**Supplemental Material**

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

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## Supplementary Methods:

*ICU population, nutrition and ICU care*

The cohort comprised all admissions from February 1st, 2012 to May 1st, 2016. We considered all trauma admissions to the emergency department (ED) of the Royal London Hospital that were admitted either directly to the adult ICU or via the operating theatre. All trauma patients are fed enterally as soon as possible, unless contraindicated. This follows the ESPEN guidelines in terms of calories delivered, feed constitution and the use of pro-kinetic drugs. Patients' nutritional requirements are reviewed daily by the medical team, as well as the nutrition team and supplemented or replaced with parental nutrition where the enteral route is not wholly adequate or contraindicated. Blood sugars are maintained between 5-10 mmol/l using insulin sliding scales as necessary. Mechanically ventilated patients have sedation holds daily where applicable with aim to extubation or ventilator wean as soon as possible. Patients are encouraged to mobilise as soon as possible and are seen daily by physiotherapists. Individual patient data on nutritional intake was not available in this study.

*Secondary analyses*

To assess further the relationship between duration of ICU admission and blood test trajectories we stratified patients into 4 groups based on ICU length of stay (LoS) – 1-4 days, 5-9 days, 10-19 days and ≥20 days. To assess any influence of AKI on renal parameters we plotted trajectories of urea, serum creatinine and urea:creatinine stratified by peak AKI stage and need for RRT. As AKI is strongly associated with risk of death, in this analysis we included all patients including early deaths. Baseline

serum creatinine for the acute trauma population was defined as the first documented in hospital. We used the KDIGO creatinine guidelines to define AKI.

*Statistical analysis*

Statistical analysis was performed in R v3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) using RStudio v1.0.136 (RStudio Inc, Boston, MA, USA). Continuous data are presented median with interquartile range (IQR) or range and were compared using the Wilcoxon rank sum test. Categorical data were compared using the Fisher's test or Chi squared tests. Comparisons between multiple groups were made using the Kruskal-Wallis test. Trajectories of daily blood test results are displayed as rolling medians with 95% confidence-intervals of the point estimate of the median value which were determined using constrained B-Splines Nonparametric Regression Quantiles - using quadratic splines with curves constrained to pass through the median admission value (COBS, R package version 1.3-3 https://CRAN.R-project.org/package=cobs). For discrimination of persistent need for intensive care logistic regression models were 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. We then selected those variables retained after selection on at least 50% of days from day 10 to 25 and computed final daily logistic regression models for persistent need for intensive care based on these variables and compared with models based on baseline illness severity and antecedent demographics. Logistic regression receiver-operative characteristic curve areas under the curve (ROC-AUC) were calculated with 95% confidence intervals using DeLong's variance estimate with comparison using DeLong's test. Linear regression for changes in muscle cross-sectional area over time was performed using ordinal least squares and the coefficient of determination ($R^2$) was determined from the Pearson correlation coefficient, slopes were compared by inclusion of group allocation as a dummy variable in multiple linear regression including all patients with change in muscle area as the dependent variable and assessing the significance of an interaction term between group allocation and time in hospital.

*Biochemical signature of persistent critical illness*

We adapted the methodology reported by Iwashyna et al [1] to calculate the timing of persistent critical illness in the trauma population. We developed a simple prediction model of hospital mortality in patients on each day up to day 21 based on either, i) acute risk factors (New Injury Severity Score; documenting severity of traumatic injury, and APACHE 2 score without age; indicating extent of physiological instability) or ii) antecedent patient characteristics (age and Charlson Comorbidity Index). After confirmation of the persistent critical illness timeframe, we used similar methodology

to understand the associations of persistent critical illness with data from routine bloods. Our primary outcome was persistent need for intensive care. We assessed ability of data from routine blood tests measured on each day of hospitalisation to discriminate persistent need for intensive care and compared this to models derived from a combination of both antecedent patient characteristics and initial illness severity.

We adapted the analytic approach of both Iwashnyna et al [1] and Bagshaw et al [2]. First, we built a predictive logistic regression model of in-hospital mortality based on antecedent and acute illness characteristics at ICU admission. Second, we measured predictive abilities of the antecedent characteristics and acute illness component for patients alive and in the ICU on each day up to day 21. Lastly, to confirm the persistent critical illness timeframe, differences in c-statistics were used to compare the strength of the association between the acute and antecedent risk scores to in-hospital mortality.

This analysis was based on hypotheses generated from work presented at the ESICM LIVES 2017 (0488 Differential time course of creatinine and urea after major trauma and their association with duration of hospitalisation, Intensive Care Medicine Experimental 2017, 5(Suppl 2):0488, doi: https://doi.org/10.1186/s40635-017-0151-4) [3].

*Computed Tomography image acquisition and analysis*

CT scan images were retrieved from the local picture archiving and communication system (PACS) and selected slices were retrieved for analysis as anonymized DICOM image files. Then, after manual exclusion of the intra-abdominal contents the total muscle CSA of the abdominal wall at the L3 level was defined using tissue specific attenuation of skeletal muscle (-29 to +150 Hounsfield Units). Prior to analysis images were reviewed and rejected if major confounders of assessment were present – major CT artefact due to metallic implants (i.e. spinal fixation) or anatomical disruption of the abdominal wall (laparostomy). Using the level of the vertebral vein as a landmark, a region of interest was manually defined around the psoas muscle.

CT slices were analysed in random order and independent investigators performed the abdominal L3 and L4 psoas assessments. Representative images of L4 psoas were reviewed by a senior radiologist and serial replicates of L3 analysis were performed to assess consistency of assessment. In both methods muscle areas were normalised to patient size by dividing the area in centimetres squared ($cm^2$) by the square of the patient's height in metres (m). We employed predefined cut offs for

sarcopenia as L3 muscle CSA of less than 55.4 $cm^2/m^2$ for males and 38.9 $cm^2/m^2$ for females [4]. We used ImageJ image-processing software [5]. Patients were divided into two groups; those with evolving, current or recent persistent critical illness at time of second CT (defined as patients with ICU length of stays of ≥10 days, or death in ICU before day 10, who had second CT either in ICU or within 7 days of ICU discharge) and those who did not develop or had resolved persistent critical illness at time of second CT (defined as patients who were alive and out of ICU at day 10 or patients who had their 2nd CT at least 7 days after ICU discharge). We assessed for correlation between muscle loss and time of second scan from admission using linear regression as described above and similarly assessed relationship between urea:creatinine and muscle area at time or first and second CT scans. This analysis was based on preliminary work presented at the 37th ISICEM 2017 (P459 Assessment of skeletal muscle wasting in critically ill trauma patients using serial computed tomography imaging, https://doi.org/10.1186/s13054-017-1629-x.)

**Table S1:** Logistic regression models were developed to discriminate persistent need for intensive care in all patients remaining in hospital with blood tests that day. Backward selection was based on the pooled residual chi-square of the model and minimization of the Akaike's information criterion. Variables considered were urea, creatinine, urea:creatinine (UCR), albumin, haemoglobin, CRP, neutrophil count, lymphocyte count, urea:creatinine appeared in 18/24 (13/16 from day 10 onward) models and Haemoglobin in 9/24 (8/16 from day 10). Accordingly, we then constructed daily logistic models based on urea:creatinine and haemoglobin (the two best discriminating variables) to discriminate persistent need for intensive care daily and compared these to admission illness severity and age (see Fig S6).

| DAY | VARIABLES RETAINED IN LOGISTIC MODEL AFTER BACKWARD SELECTION |
|---|---|
| *2* | Albumin |
| *3* | Albumin |
| *4* | Albumin |
| *5* | UCR, Albumin |
| *6* | UCR, CRP |
| *7* | UCR, Albumin |
| *8* | UCR, Albumin, Lymphocytes |
| *9* | UCR, CRP, Haemoglobin |
| *10* | UCR, Albumin, Lymphocytes, Neutrophils |
| *11* | Urea, Creatinine, Haemoglobin |
| *12* | UCR, Haemoglobin |
| *13* | UCR, Haemoglobin |
| *14* | UCR, Lymphocytes |
| *15* | UCR |
| *16* | UCR, Haemoglobin |
| *17* | Haemoglobin |
| *18* | UCR |
| *19* | UCR, Haemoglobin |
| *20* | UCR, Haemoglobin |
| *21* | UCR |
| *22* | UCR |
| *23* | UCR |
| *24* | UCR, Haemoglobin |
| *25* | None |

**Table S2.** Patient characteristics showing comparisons between the whole ICU trauma cohort and those with two or more abdominal CT scans analysed. Medians and interquartile ranges or proportions. Wilcoxon Rank Sum test, Fisher exact test of 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.

