availability from routine daily blood tests and biologically plausible relationships with persistent critical illness phenotypes (Box 1). To reduce bias arising from over-representation of rapidly repeated blood tests, we considered only the first result in each 24 h period for any patient. Acute Kidney Injury (AKI) was defined using 2012 KDIGO AKI creatinine criteria [24].

Primary analysis

Our primary outcome was development of persistent critical illness, prospectively defined as an ICU length of stay (LoS) of 10 or more days [1, 2]. Trajectories of blood tests in patients developing persistent critical illness were compared with those of patients discharged from ICU and still alive at day 10. The biochemical signature of those patients with a persistent need for intensive care was then assessed.

Secondary analyses

We re-assessed trajectories after stratifying patients into 4 groups based on ICU LoS (1–4 days, 5–9 days, 10–19 days, and ≥ 20 days). In addition, to assess any influence of AKI on urea, creatinine, and urea:creatinine, we plotted trajectories stratified by peak AKI stage. As AKI is strongly associated with risk of death, in this sensitivity analysis, we included deaths prior to 10 days as well as patients requiring RRT for AKI.

Biochemical signature of persistent critical illness

We adapted the methodology reported by Iwashyna et al. [1] to verify the timing of onset of persistent critical illness in our trauma population by examining the relationship between acute illness and antecedent characteristics and risk of death. We assessed, on each day, the factors associated with remaining in the ICU compared to having been discharged (development and continuation of persistent critical illness). To understand factors discriminating patients still admitted to ICU from those discharged from ICU, but still in hospital, we compared models based on the measurements of daily routine blood tests, to ones derived from a combination of both antecedent patient characteristics and initial illness severity.

Sub-group assessment of muscle area

Muscle cross-sectional area (CSA) was assessed in a sub-group of patients in the Royal London cohort with abdominal CT scans on hospital admission and at least one more in-hospital follow-up CT. Total abdominal muscle CSA was measured at the level of the third lumbar (L3) vertebrae [25], and psoas muscle CSA was calculated at the L4 level (see detailed methods in appendix). We examined change in muscle area over time after hospital admission comparing two groups based on the time of a second CT scan. First, a group of patients with evolving, current, or recent persistent critical illness (defined as patients with ICU length of stay of ≥ 10 days, or death in ICU before day 10) who had a second CT either in ICU or within 7 days of ICU discharge. We compared this group to a second group who did not develop or had resolved persistent critical illness (defined as patients who were alive and out of ICU at day 10 or patients who had a second CT at least 7 days after ICU discharge). We then examined the relationship between serum urea:creatinine and muscle in these groups using scatter plots of muscle CSA and urea:creatinine at admission and at time of the second CT.

Statistical analysis

Statistical analysis was performed in R v3.4.4. Continuous data are presented median with interquartile range (IQR) or range and were compared using the Wilcoxon rank sum test or the Wilcoxon signed rank test for paired data. Categorical data were compared using the Fisher's test or Chi-squared tests. Trajectories of daily blood test results are displayed as rolling medians with 95% confidence interval of the median. For the assessment of the biochemical signature of persistent critical illness logistic regression models was derived on each day using all blood test variables, with backward selection based on the minimisation of the Akaike information criterion (AIC) derived from the pooled residual Chi square. Ability of individual blood tests or combinations of blood tests or logistic regression models to discriminate the group of patients still in ICU from those discharged on any given day was assessed by the calculation of the area under the received-operating characteristic (ROC-AUC) with 95% confidence interval. Detailed statistical methods are described in the supplement. In these analyses, missing data points were excluded and numbers reported.

Results

Patient characteristics

Of 1394 patients admitted to ICU after polytrauma in the London data set [21], we were able to extract pathology and radiology records reflecting the entire admission in 1376 (Fig. S1). Of these, 203 (15%) died in the first 10 days in hospital leaving 1173 patients alive at day 10 for our primary analysis. Of these, 467 (34% of total cohort) were still in ICU at day 10, fulfilling criteria for persistent critical illness, while 706 (51.3%) were discharged from ICU and alive at day 10 (Table 1). Those with persistent critical illness accounted for 71% of the total ICU-bed days and 62% of the total trauma-hospital bed days. Furthermore, 51% went on to be transferred to another acute hospital or rehabilitation facility, while by comparison 71% of patients who were alive and out of ICU at day 10 were discharged directly home (Table 1). Patients with persistent critical illness were comparatively older; more severely injured and had greater rates of traumatic brain or spinal injuries and more prior comorbidities (Table 1). Logistic regression models for hospital mortality based on initial illness severity had good discriminatory ability when predicting hospital death from time of admission (ROC-AUC 0.83; 95% CI 0.80–0.86), but progressively lost predictive ability over time and were not better than antecedent characteristics after 9 days in hospital (Fig. S2), in keeping with the definition and timing of persistent critical illness described previously [1, 2].

Trajectories of laboratory tests in patients with and without persistent critical illness after ICU admission

Trajectories of urea:creatinine differed between patients with and without persistent critical illness from day 5 onwards. Median values more than doubled by day 10 for patients with persistent critical illness compared to a modest rise and then progressive fall in those discharged from ICU by day 10 (Fig. 1, Table 2). Trajectories of CRP, neutrophil count, and neutrophil:lymphocyte ratio less clearly differentiated those with and without persistent critical illness (Figs. S3, S4, Table 2). Median albumin and haemoglobin concentrations fell rapidly in both groups after trauma-ICU admission, but falls were greater and more lasting in those with persistent critical illness (Figs. S3, S4, Table 2). These patterns persisted when trajectories were stratified into four categories of ICU LoS: < 5 days ($n = 424$), 5–9 days ($n = 275$), 10–19 days ($n = 277$), and 20 days ($n = 159$), (Fig. 1). The presence of AKI distinctly influenced the trajectories of serum creatinine and urea, but only modestly attenuated the rise in urea:creatinine over time after ICU admission (Fig. S5).

Variables associated with prolonged ICU admission

Biochemical data differentiating patients with or without persistent critical illness are presented in Table 2. No variables effectively discriminated eventual persistent critical illness at ICU admission (day 0). At onset of persistent critical illness (pre-defined as day 10), urea:creatinine, urea alone and haemoglobin discriminated the group of patients still remaining in ICU from those discharged and alive, ROC-AUC 0.74 (95% CI 0.70–0.79), 0.71 (0.67–0.71), and 0.70 (0.65–0.75), respectively. Serum creatinine, CRP, albumin, neutrophil count, and lymphocyte count either poorly (ROC-AUC < 0.7) or failed (ROC-AUC < 0.6) to discriminate those patients with persistent critical illness at this timepoint (Table 2). When considering the ability of each parameter to discriminate a patient group with continuing need for intensive care on each day in hospital only urea:creatinine, urea and haemoglobin consistently exceeded a ROC-AUC of 0.7 at any stage after day 10, while by comparison a combination of initial illness severity, demographics and comorbidity displayed decreasing ability to discriminate the population remaining in ICU on any day over time (Fig. S7). When combined in multivariable models (Table S1) urea:creatinine and haemoglobin increasingly discriminated persistent need for intensive care over time. After day 10, the biochemical signature of a raised urea:creatinine and low haemoglobin better discriminated persistent need for intensive care than a combination of admission illness

Table 1 Patient characteristics in 1376 major trauma-ICU patients comparing patients still in ICU at day 10 (persistent critical illness), those discharged alive from ICU and alive at day 10, and those who died before day 10

	In ICU at day 10	Discharged ICU and alive at day 10	*p* value in ICU vs. discharged day 10	Died on or before day 10
Number (%)	467 (33.9)	706 (51.3)		203 (14.8)
Age [years (median [IQR])]	45.00 [28.50, 58.00]	37.00 [26.00, 53.00]	< 0.001	51.00 [32.00, 71.50]
Sex = male (%)	376 (80.5)	568 (80.5)	1.0	154 (75.9)
ISS (median [IQR])	29.00 [24.00, 38.00]	18.00 [10.25, 25.00]	< 0.001	29.00 [25.00, 38.00]
NISS (median [IQR])	43.00 [29.00, 57.00]	27.00 [17.00, 36.00]	< 0.001	50.00 [34.00, 66.00]
APACHE 2 (median [IQR])[a]	11.00 [8.00, 15.00]	9.00 [7.00, 13.00]	< 0.001	19.00 [14.00, 26.00]
SAPS 2 (median [IQR])[a]	35.00 [28.00, 43.00]	34.00 [26.00, 42.00]	0.042	40.00 [34.00, 50.00]
Charlson comorbidity index (%)			< 0.001	
0	315 (67.5)	563 (79.7)		152 (74.9)
1	92 (19.7)	91 (12.9)		26 (12.8)
2	43 (9.2)	36 (5.1)		23 (11.3)
≥ 3	17 (3.6)	16 (2.3)		2 (1)
Died in hospital	37 (7.9)	11 (1.6)	*	203 (100.0)
ICU LoS [days (median [IQR])]	17.00 [12.50, 23.00]	4.00 [2.00, 6.00]	*	4.00 [2.00, 6.00]
Trauma-hospital LoS [days (median [IQR])]	40.00 [26.00, 57.50]	13.00 [7.00, 24.00]	*	4.00 [3.00, 7.00]
Total ICU bed [days (%)]	9368 (71.4)	2889 (22.0)	*	855 (6.5)
Total trauma-hospital bed [days (%)]	36,908 (61.9)	13,114 (35.5)	*	948 (2.7)
Discharge destination (%)			< 0.001	
Died	37 (7.9)	11 (1.6)		203 (100.0)
Home	168 (36.0)	505 (71.5)		0 (0.0)
Other hospital/rehabilitation	238 (50.9)	148 (21)		0 (0.0)
Psychiatric hospital	2 (0.4)	19 (2.7)		0 (0.0)
Unknown	22 (4.7)	23 (3.3)		0 (0.0)
Acute kidney injury (%)			< 0.001	
None	354 (75.8)	636 (90.1)		131 (64.5)
AKI-1	74 (15.8)	52 (7.4)		34 (16.7)
AKI-2	3 (0.6)	8 (1.1)		6 (3.0)
AKI-3	36 (7.7)	10 (1.4)		32 (15.8)
Renal replacement therapy	31 (6.6)	7 (1.0)	< 0.001	26 (12.8)
Sites of injuries				
Brain (%)	278 (59.5)	257 (36.4)	< 0.001	149 (73.4)
Spine (%)	80 (17.1)	58 (8.2)	< 0.001	18 (8.9)
Abdomen (%)	52 (11.1)	103 (14.6)	0.105	15 (7.4)
Chest (%)	169 (36.2)	218 (30.9)	0.067	47 (23.2)
Pelvis (%)	61 (13.1)	56 (7.9)	0.006	16 (7.9)
Limbs (%)	38 (8.1)	86 (12.2)	0.034	8 (3.9)
Face/neck (%)	30 (6.4)	58 (8.2)	0.306	11 (5.4)
Admission blood tests (median [IQR])				
Creatinine (μmol/L)	84.00 [67.00, 105.00]	82.00 [66.00, 99.00]	0.079	90.00 [67.50, 117.00]
Urea (mmol/L)	5.00 [4.00, 6.60]	4.80 [3.70, 6.00]	0.001	5.00 [3.90, 7.15]
Urea:creatinine	60.92 [45.45, 75.87]	58.93 [44.21, 73.33]	0.131	57.14 [43.68, 77.54]
CRP (mg/L)	5.00 [5.00, 14.00]	5.00 [5.00, 9.00]	< 0.001	5.00 [5.00, 16.00]
Albumin (g/L)	38.00 [34.00, 42.00]	40.00 [37.00, 44.00]	< 0.001	37.00 [32.00, 42.00]
Neutrophil count ($\times 10^9$ cells/L)	11.20 [7.40, 16.20]	9.50 [6.20, 14.15]	< 0.001	9.70 [6.15, 14.45]
Lymphocyte count ($\times 10^9$ cells/L)	1.80 [1.10, 3.10]	1.90 [1.20, 2.90]	0.867	1.90 [0.90, 3.30]
Neutrophil:lymphocyte	5.92 [3.23, 10.17]	5.15 [2.73, 9.80]	0.038	5.22 [2.70, 12.58]
Haemoglobin (g/dL)	13.20 [11.80, 14.60]	13.60 [12.20, 14.70]	0.009	12.80 [11.30, 14.00]
Discharge creatinine (μmol/L)	54.00 [42.00, 66.00]	62.00 [51.00, 74.00]	< 0.001	86.00 [61.00, 139.00]