| Patient characteristics | Trauma cohort (excluding muscle assessment) | Muscle assessment cohort | p-value |
|---|---|---|---|
| | 1269 | 107 | |
| **Age - years (median [IQR])** | 43.00 [28.00, 58.00] | 37.00 [23.00, 53.00] | 0.025 |
| **Sex = Male (%)** | 1009 (79.5) | 89 (83.2) | 0.434 |
| **ISS (median [IQR])** | 25.00 [16.00, 33.00] | 32.00 [22.00, 43.00] | <0.001 |
| **NISS (median [IQR])** | 34.00 [22.00, 50.00] | 41.00 [28.00, 50.00] | 0.004 |
| **Charlson Comorbidity Index (%)** | | | 0.240 |
| **0** | 961 (75.7) | 69 (64.5) | |
| **1** | 186 (14.7) | 23 (21.5) | |
| **≥2** | 123 (9.7) | 15 (14.0) | |
| **Hospital length of stay - days (median [IQR])** | 16.00 [7.00, 33.00] | 39.00 [19.00, 65.50] | <0.001 |
| **ICU length of stay - days (median [IQR])** | 5.14 [2.12, 11.40] | 11.33 [5.54, 25.14] | <0.001 |
| **Albumin - g/L (median [IQR])** | 38.00 [34.00, 42.00] | 35.00 [30.50, 40.00] | <0.001 |
| **Urea - mmol/L (median [IQR])** | 4.80 [3.80, 6.30] | 5.40 [4.35, 6.85] | 0.004 |
| **Haemoglobin - g/dl (median [IQR])** | 13.50 [12.70, 14.50] | 14.10 [12.90, 14.80] | 0.027 |
| **Hospital admission creatinine - µmol/L (median [IQR])** | 82.00 [66.00, 102.00] | 100.00 [86.00, 123.50] | <0.001 |
| **Hospital discharge creatinine - µmol/L (median [IQR])** | 62.00 [49.00, 76.00] | 56.00 [41.50, 71.50] | 0.004 |
| **Time of last creatinine from admission - days (median [IQR])** | 11.70 [3.89, 27.64] | 33.54 [17.61, 60.65] | <0.001 |
| **Renal replacement therapy (%)** | 46 (3.6) | 18 (16.8) | <0.001 |

| | | | |
|---|---|---|---|
| **AKI KDIGO stage (%)** | | | <0.001 |
| **0** | 1062 (83.7) | 59 (55.1) | |
| **1** | 132 (10.4) | 28 (26.2) | |
| **2** | 16 (1.3) | 1 (0.9) | |
| **3** | 59 (4.6) | 19 (17.8) | |
| **Hospital mortality (%)** | 239 (18.8) | 12 (11.2) | 0.067 |
| **Site of Injury (%)** | | | |
| **Brain injury** | 661 (52.1) | 23 (21.5) | <0.001 |
| **Isolated brain injury** | 395 (31.1) | 13 (12.1) | <0.001 |
| **Abdomen** | 128 (10.1) | 42 (39.3) | <0.001 |
| **Chest** | 388 (30.6) | 46 (43.0) | 0.011 |
| **Pelvis** | 103 (8.1) | 30 (28.0) | <0.001 |
| **Limbs** | 119 (9.4) | 13 (12.1) | 0.446 |
| **Face and/or Neck** | 93 (7.3) | 6 (5.6) | 0.638 |
| **Other** | 64 (5.1) | 5 (4.7) | 1 |
| **Spine** | 142 (11.2) | 14 (13.1) | 0.664 |
| **APACHE II (median [IQR])** | 11.00 [8.00, 16.00] | 11.00 [8.00, 15.00] | 0.960 |
| **SAPS II (median [IQR])** | 35.00 [28.00, 43.00] | 33.50 [28.00, 43.00] | 0.627 |

**Table S3:** Comparison of CT-scan muscle cross-sectional area, serum urea and creatinine between admission (scan 1) and second inpatient scan (scan2). Patients categorized into groups as follows i) patients developing persistent critical illness re-scanned before day 10 (including early deaths in ICU), ii) patients who did not develop persistent critical illness re-scanned before day 10, iii) patients with persistent critical illness re-scanned in ICU from day 10 or within 1 week of ICU discharge, iv) patients scanned from day 10 who either did not have persistent critical illness or who were rescanned at least 1 week after ICU discharge. Continuous parameters are presented as median [Inter quartile range] and categorical parameters are presented as n (%). . Comparisons using Wilcoxon signed rank test for paired continuous data or Fisher's test for categorical data. *LoS* Length of Stay, *IQR* interquartile range, *CSA* cross-sectional area

| **Time between scans:** | **Scanned 1-9 days** | | | | | | **Scanned on or after day 10** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | i) Died or in ICU day 10 N=28, Scan 2 median day 6 [5, 8], Median ICU LoS 15 [11,26] | | | ii) Discharged ICU and alive d10 N=31, Scan 2 median day 4 [1,7], Median ICU LoS 5 [3,8] | | | iii) ICU LoS >10d, Scan 2 in ICU or within 7 days of ICU discharge N=25, Scan 2 Median day 16 [13, 23], Median ICU LoS 26 [17,36] | | | iv) ICU LoS ≥10d or scanned >7 days after ICU discharge N=23, Scan 2 median day 44 [28, 59], Median ICU LoS 13 [7,25] | | |
| | **Admission** | **Scan 2** | **p** | **Admission** | **Scan 2** | **p** | **Admission** | **Scan 2** | **p** | **Admission** | **Scan 2** | **p** |
| **L4 Psoas CSA cm² median [IQR]** | 32.7 [28.5, 38.0] | 31.1 [22.7, 36.4] | <0.001 | 31.1 [22.7, 26.4] | 27.6 [22.6, 33.9] | 0.016 | 34.6 [25.2, 41.2] | 23.0 [13.2, 29.6] | <0.001 | 30.0 [27.5, 37,7] | 21.6 [15.7, 26.3] | <0.001 |
| **L4 Psoas index cm²/m² median [IQR]** | 10.8 [9.6,11.9] | 10.3 [8.5, 11.3] | <0.001 | 9.9 [7.5, 11.6] | 9.3 [7.5, 10.6] | 0.016 | 10.7 [8.5, 13.0] | 7.1 [4.9, 10.3] | <0.001 | 9.9 [8.4, 11.6] | 6.8 [5.5, 8.5] | <0.001 |
| **L3 CSA cm² median [IQR]** | 185 [175, 209] | 187 [159, 207] | 0.080 | 176 [145, 183] | 167 [134, 183] | 0.200 | 174 [149, 202] | 138 [100, 176] | <0.001 | 174 [157, 197] | 140 [119, 151] | <0.001 |
| **L3 Muscle index cm²/m² median [IQR]** | 61 [55, 71] | 60 [53, 64] | 0.113 | 56 [49, 68] | 54 [50, 60] | 0.210 | 56 [49, 68] | 41 [36, 55] | <0.001 | 56 [50, 62] | 44 [40, 49] | <0.001 |
| **Sarcopenia n (%)** | 2/24 (8%) | 4/24 (16%) | 0.666 | 9/25 (36%) | 12/25 (48%) | 0.017 | 7/19 (36%) | 14/19 (74%) | 0.049 | 6/22 (27%) | 19/21 (86%) | <0.001 |
| **Creatinine Median - µmol/L [IQR]** | 106 [91, 124] | 76 [50, 150] | 0.355 | 96 [74, 110] | 63 [53, 88] | 0.002 | 103 [83, 129] | 64 [45, 80] | 0.002 | 107 [89, 142] | 62 [44, 73] | <0.001 |
| **Urea Median - mmol/L [IQR]** | 5.4 [4.3, 6.4] | 7.0 [5.2, 11.3] | <0.001 | 5.2 [4.0, 6.6] | 5.2 [4.3, 8.0] | 0.472 | 5.6 [4.1, 6.8] | 9.1 [6.7, 14.8] | <0.001 | 5.7 [4.7, 7.0] | 4.1 [3.1, 6.1] | 0.061 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Urea:creatinine - mmol/mmol Median [IQR]** | 52 [40, 99] | 93 [68, 124] | <0.001 | 55 [78, 102] | 79 [63,92] | <0.001 | 51 [44, 67] | 164 [109, 200] | <0.001 | 44 [36, 68] | 68 [52, 113] | <0.001 |