Table 1 (continued)

	In ICU at day 10	Discharged ICU and alive at day 10	*p* value in ICU vs. discharged day 10	Died on or before day 10
Discharge urea (mmol/L)	5.20 [3.80, 7.10]	4.20 [3.20, 5.50]	< 0.001	7.20 [4.75, 11.00]
Discharge urea:creatinine	99.35 [72.07, 134.47]	66.67 [51.28, 87.50]	< 0.001	73.33 [56.35, 112.66]

Medians and interquartile ranges or proportions. Wilcoxon Rank Sum test, Fisher exact test, Chi-squared test were used for continuous, dichotomous, or multiple category dichotomous data, respectively

ISS injury severity score, *NISS* new injury severity score, *ICU* intensive care unit, *AKI* acute kidney injury, APACHE II acute physiology and chronic health evaluation II, *SAPS* simplified acute physiology score, *KDIGO* kidney disease improving global outcomes, *CRP* C-reactive protein, *LoS* length of stay, *ISS* Injury Severity Score, *NISS* New Injury Severity Score

*Comparison not made as defined by group categorization

[a] ICU illness severity data available in 1351/1376 patients

severity, age, and comorbidity [day 11 ROC-AUC 0.81 (0.76–0.85) vs. 0.72 (0.66–0.76), respectively, $p = 0.002$—Fig. S6].

Psoas and abdominal cross-sectional skeletal muscle area

From the 1472 London polytrauma patients, we identified a sub-group of 107 patients undergoing multiple abdominal CTs. This group was younger, more severely injured, had longer hospital and ICU LoS, a lower incidence of major brain injury, but a higher proportion of chest, abdominal, and pelvic injury (Table S2). ICU admission severity scores were similar to the whole trauma-ICU cohort. Serial L4 psoas CSA muscle measurements were made in all 107 patients, and L3 muscle CSA were possible in 92. Representative images are shown in Fig. 2. Repeat CT scans were performed a median of 8 days (range 1–83) after admission. L4 psoas and L3 total muscle CSA measurements correlated consistently both at admission and at the subsequent CT scan ($R^2 = 0.68$, $n = 92$, $p < 0.001$ and $R^2 = 0.69$, $n = 92$, $p < 0.001$, respectively, Fig. S8).

In the majority of patients, CT-measured L4 psoas and L3 muscle CSA consistently decreased over time after hospital admission (R^2 0.64 and 0.59, respectively—Fig. 2). In patients with a CT scan performed ≥ 10 days after admission allowing an L3 total muscle CSA measurement, 33 (81%) met criteria for sarcopenia compared to 13 of 41 (32%) at admission ($p < 0.001$, Fig. S9). 53 patients had evolving, current or recent persistent critical illness at time of the second CT, while 54 did not have or had resolved persistent critical illness at the second CT. In multiple linear regression, muscle area decrease was more rapid in those with evolving current or recent persistent critical illness, p value < 0.001 for interaction term with group assignment (Fig. 2).

Relationship between measured muscle area and creatinine, urea, and urea:creatinine ratio

When considering the 53 patients with the second CT during evolving, current, or recent persistent critical illness, serum creatinine and muscle areas declined, while at the same time, urea rose (Fig. 3, Table S3). As a consequence, urea:creatinine became substantially elevated reflecting the divergent changes in urea and creatinine (Table S3, Fig. 3). In 25 of these 53 patients, where the second CT was obtained on or after day 10 (current or recent persistent critical illness), median L4-psoas area had decreased by 34% from 35 cm^2 [25–41] to 23 cm^2 [13–29], $p < 0.001$ and L3 muscle area by 21%, 174 cm^2 [149–202] to 138 cm^2 [100–176], $p < 0.001$, while concurrently, urea:creatinine ratio increased by 221% from 51 [44–67] to 164 [109–200], $p < 0.001$ (Table S3). In all patients, urea:creatinine and muscle CSA showed no correlation at ICU admission (Fig. S10); however, in those with evolving, current or recent persistent critical illness, urea:creatinine was negatively correlated with L4 psoas and L3 muscle CSA (R^2 0.39 and 0.44, respectively), this association was not consistently seen in patients without or with resolved persistent critical illness with a second CT (Fig. S10).

MIMIC-III cohort

From MIMIC-III, we extracted 3119 trauma-ICU admissions with 2876 alive at day 10, and 432 (13.9%) with an ICU LoS of ≥ 10 days (Fig. S11, Table S4). Trajectories of urea:creatinine discriminated both persistent critical illness and differing ICU LoS (Fig. 1, Fig. S12, Table S5). As in the London cohort (Fig. S6), urea:creatinine and haemoglobin increasingly discriminated persistent need for intensive care from admission through to day 10, thereafter performing comparably to daily models based on initial illness severity and age (Fig. S13).

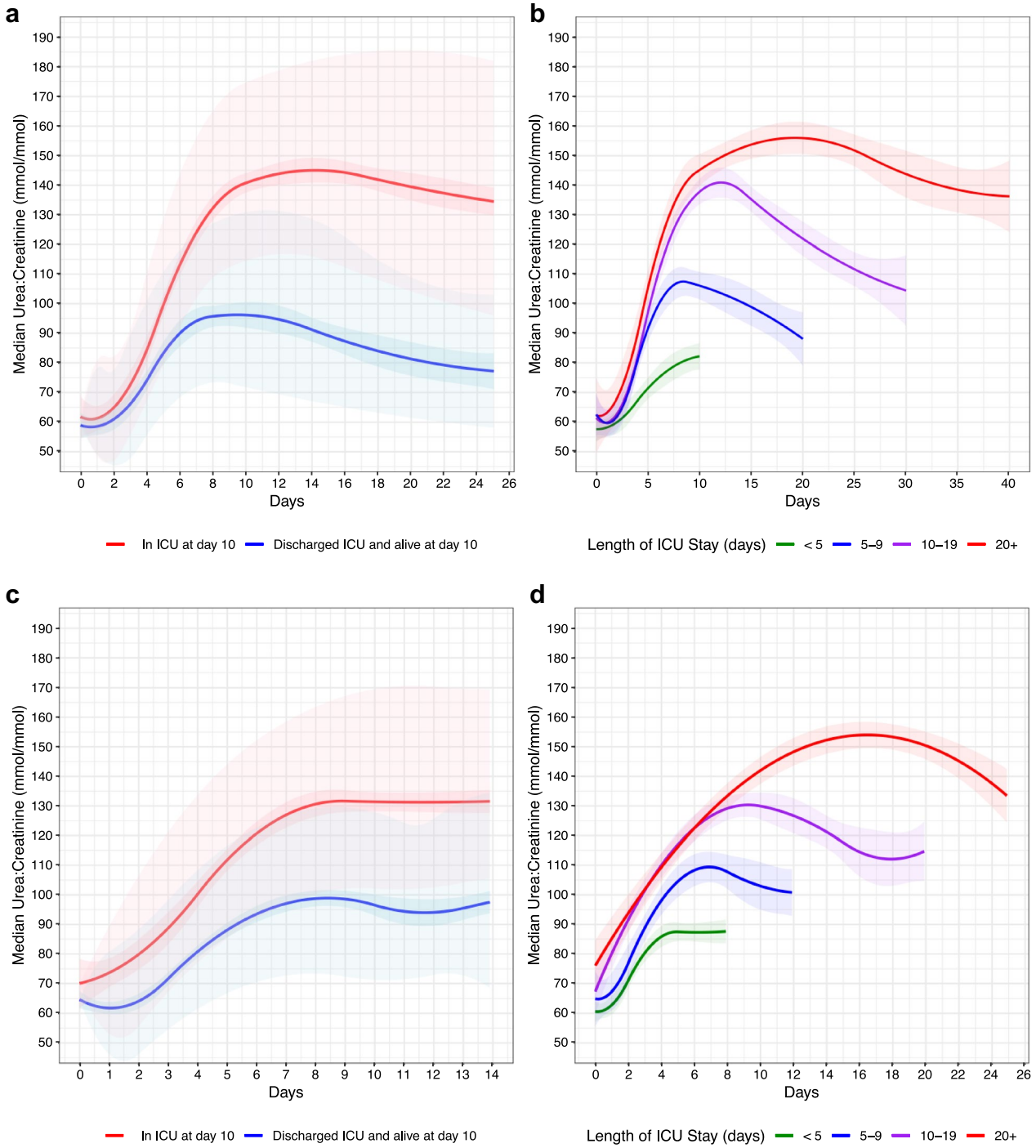

Fig. 1 Trajectories of urea:creatinine. **a** Of 1135 major trauma patients admitted to ICU who survived to day 10 without requiring RRT, 436 patients with persistent critical illness (still in ICU at day 10 after admission) are compared to 699 without (patients initially admitted to ICU but discharged and still alive at day 10). **b** Trajectories stratified by ICU length of stay: < 5 days ($n = 424$), 5–9 days ($n = 275$), 10–19 days ($n = 277$) and > 20 days ($n = 159$). Consistent findings in 2901 trauma-ICU patients from the MIMIC-III database; **c** 443 patients with persistent critical illness were compared to 2458 without and **d** stratified by ICU length of stay: < 5 days ($n = 2125$), 5–9 days ($n = 306$), 10–19 days ($n = 319$) and > 20 days ($n = 124$). Rolling medians with 95%-confidence intervals of the rolling estimate of the median value (darker shading) are shown using quadratic splines with the curve constrained to pass through the median admission value. Lighter shading in plots **a** and **c** represents areas between rolling values for the 25th and 75th centiles (interquartile range). *ICU* intensive care unit; *RRT* renal replacement therapy

Table 2 Changes in routinely measured renal, metabolic, and inflammatory parameters in trauma-ICU patients during hospitalization, comparing those developing persistent critical illness (in ICU at day 10) *n* = 436 (Group 1) with those discharged from ICU and alive at day 10 after admission *n* = 699 (Group 2)