**Figure S1**: Patient flow diagram for the London Trauma-ICU cohort.

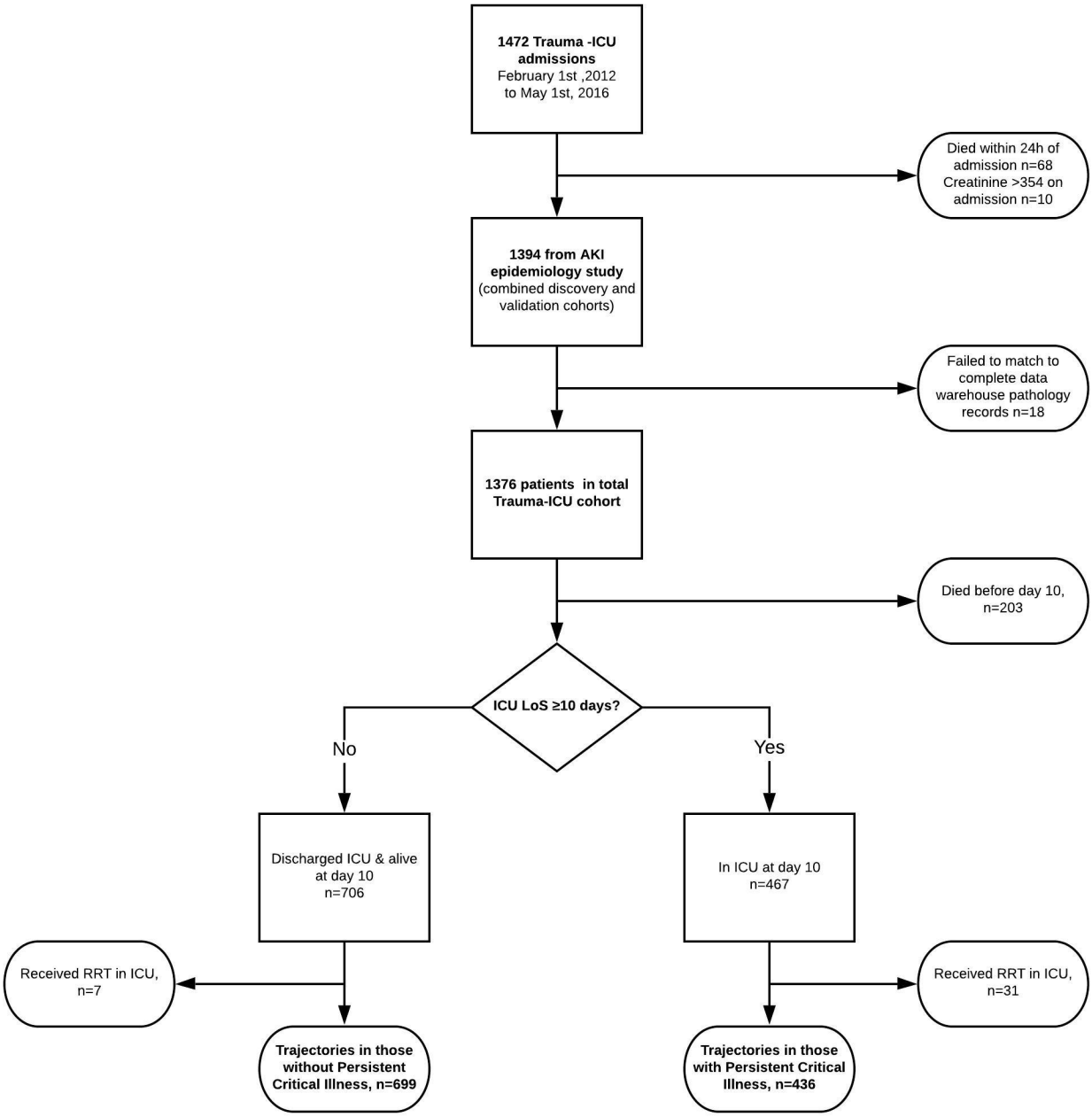


**Figure S2:** Predictiveness of severity of illness at ICU admission or antecedent characteristics for hospital mortality for the entire trauma cohort. Shaded areas are 95% CIs. *AUC* - area under the curve. Total numbers of patients in still hospital on each day and number of these who subsequently dies are appended to the plot, of 1376 patients 25 were excluded for missing illness severity score at ICU admission.

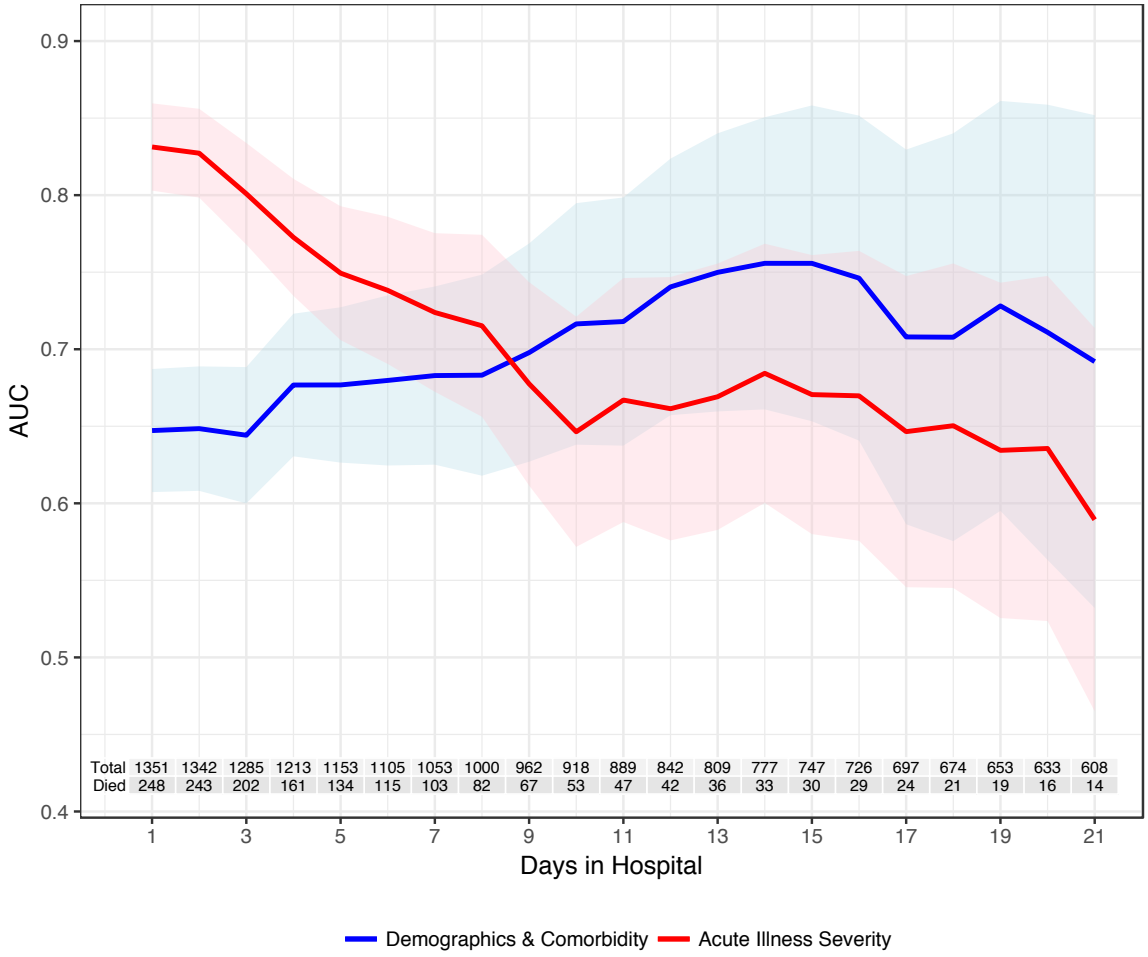


**Figure S3:** Trajectories routinely measured metabolic and inflammatory parameters in 1135 major trauma ICU patients, surviving to day 10 without RRT. 436 patients with persistent critical illness (still in ICU at day 10 after admission) are compared to 699 without (patients initially admitted to ICU but discharged and still alive at day 10). Rolling medians with 95% confidence-intervals of the rolling estimate of the median value are shown using quadratic splines with the curve constrained to pass through the median admission value.