Analyte	Day of blood test	In ICU at day 10 (Group 1)				Alive and out of ICU at day 10 (Group 2)				*p* value Group 1 vs. Group 2	AUC for in ICU at day 10 (95% CI)
		Number with bloods	Median daily value [IQR]	Day 0 Median [IQR]	% change from Day 0 Median [IQR]	Number with bloods	Median Daily value [IQR]	Day 0 Median [IQR]	% change from Day 0 Median [IQR]		
Creatinine (μmol/L)	Day 0	436	82 [66, 103]	–	–	699	82 [66, 99]	–	–	0.440	0.51 (0.48–0.55)
	Day 10	363	56 [45, 73.5]	83 [67, 103]	−30% [−46, −11]	164	60.5 [50, 74]	83 [66, 107]	−26% [−42, −5]	0.051	0.55 (0.50–0.60)
	Day 15	242	54 [44, 66]	84 [68, 107]	−34% [−49, −17]	93	57 [46, 68]	77 [66, 99]	−27% [−42, −14]	0.294	0.55 (0.47–0.60)
	Day 20	180	50.5 [41, 61]	84 [68, 103]	−38% [−50, −23]	60	59 [43, 68]	82 [68, 102]	−34% [−46, −17]	0.058	0.58 (0.50–0.67)
Urea (mmol/L)	Day 0	436	5.0 [4.0, 6.6]	–	–	699	4.7 [3.7, 5.9]	–	–	0.002	0.56 (0.52–0.59)
	Day 10	363	8.0 [6.1, 10.9]	5.1 [4.0, 6.6]	+56% [+21, +115]	164	5.5 [4.4, 7.7]	5.0 [3.9, 6.3]	+17% [−19, +63]	<0.001	0.71 (0.66–0.76)
	Day 15	242	8.0 [6.0, 10.6]	5.1 [4.0, 6.6]	+61% [+14, +115]	93	4.8 [3.6, 7.3]	4.9 [3.8, 6.5]	+1% [−29, +63]	<0.001	0.76 (0.70–0.82)
	Day 20	180	6.7 [5.2, 9.0]	5.3 [4.0, 6.6]	+32% [−4, +85]	60	4.2 [3.2, 6.3]	5.2 [3.9, 6.7]	−17% [−41, +14]	<0.001	0.74 (0.66–0.82)
Urea:creatinine	Day 0	436	62 [46, 77]	–	–	699	59 [44, 73]	–	–	0.028	0.54 (0.51–0.58)
	Day 10	363	141 [114, 178]	62 [46, 78]	+133% [+72, +215%]	164	97 [67, 128]	61 [45, 75]	+59% [+11, +122]	<0.001	0.75 (0.70–0.80)
	Day 15	242	145 [114, 185]	59 [45, 76]	+145% [+76, +237]	93	88 [62, 122]	64 [44, 77]	+47% [+9, 119]	<0.001	0.78 (0.72–0.84)
	Day 20	180	139 [101, 178]	61 [45, 75]	+125% [+51, +215]	60	77 [58, 110]	66 [50, 78]	+24% [−6, +80.4]	<0.001	0.78 (0.72–0.85)
Albumin (g/L)	Day 0	387	39 [34, 42]	–	–	605	40 [37, 44]	–	–	<0.001	0.59 (0.55–0.62)
	Day 10	360	28 [25, 32]	39 [34, 42]	−25% [−34, −13]	100	31.5 [27, 37]	39 [35, 24]	−14 [−23, −4]	<0.001	0.66 (0.60–0.72)
	Day 15	223	29 [25, 33]	38 [34, 42]	−23% [−32, −12]	50	31 [26.25, 34]	38 [32, 42]	−17 [−31, −1]	0.049	0.58 (0.50–0.68)
	Day 20	148	30 [27, 35]	39 [34, 42]	−18% [−30, −5]	32	32 [29, 37.5]	38 [34, 42]	−11 [−23, +3]	0.037	0.62 (0.51–0.72)
Haemoglobin (g/dL)	Day 0	428	13.2 [11.9, 14.6]	–	–	692	13.6 [12.2, 14.7]	–	–	0.006	0.55 (0.51–0.58)
	Day 10	358	8.8 [8.1, 9.8]	13.3 [12.0, 14.6]	−32% [−38, −21]	155	9.9 [8.85, 11.2]	13.0 [11.9, 14.5]	−21% [−31, −8.5]	<0.001	0.70 (0.65–0.75)
	Day 15	234	9 [8.1, 9.9]	13.2 [11.9, 14.6]	−31% [−38, −22]	90	9.9 [9.0, 11.2]	13.0 [11.5, 14.3]	−20% [−32, −10]	<0.001	0.68 (0.61–0.75)
	Day 20	172	9.3 [8.4, 10.2]	13.1 [12.1, 14.6]	−29% [−35, −20]	59	10 [9.3, 10.8]	13.2 [11.8, 14.6]	−21% [−33, −13]	0.002	0.64 (0.56–0.72)
CRP (mg/L)	Day 0	336	5 [5, 14]	–	–	512	5 [5, 9]	–	–	<0.001	0.57 (0.53–0.61)
	Day 10	356	88 [52, 148]	5 [5, 14]	+1023% [+343, +2025]	128	67 [34, 125]	5 [5, 15]	+710% [+105, +1460]	0.002	0.59 (0.53–0.65)
	Day 15	228	57 [30, 113]	6 [5, 17]	+483% [+140, +1240]	67	40 [22, 96]	5 [5, 7]	+480% [+76, +940]	0.034	0.58 (0.51–0.66)
	Day 20	164	42 [14, 79]	6 [5, 16]	+200% [0, +871]	44	39 [18, 116]	5 [5, 13]	+345% [+2, +1040]	0.360	0.54 (0.45–0.64)

Table 2 (continued)

Analyte	Day of blood test	In ICU at day 10 (Group 1)				Alive and out of ICU at day 10 (Group 2)				*p* value Group 1 vs. Group 2	AUC for in ICU at day 10 (95% CI)
		Number with bloods	Median daily value [IQR]	Day 0 Median [IQR]	% change from Day 0 Median [IQR]	Number with bloods	Median Daily value [IQR]	Day 0 Median [IQR]	% change from Day 0 Median [IQR]		
Neutrophil count ($\times 10^9$ cells/L)	Day 0	426	11.3 [7.4, 16.1]	–	–	672	9.5 [6.2, 14.1]	–	–	< 0.001	0.57 (0.54–0.60)
	Day 10	349	11.2 [8.7, 14.6]	11.7 [7.7, 16.4]	+ 1% [− 26, + 43]	149	9.9 [7.1, 14.8]	10.9 [6.7, 16.1]	− 12.8% [− 42, + 53]	0.012	0.57 (0.51–0.61)
	Day 15	230	9.7 [7.6, 11.5]	12.4 [7.7, 17.1]	− 19% [− 46, + 23]	81	8.4 [5.8, 10.9]	9.0 [6.5, 14.8]	− 14.8% [− 38, + 49]	0.004	0.61 (0.53–0.68)
	Day 20	168	7.1 [5.6, 10.0]	12.9 [8.1, 17.2]	− 42% [− 61, − 2]	54	6.4 [4.8, 8.1]	9.5 [6.6, 15.8]	− 41% [− 66, + 13]	0.035	0.60 (0.51–0.68)
Lymphocyte count ($\times 10^9$ cells/L)	Day 0	426	1.8 [1.1, 2.9]	–	–	672	1.9 [1.2, 2.9]	–	–	0.551	0.49 (0.45–0.52)
	Day 10	349	1.7 [1.3, 2.2]	1.8 [1.1, 3.2]	− 15% [− 45, + 47]	149	1.7 [1.2, 2]	1.6 [1.1, 2.7]	− 11% [− 39, + 71]	0.489	0.52 (0.47–0.56)
	Day 15	230	1.6 [1.2, 2.2]	1.9 [1.2, 3.3]	− 16% [− 51, + 29]	81	1.5 [1.2, 1.9]	1.8 [1.1, 2.5]	− 17% [− 48, + 34]	0.102	0.56 (0.49–0.63)
	Day 20	168	1.5 [1.2, 2]	2.0 [1.1, 3.4]	− 25% [− 56, + 20]	54	1.4 [1, 1.9]	1.9 [1.0, 3.2]	− 20% [− 49, 26]	0.04	0.59 (0.50–0.68)
Neutrophil: lymphocyte	Day 0	426	6.1 [3.3, 10.2]	–	–	672	5.1 [2.7, 9.8]	–	–	0.008	0.55 (0.51–0.58)
	Day 10	349	6.8 [4.9, 9.4]	6.2 [3.4, 10.5]	+ 14% [− 38, + 100]	149	6.1 [4.1, 9.4]	6.8 [3.4, 11.9]	0% [− 56, + 117]	0.110	0.54 (0.49–0.60)
	Day 15	230	5.9 [4.3, 7.8]	6.0 [3.4, 10.2]	0% [− 44, + 81]	81	5.2 [4, 7.8]	5.6 [3.3, 11.0]	2% [− 48, + 99]	0.232	0.54 (0.47–0.62)
	Day 20	168	4.7 [3.3, 6.7]	6.8 [3.4, 11.9]	− 18% [− 55, + 51]	54	4.8 [3.4, 6.4]	6.1 [3.2, 10.8]	− 24% [− 59, 27]	0.830	0.51 (0.42–0.60)

Patients who died before day 10 ($n = 203$) and those who received renal replacement therapy ($n = 38$) are excluded. Medians with interquartile ranges and receiver-operating characteristic area under the curves for discrimination of ICU status at day 10 with 95% confidence interval are shown. *p* values represent non-parametric comparison of distribution values between Group 1 and Group 2 using Wilcoxon rank sum test

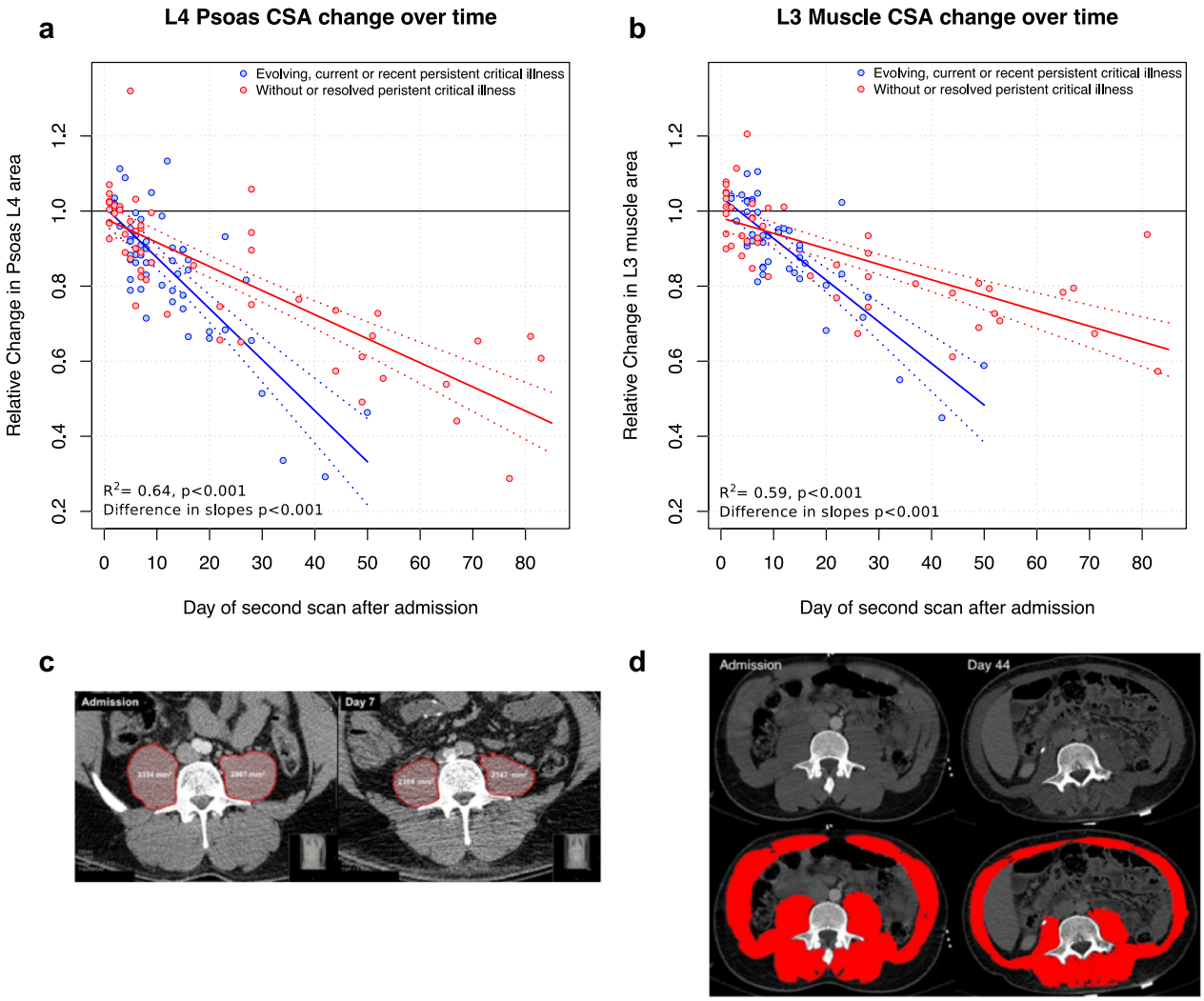

Fig. 2 Multiple linear regression for loss of muscle area over time in ICU in 107 patients with serial abdominal CT scans after major trauma. Overall CT-measured L4 psoas (**a**) and L3 muscle cross-sectional area (CSA) (**b**) consistently decreased over time after hospital admission (R^2 0.64, $p < 0.001$ and 0.59, $p < 0.001$, respectively). In 53 patients who had evolving, current or recent persistent critical illness at time or second CT (ICU length of stay of ≥ 10 days or death in ICU before day 10, who had second CT either in ICU or within 7 days of ICU discharge) muscle CSA decrease was more rapid than in 54 patients who did not have or had resolved persistent critical illness at second CT (those alive and out of ICU at day 10 or those having the second CT at least 7 days after ICU discharge) with a significant interaction term for group assignment in the multiple regression models $p < 0.001$ for both L3 CSA and L4 psoas. **c** Representative analysis shows psoas muscle cross-sectional area at the L4 level outlined in red, at admission and after 7 days. **d** Representative CT image slices at the third lumbar vertebrae showing the same patient at admission (left column) and after 44 days in hospital (right column), analysed images show muscle tissue CSA (red). *CT* computerised tomography, *CSA* cross-sectional area, *L3* third lumbar vertebrae, *L4* fourth lumbar vertebrae