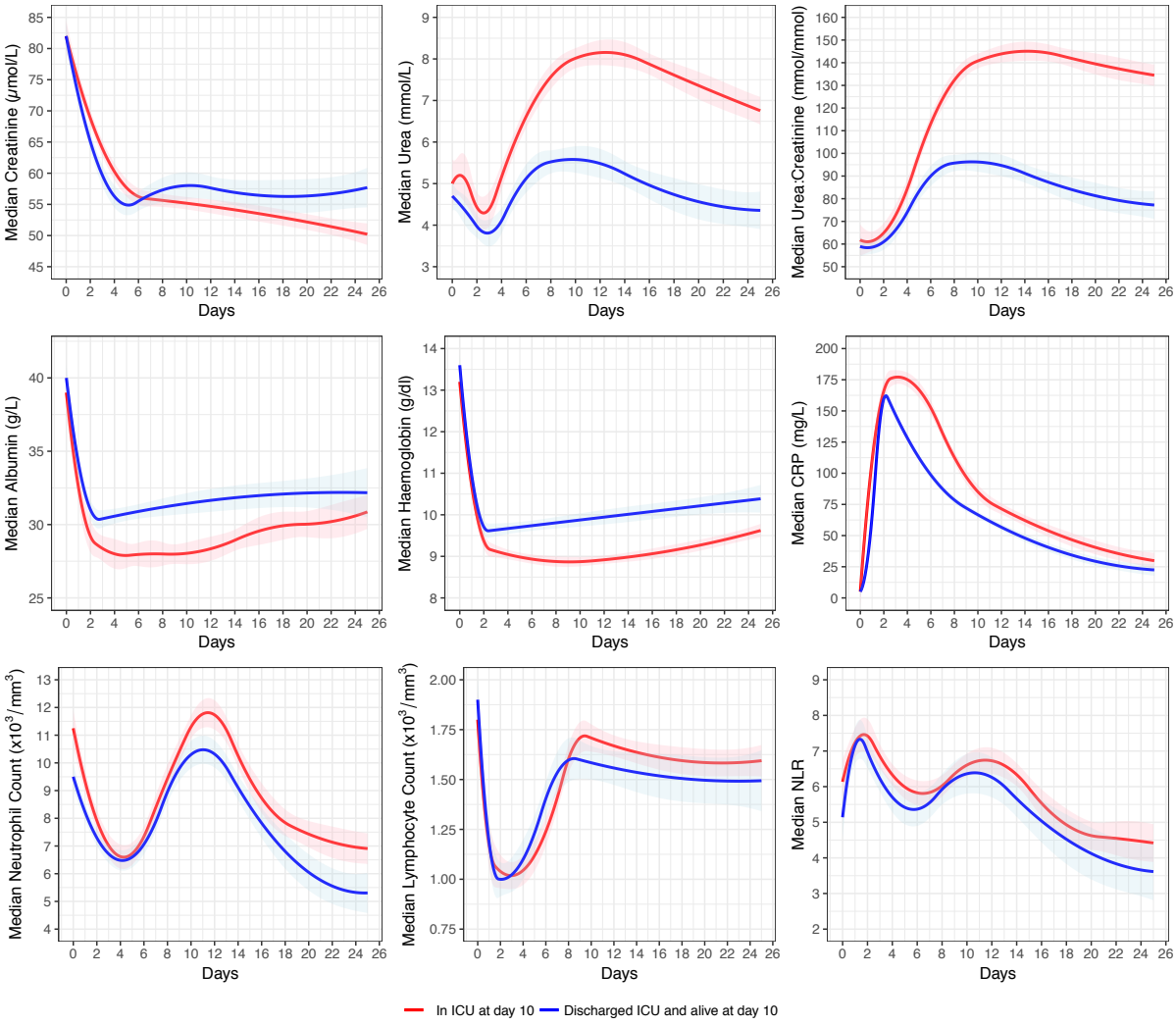


**Figure S4**: Trajectories of routinely measured metabolic and inflammatory parameters in 1135 major trauma ICU patients, surviving to day 10 without RRT stratified by ICU length of stay: <5 days (n=424), 5-9 days (n=275), 10-19 days (n=277) and >20 days (n=159). Rolling medians with 95% confidence-intervals of the rolling estimate of the median value are shown using quadratic splines with the curve constrained to pass through the median admission value.

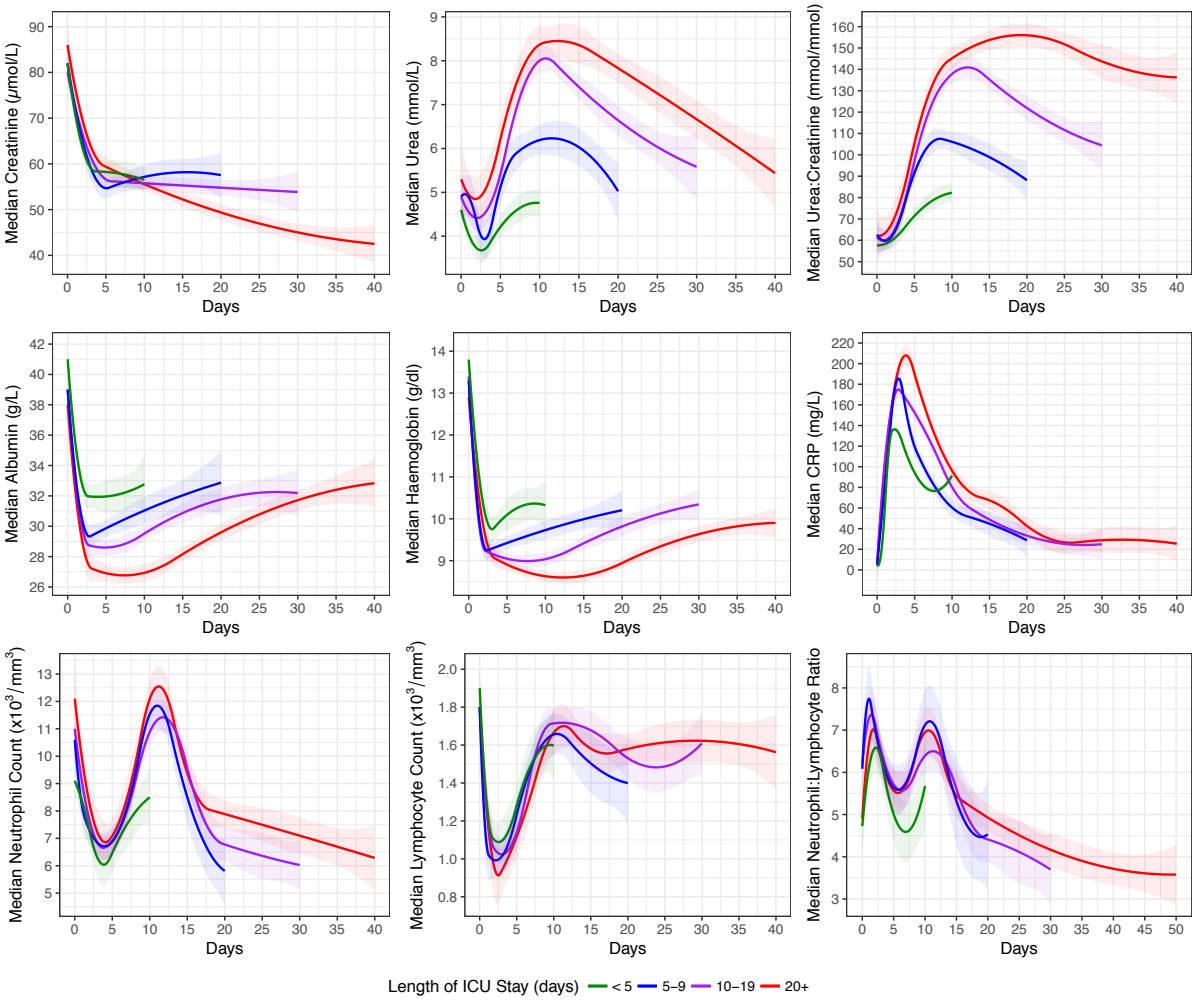


**Figure S5:** Trajectories of serum creatinine, urea and urea:creatinine in all 1376 patients across the first 20 days of hospital admission by maximal AKI status or need for RRT. Rolling medians with 95% confidence-intervals of the point estimate of the median value using quadratic splines with the curve constrained to pass through the median admission value.

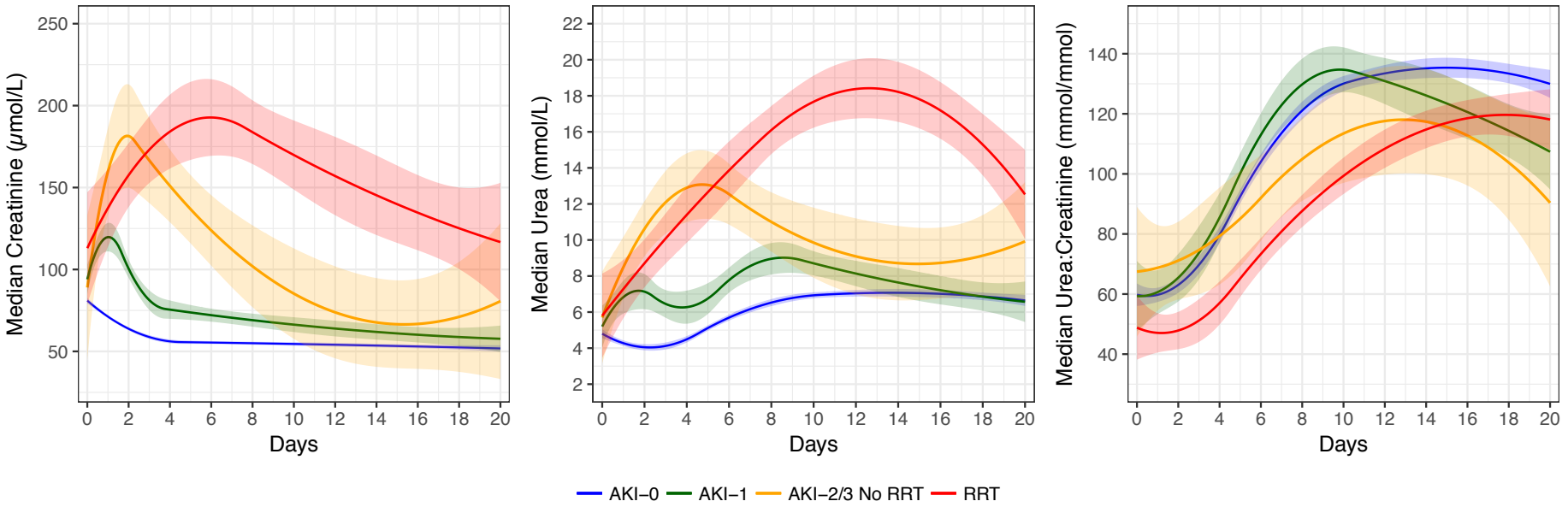


**Figure S6:** Discrimination of persistent need for intensive care from 1351 trauma-ICU patients (25 patients without recorded admission APACHE II score excluded). Patients in hospital with blood tests available on each day were considered. For each day logistic regression models were constructed with persistent need for intensive care on that day as the dependent variable using as explanatory variables: model i) initial illness severity, age and comorbidity (New Injury Severity Score, APACHE 2, Age & Charlson Index) or model ii) urea:creatinine and haemoglobin concentration on that day (see table S1). Model AUC (c-statistics) with 95% confidence intervals are plotted. Total numbers of patients with blood tests on each day and number of these still in ICU are appended. By day 10 urea:creatinine and haemoglobin concentration discriminate persistent need for intensive care better than a combination of acute and chronic admission variables. Using Delong test for comparison of AUC, model 'i' (baseline characteristics) is superior to 'ii' (urea:creatinine and haemoglobin) on days 2, 3 and 4 ($p<0.05$) while model 'ii' was superior to model 'i' on days 11 to 25 ($p<0.05$).