Discussion

Summary of findings

In a major trauma population, patients with ICU length of stay ≥ 10 days fulfilled features of persistent critical illness [1, 2], so that by day 10 severity of critical illness at ICU admission was no more predictive of subsequent in-hospital mortality than premorbid patient characteristics. In parallel with the previous descriptions, this persistently critically ill group consumed the majority of ICU and hospital bed days, had higher late mortality and a lower chance of returning directly home. Importantly, we identified phenotypes associated with transition to persistent critical illness and the continuation of ICU admission. In our data set a persistent elevation in urea:creatinine, a potential marker of catabolism [26], characterised the persistently critically ill population, a finding replicated in the MIMIC-III data set. In polytrauma patients with serial CT scans, substantial muscle

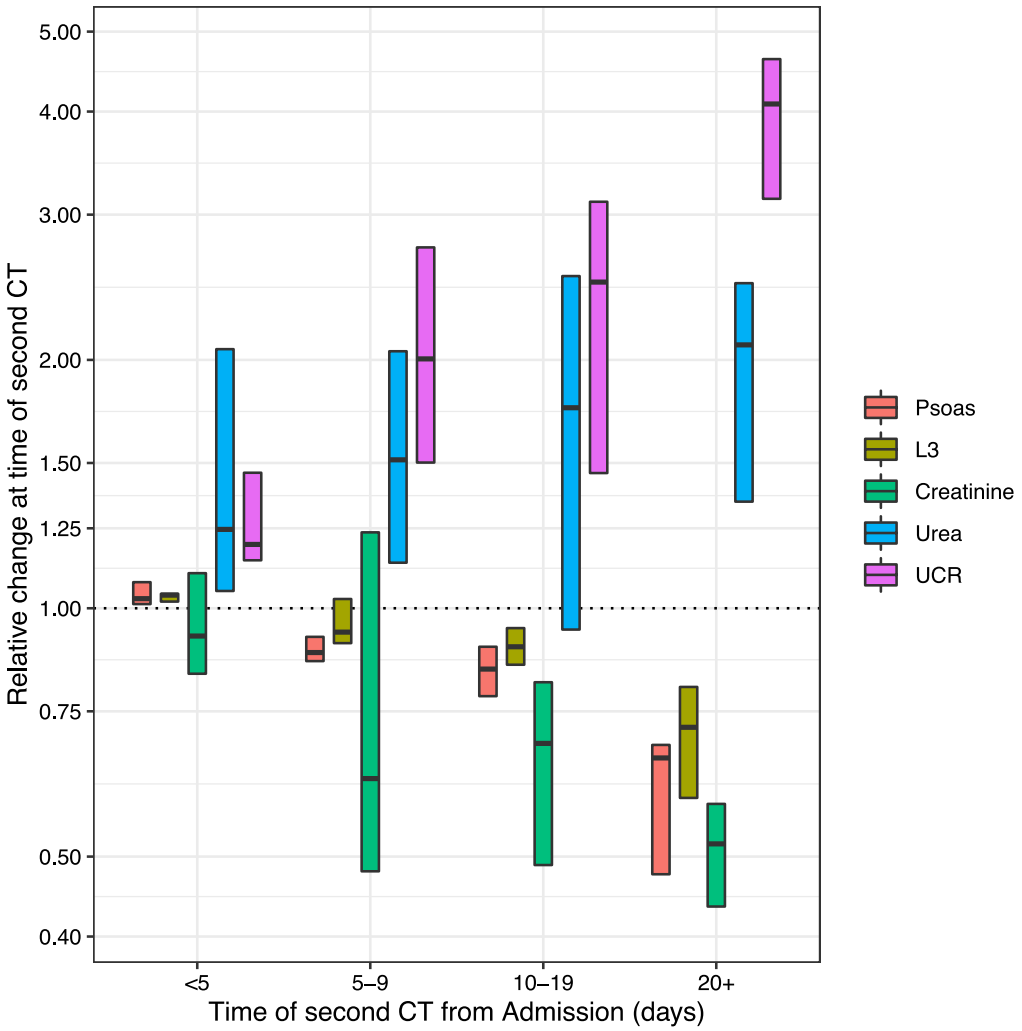

Fig. 3 Relative changes in median L3 total or L4 psoas muscle cross-sectional areas from admission to second CT scan across time between CT scans in 53 patients with evolving, current or recent persistent critical illness after major trauma (ICU length of stay of ≥ 10 days or death in ICU before day 10, who had the second CT either in ICU or within 7 days of ICU discharge). Accompanying relative changes in serum creatinine, serum urea, and urea:creatinine assessed at the same timepoints

loss occurred over time, with a more rapid decline associated with evolving, current, or recent persistent critical illness at time of the second CT. In a post hoc analysis of this sub-group, a rising urea:creatinine correlated with lower muscle area at the time of the second CT scan, supporting the biological relevance of urea:creatinine as a biochemical signature of persistent critical illness and as a potential indicator of ongoing muscle catabolism.

What potential mechanism underlies the observed association between elevated urea:creatinine, muscle wasting, and development of persistent critical illness? Soon after major trauma, there is a rapid, sustained fall in serum creatinine during the first 4 days [27]. In a different exploratory study, reduction in muscle phospho-creatine content has been demonstrated in 33 patients early in critical illness, prior to reduction in total muscle volume or total creatine content [28] both of which decrease over the first week. Serum creatinine and intramuscular creatine concentrations are tightly linked [29]. Initial decreases in serum creatinine may, therefore, result from altered metabolism and reflect bioenergetic failure. Interestingly, the initial decrease in serum creatinine seemed to be universal, irrespective of eventual length of ICU stay; however, the subsequent continued fall in serum creatinine reflected length of ICU stay and length of hospitalization and by implication skeletal muscle

loss (decreasing creatinine production) [30, 31]. In contrast, from 3 to 4 days after ICU admission urea progressively rises, with a higher peak and greater duration of elevation in those patients remaining longer in ICU. We suggest that persistent elevation in urea may reflect increased production from muscle catabolism, amino acid liberation, and metabolism. Based on the observed trajectory of urea, this catabolic state appears to persist throughout ICU admission [32]. Consequently, elevated urea:creatinine may reflect a combination of muscle bioenergetic failure [28], muscle catabolism/altered protein homeostasis [33], and persistent muscle wasting [34], providing a metabolic signature of the effects of prolonged critical illness.