*ICU* - Intensive care unit; *APACHE II* - acute physiology and chronic health evaluation II, *AUC* - Area under curve.

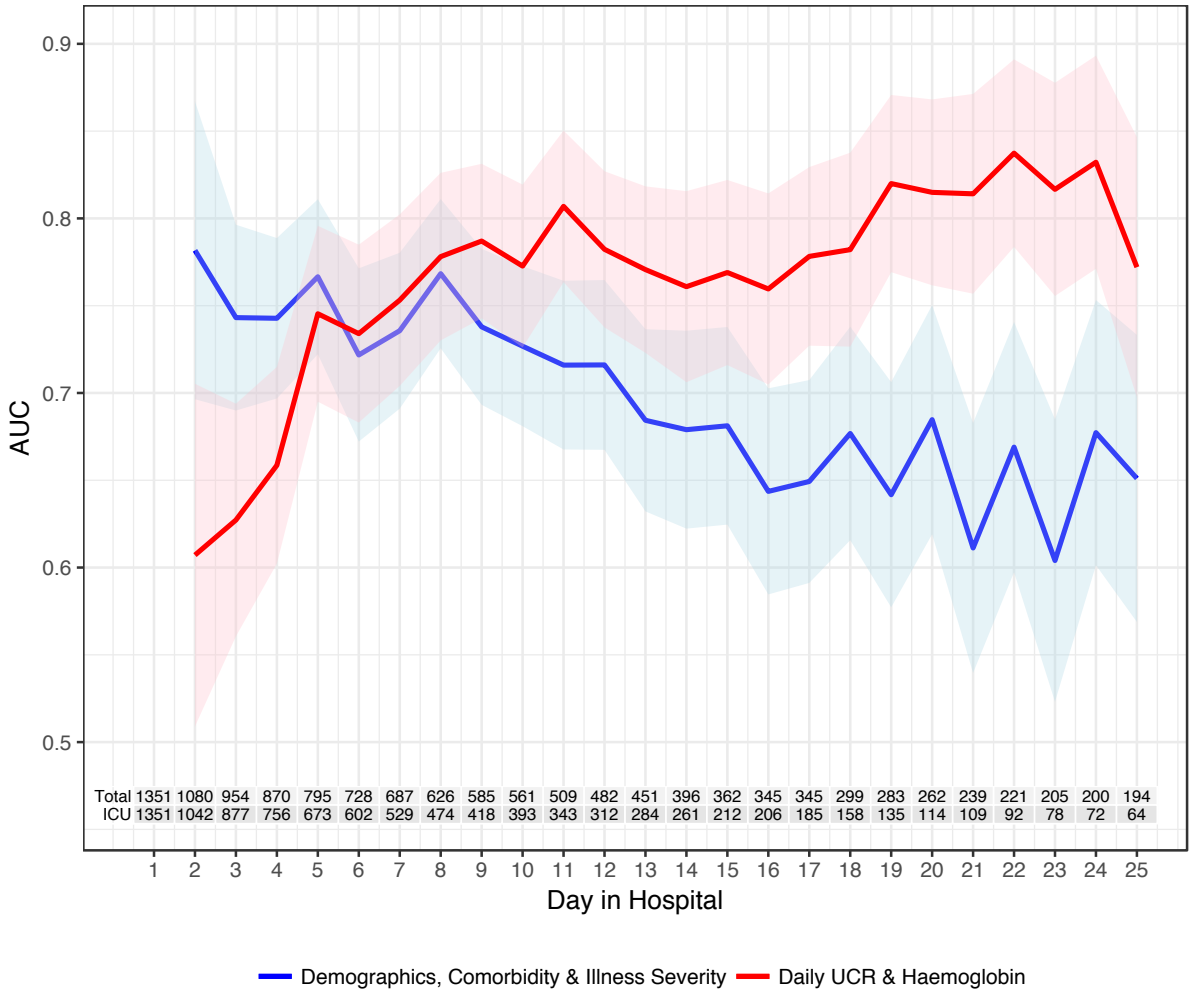


**Figure S7:** Discrimination of persistent need for intensive care from 1351 trauma-ICU patients (25 patients without recorded admission APACHE 2 score excluded). Patients in hospital with blood tests available on each day were considered. For each day logistic regression models were constructed with persistent need for intensive care on that day as the dependent variable using as explanatory variables: i) initial illness severity, age and comorbidity (New Injury Severity Score, APACHE 2, Age & Charlson Index) or ii) daily values for routinely measured metabolic and inflammatory parameters examined in this study. Model AUC (c-statistics) with 95% confidence intervals are plotted.

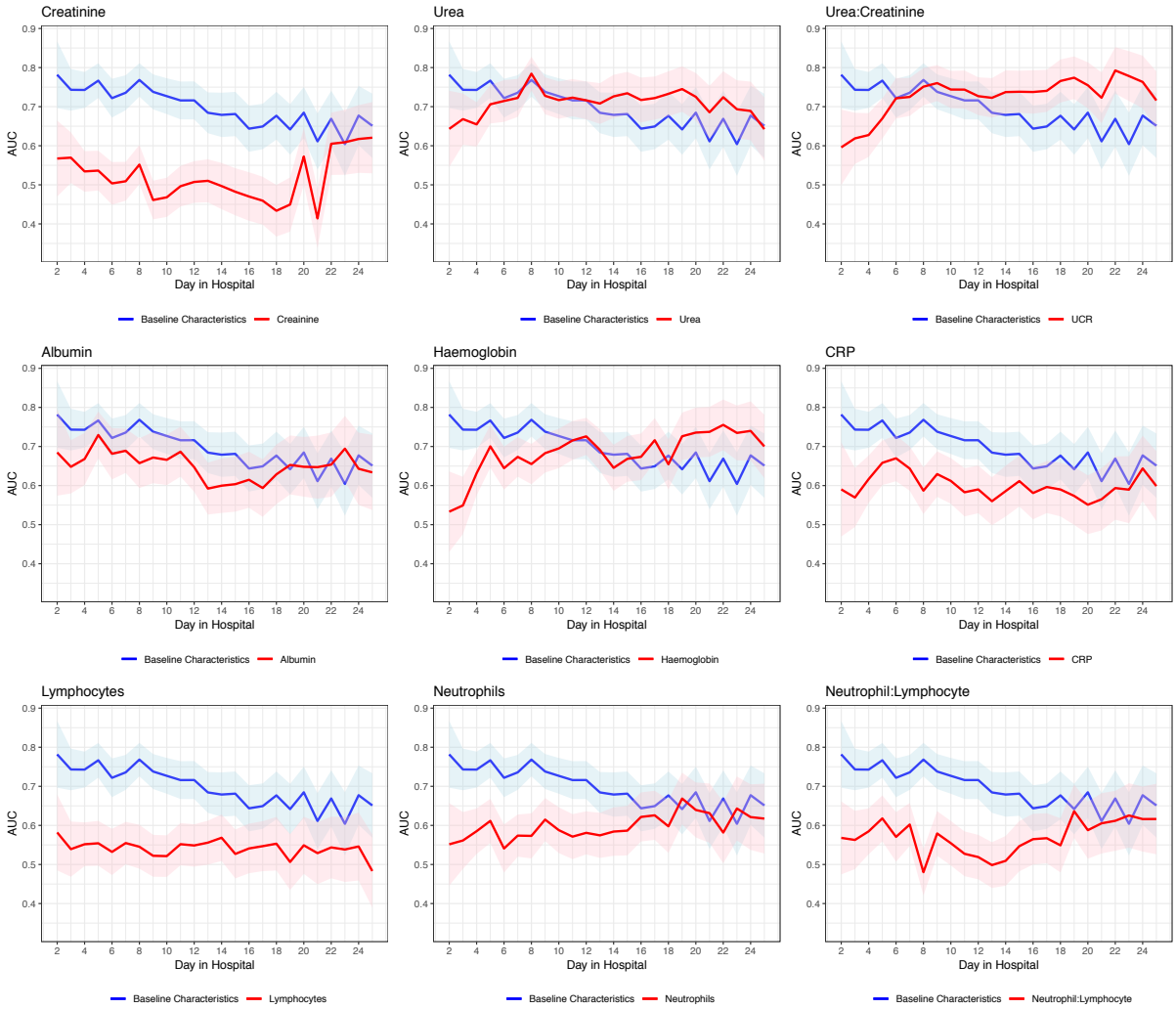


**Figure S8.** Correlation between L3 CSA and L4 psoas muscle cross-sectional areas

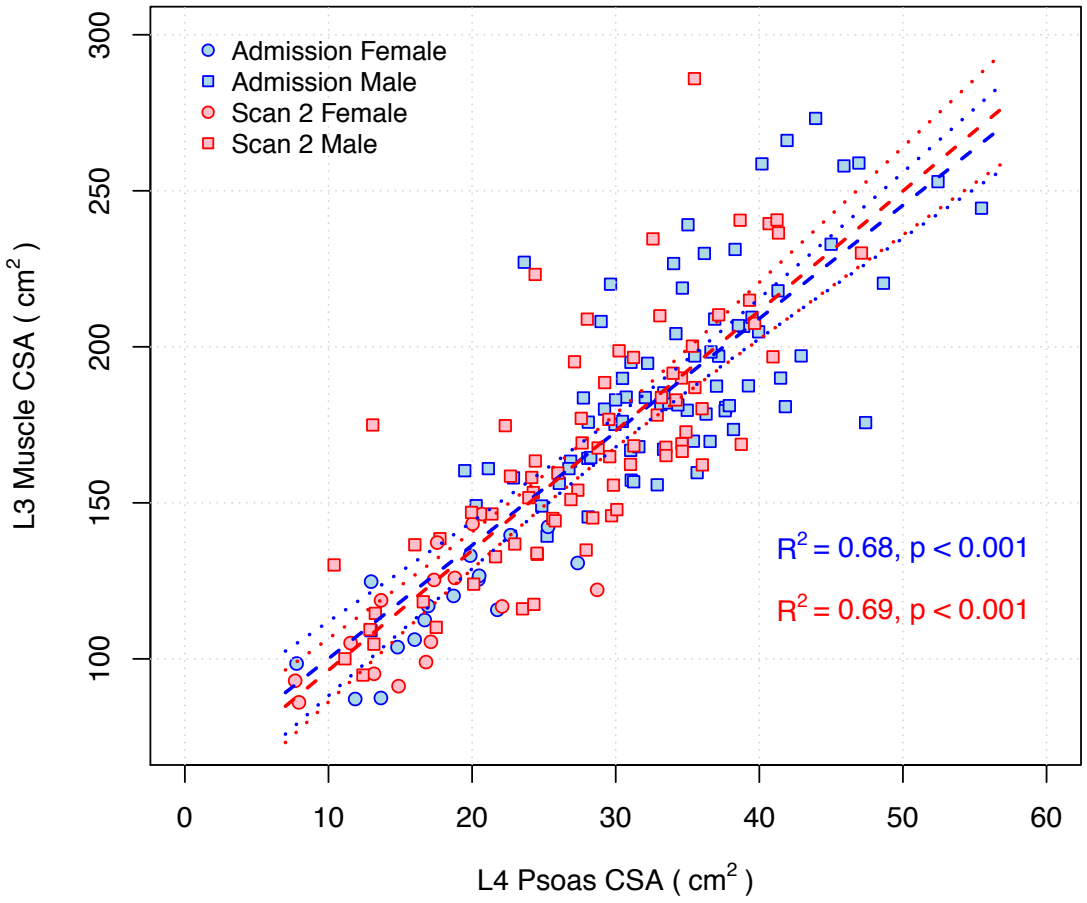
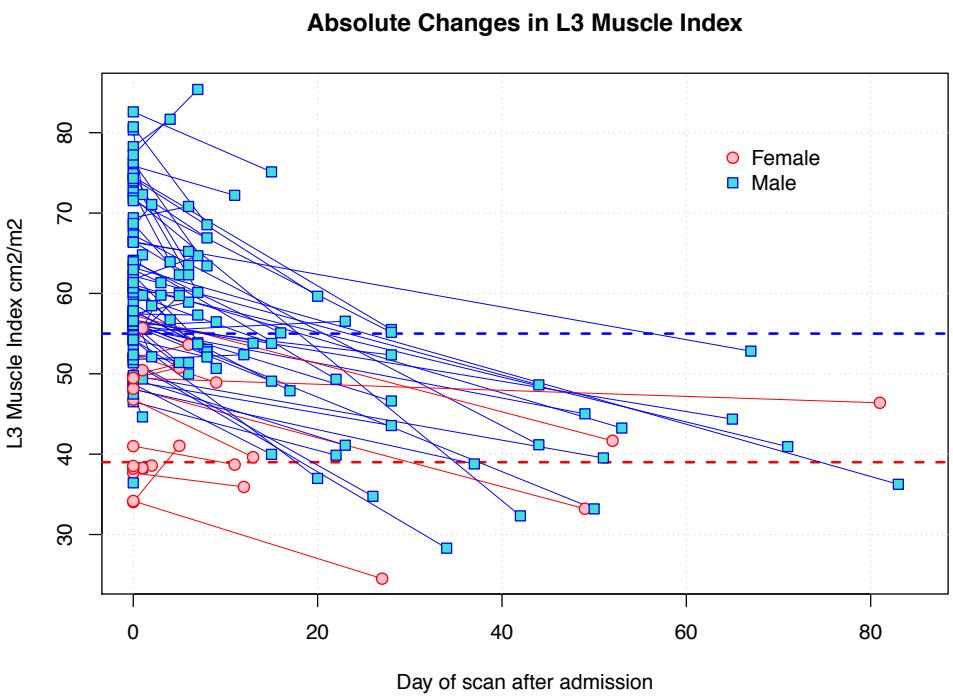


**Figure S9.** (A) Individual patients L3 muscle index (L3 cross-sectional area $cm^2$ / $m^2$ height) between admission and second computed tomography image. Blue and red dashed lines represent male and female sarcopaenia thresholds for males (<55.4 $cm^2/m^2$) and females (<38.9 $cm^2/m^2$) respectively [4]. (B) Individual patients L4 psoas muscle index (L4 psoas cross-sectional area/$m^2$ height) between admission and second computed tomography image.