Importantly, while the timeline and extent of changes in both urea and serum creatinine concentrations will be affected by changes in kidney function, their ratio is less affected (Fig. S5), as the excretion of serum creatinine and urea will be similarly decreased by diminished glomerular filtration. Although altered tubular reabsorption of urea (normally 40–50%) can affect serum urea:creatinine, classically increased urea retention occurs during severe dehydration with preserved tubular function, a context rarely seen in ICU patients. Conversely, tubular injury in AKI will lessen concentrating capacity, thereby lessening urea:creatinine, thus any confounding effect of AKI in this study would be unlikely to accentuate our observations. In addition, in patients receiving RRT, there is an equimolar removal of creatinine and urea in the extracorporeal circuit (unlike the kidney) that attenuates any increase of urea:creatinine. Finally, the metabolic alterations in creatinine and urea generation, suggested by our observations, substantially confound our ability to accurately assess AKI and in particular to assess its outcomes in the trauma population.

Relation to previous studies

The catabolic phenotype reported in critically ill patients [8, 9] has been associated with increases in urea generation [35] which, subsequently, has been associated with worse outcomes [36, 37]. Previously published data have challenged the conventional interpretation of a raised urea:creatinine representing tubular concentration in reversible 'pre-renal' failure. Instead, a raised urea:creatinine has been shown to be a risk factor for death in AKI, with increased protein catabolism a plausible mechanism [38, 39]. The association of an increasing urea:creatinine with persistent critical illness in this study supports a hypothesised association between ongoing catabolism and worse patient outcomes. The previous studies have also highlighted the fall in serum creatinine in critically ill populations and the association of a low serum creatinine with poorer outcomes [27, 30]. However, longitudinal analysis of serum creatinine and urea:creatinine with muscle mass quantification is, to our knowledge, unique to this study.

Development of anaemia is common in critically ill patients [14]. Similar to anaemia of chronic disease, the transition to persistent critical illness may involve cytokine-induced attenuation of the erythropoietin response; in addition, initial haemorrhage, conservative transfusion strategies, and frequent blood sampling may further contribute to persistent anaemia. Surprisingly, markers of inflammation poorly discriminated persistent need for intensive care. It is possible that levels of CRP or WBC did not accurately reflect persistent inflammation or, alternatively, inflammation may be a less-defining feature of persistent critical illness after major trauma.

Strengths and weaknesses

This study has several strengths. First, our sample size was sufficient to confirm the transition point to persistent critical illness in a polytrauma population. Second, the replication of these associations in an external cohort increases the strength of our conclusions. Finally, we supported biochemical findings utilising CT images to compare changes in body composition. However, this study does have several intrinsic limitations. These findings may not apply to non-trauma populations. Second, we did not have data available on nutritional input which could alter urea metabolism [26]. Third, we were limited by the availability of biochemical tests ordered as routine care and, therefore, could not characterise the role of inflammation in more detail [9, 40]. Fourth, despite the use of rolling trajectories to harness more than a single day's biochemical result, there were a greater number of missing results for those patients discharged from ICU before day 10. While we would expect missing data to be in less-sick individuals without need for blood tests and accordingly closer to baseline values, a prospective study would be required to confirm this inference. Fifth, in the muscle assessment group, the main inclusion criteria of requiring two inpatient CT scans resulted in the assessment of a specific population of trauma patients that had greater length of stay with injuries more commonly affecting the pelvis and abdomen. Finally, to explore muscle mass and urea:creatinine in a group with CT measurements made during the course of a critical illness lasting 10 or more days, we made several post hoc assumptions in our definition. Due to these assumptions and small numbers, the CT analysis should be regarded only as an initial exploration of hypothetical mechanisms underlying our biochemical and metabolic findings.

Conclusion

Elevated urea:creatinine ratio is a simple and potentially useful biochemical signature characterising persistent critical illness after major trauma. This association suggests catabolism and acquisition of muscle wasting may be a defining feature of this population. Furthermore, urea:creatinine is readily available from routine clinical data and could be used at a population level as a surrogate of catabolism in the analysis of epidemiological data and outcomes of interventional studies to help understand mechanisms of disease and improve care in this important group of patients. However, while our findings are in keeping with current understanding of muscle biology in critical illness, they require confirmation in prospective studies.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05760-5) contains supplementary material, which is available to authorized users.

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Author contributions

All authors reviewed and approved the final manuscript. JP and PZ were responsible for the study concept and RH, PZ, ZP, and JP for study design. Data extraction was undertaken by RH, PZ, and JP. RH, PZ, ZP, and JP were responsible for data analysis and JP, PZ, ZP, YW, and RP provided comments and review of draft analyses.

Compliance with ethical standards

Conflicts of interest

ZP is on specialist advisor boards for GlaxoSmithkline, Fresunius Kabi and Faraday Pharmaceuticals and has given lectures and/or performed consultancy work for Lyric Pharmaceuticals, Faraday Pharmaceuticals, Orion Pharmaceuticals and Nestle. RP holds research grants, has given lectures and/or performed consultancy work for BBraun, GlaxoSmithkline, Medtronic, Intersurgical and Edwards Lifesciences. JP has given lectures and/or performed consultancy work for Fresenius Medical, Baxter, Nikkiso, Biomerieux, Abbott, Medibeacon and Quark Pharma.

Data sharing

As this study was carried out on the basis of analysis of routinely collected data by the usual care team, consent for sharing of anonymised patient level data is not available. The investigators will consider proposals for sub-analyses on a collaborative basis.

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