**A**




**B**

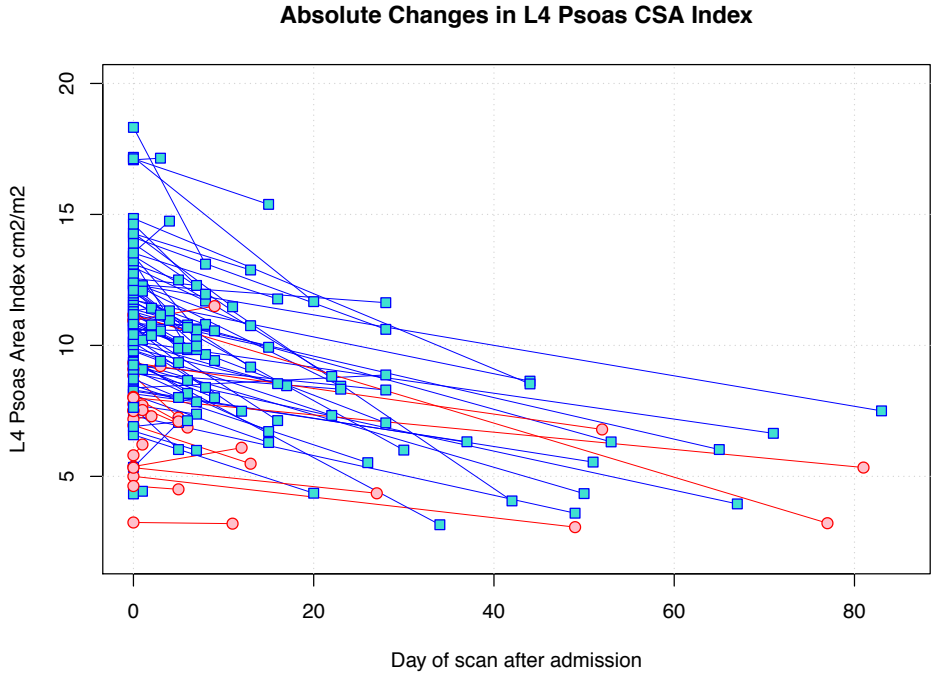
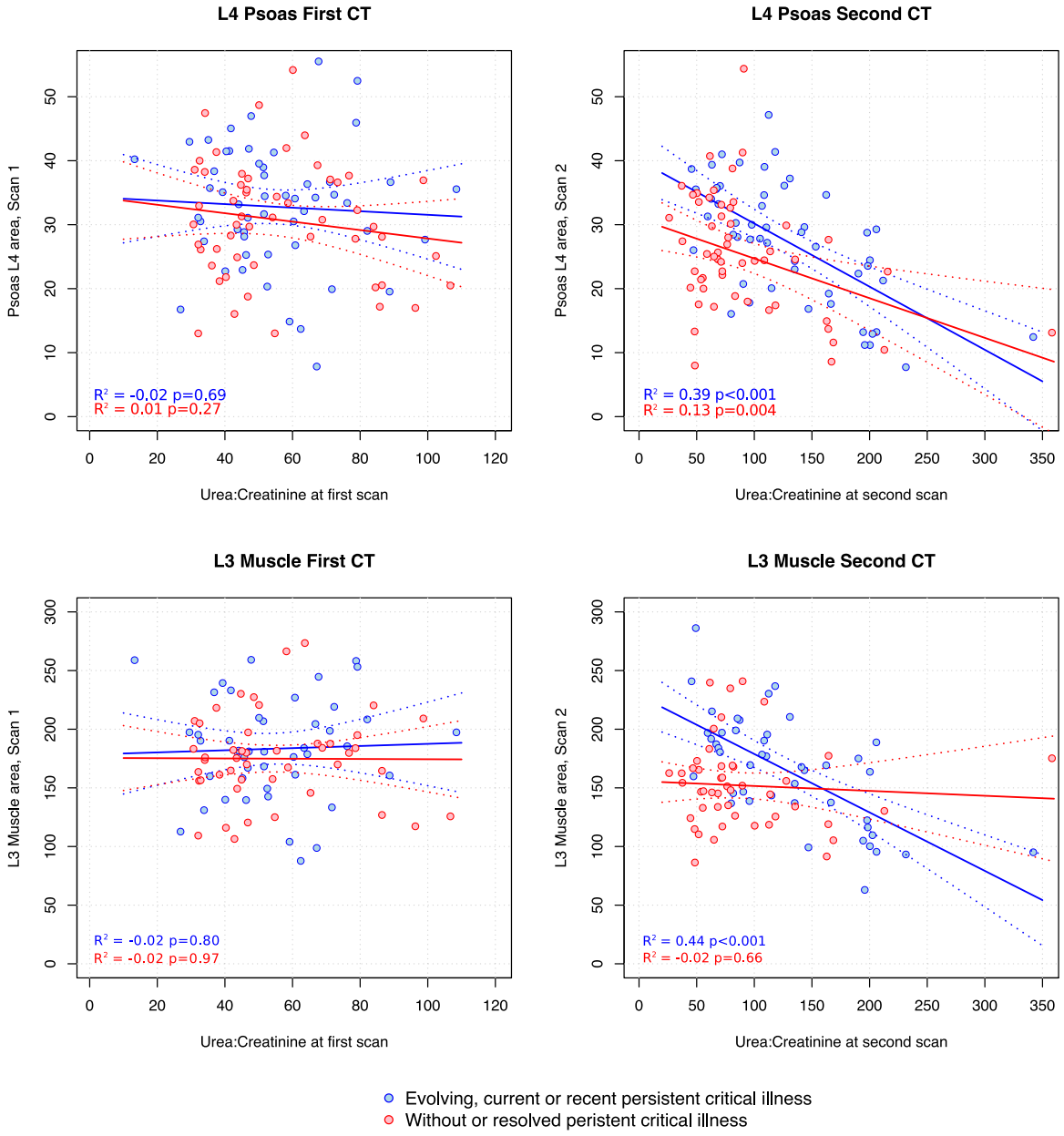


**Figure S10:** Corrleation between CT-assessed muscle cross-sectional area and urea:creatinine in muscle assessment patients with evolving, current or recent persistent critical illness at time of second CT and those who did not develop or had resolved persistent critical illness at time of second CT (see methods). Urea:creatinine was unrelated to muscle area at baseline however it was correlated with a lower muscle area in those with evolving, current or recent persistent critical illness. This assocition was not consistently seen in patients without or resolved persitent critical illness. Pearson $R^2$ and associated p-values are shown with regression lines and 95% confidence intervals.



## Analysis using the MIMIC-III dataset

To assess the generalisability of results we analysed data from the MIMIC-III database which documents 53,423 distinct hospital admissions of adult patients (aged 16 years or above) admitted to critical care units at the Beth Israel Deaconess Medical Center, Boston, Massachusetts (a level 1 trauma centre) between 2001 and 2012. (*MIMIC-III, a freely accessible critical care database* Johnson AEW, Pollard TJ, Shen L, Lehman L, Feng M, Ghassemi M, Moody B, Szolovits P, Celi LA, and Mark RG. Scientific Data (2016). DOI: 10.1038/sdata.2016.35).

For each hospital admission, ICU and Hospital LoS, age, sex, hospital mortality and responsible clinical service to identify trauma patients. Daily serum creatinine, serum urea, serum albumin, haemoglobin concentration neutrophil count and lymphocyte count were extracted. In this data extract due to the nature of the data retrieval where more than one value was available on a given day the mean of all values on that day was used. Urea:creatinine was also calculated on a daily basis. As only a small minority of patients had daily CRP values, this parameter was not analysed. Similarly, only a proportion of patients had differential white cell count so total white cell count is reported as a surrogate of Neutrophil count. Provision of RRT in the ICU was identified by current procedural terminology codes associated with dialysis (90934-91000) and presence of date time events for dialysis or CRRT procedures. The MIMIC-III dataset does not contain trauma severity scores. Simplified Acute Physiology Score II (SAPS-II) values were calculated from physiological and laboratory data within MIMIC-III from day of ICU admission. APACHE 2 scores are not currently available using this methodology.

From MIMIC-III we extracted 3148 trauma-ICU admissions with one or more relevant blood tests during ICU admission; patients with unknown date of birth or ICU length of stay were excluded. We then excluded 29 patients with first creatinine >354 or who received RRT in ICU leaving 3119 admissions for analysis. Of these 432 (13.9%) had an ICU LoS of ≥10 days. Compared to the London cohort these patients were older, had lower mortality, a higher proportion with ICU LoS of <10 days and shorter duration of both ICU and hospital length of stays in both groups (Table S4). As a measure of illness severity SAPS -2 scores were lower in patients with short ICU admissions in MIMIC-III compared to the London Cohort, 24 (IQR: 16-32) vs. 34.00 (IQR: 26-42), while SAPS-2 scores at admission in those who died and those that had ICU LoS of ≥10 days did not significantly differ between the cohorts. Overall these differences may reflect a lower threshold for 'trauma-ICU' admission in the US compared to the UK, where many lower acuity cases are admitted directly to a specialist trauma ward, and a differing demographic case-mix. MIMIC-III contains blood test results

from both during and after ICU admission, however as overall length of stay was shorter than in the London cohort, especially in the group with ICU LoS <10 days, trajectories are plotted over the first 14 days from ICU admission to avoid selection bias at timepoints more distant from admission (Fig. 1c, Fig S11, Table S5). Similarly, trajectories of urea:creatinine stratified by length of stay were generated (Fig. 1d). Finally, ability of urea:creatinine and haemoglobin to discriminate persistent need for intensive care on each day over the first 3 weeks in hospital was calculated in a similar fashion to that in our principal analysis (Fig. S12).

**Figure S11:** Patient flow diagram for the MIMIC-III trauma-ICU cohort (B)

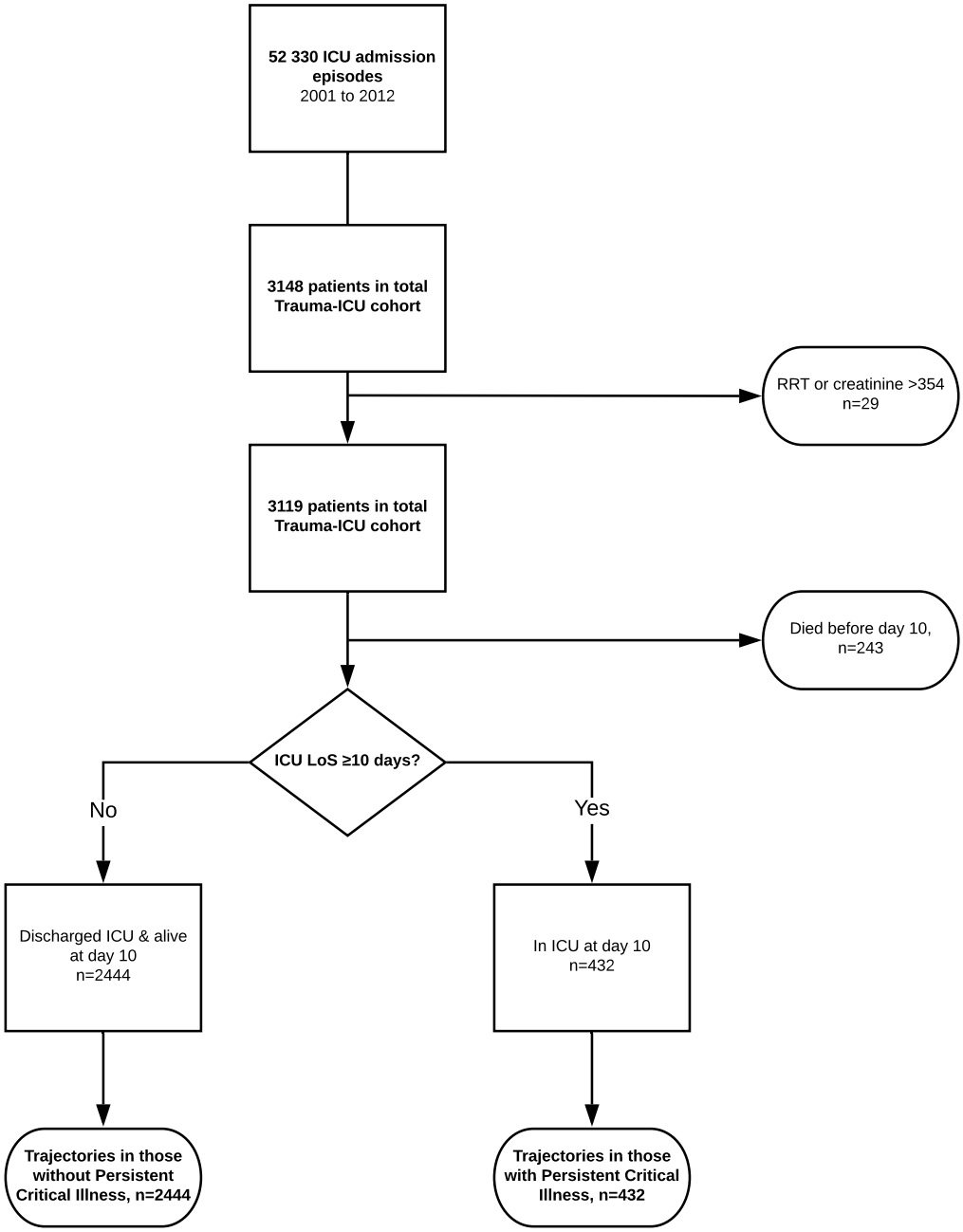


**Table S4:** Characteristics of 3119 adult trauma-ICU admissions from the MIMIC III database

| | In ICU at day 10 | Discharged ICU & Alive at day 10 | P-value in ICU vs. discharged d10 | Died on or before day 10 |
|---|---|---|---|---|
| Number (% of total) | 432 (13.9%) | 2444 (78.4%) | | 243 (7.8%) |
| Age - years (median [IQR]) | 53 [34, 72] | 48 [30, 68] | 0.020 | 70 [45, 82] |
| Sex = Male (% of category) | 299 (70.2%) | 1611 (67.3%) | 0.261 | 154 (63.3%) |
| Died in Hospital (% of category) | 52 (12.2%) | 24 (1.0%) | <0.001 | 243 (100.0%) |
| SAPS-2 Score at ICU admission (median [IQR]) | 34 [26-42] | 24 [16-32] | <0.001 | 43 [34-54] |
| ICU LoS - days (median [IQR]) | 15 [12, 21] | 2 [1,3] | * | 2 [1, 4] |
| Trauma Hospital LoS - days (median [IQR]) | 22 [17,30] | 6 [4, 11] | * | 2 [1,5] |
| Total ICU bed-days (% of total) | 7677 (52.9%) | 6100 (42.0%) | * | 738 (5.0%) |
| Total Trauma Hospital bed-days (% of total) | 11 339(33.4%) | 21 803(64.2%) | * | 802 (2.4%) |

* Comparisons not made as groups defined by length of stay

**Table S5:** Blood results adult trauma-ICU patients analysed from the MIMIC III database. Receiver-operating characteristic Area Under the Curves for discrimination of ICU status at day 10 with 95% confidence interval are shown.
* Albumin values only available in 1218 cases. **% Change calculated only from those with bloods on day 1 and day 10

| | In ICU at day 10 | | | | | Discharged ICU& Alive at day 10 | | | | | ROC-AUC (95% CI) For ICU status at day 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day 0 | Number with bloods Day 0 | Day 10 | Number with bloods Day 10 | % change Day 0 to Day 10** | Day 0 | Number with bloods Day 0 | Day 10 | Number with bloods Day 10 | % change Day 0 to Day 10** | |
| Creatinine (µmol/L) | 71 [62-88] | 426 | 62 [53-80] | 396 | -17% [-30, 0] | 71 [59-91] | 2393 | 62 [53-80] | 341 | -14% [-30, +5] | 0.50 (0.46-0.54) |
| Urea (mmol/L) | 4.6 [3.3-6.4] | 426 | 8.2 [6.1-11.4] | 396 | +58% [+18, +118] | 5.2 [3.8-7.0] | 2393 | 5.7 [4.3-8.9] | 341 | +15% [-13, +64] | 0.66 (0.62-0.70) |
| Urea:creatinine | 70 [55-89] | 426 | 127 [101-168] | 396 | +89% [+44, +145] | 65 [51-84] | 2393 | 94 [71-128] | 341 | +41% [+4%, +96%] | 0.70 (0.66-0.74) |
| Albumin (g/L)* | 30 [25-35] | 125 | 25 [21-27] | 48 | -10% [-27, 3] | 35 [31-39] | 428 | 30 [26-34] | 23 | -10% [-17, +9] | 0.71 (0.58-0.85) |
| Hemoglobin (g/dl) | 10.9 [9.9-12.2] | 420 | 9.5 [8.7-10.4] | **387** | -13% [-22, -4] | 11.5 [10.2, 12.9] | 2320 | 9.9 [9.1-10.9] | 346 | -9% [-18, +2] | 0.61 (0.57-0.65) |
| Leukocytes (x$10^3$/$mm^2$) | 11.6 [8.8-14.7] | 422 | 14.4 [11.3-18.7] | 390 | +23% [-7, +73] | 11.0 [8.8-13.7] | 2342 | 12.8 [10.1-17.7] | 347 | +14% | 0.57 (0.53-0.61) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | [-16, +46] | |

**Figure S12:** Trajectories of routinely measured metabolic and inflammatory parameters in 2876 trauma ICU patients from the MIMIC-III database, surviving to day 10. 432 patients with persistent critical illness (still in ICU at day 10 after admission) were compared to 2444 without (patients initially admitted to ICU but discharged and still alive at day 10). Rolling medians with 95% confidence-intervals of the rolling estimate of the median value are shown using quadratic splines with the curve constrained to pass through the median day 0 value. CRP was not considered due to small number of measurements in the database, similarly as differential white cell count was not consistently reported total white cell count is displayed, finally any albumin results were only available in around 1218 patients.

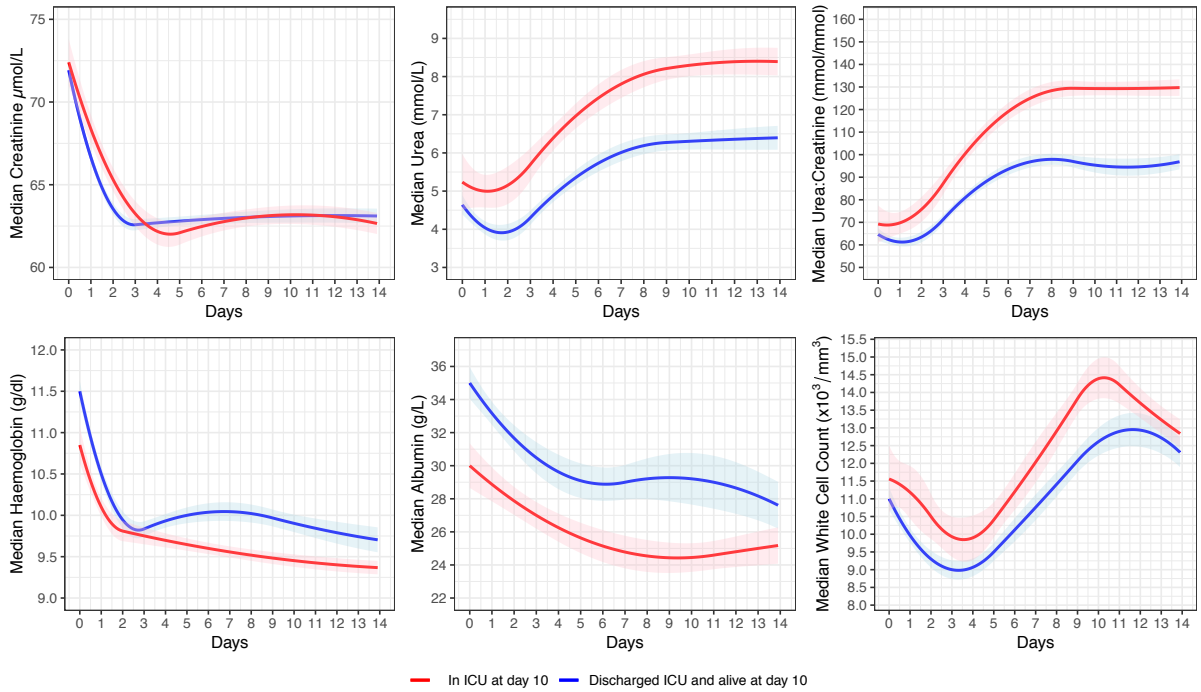
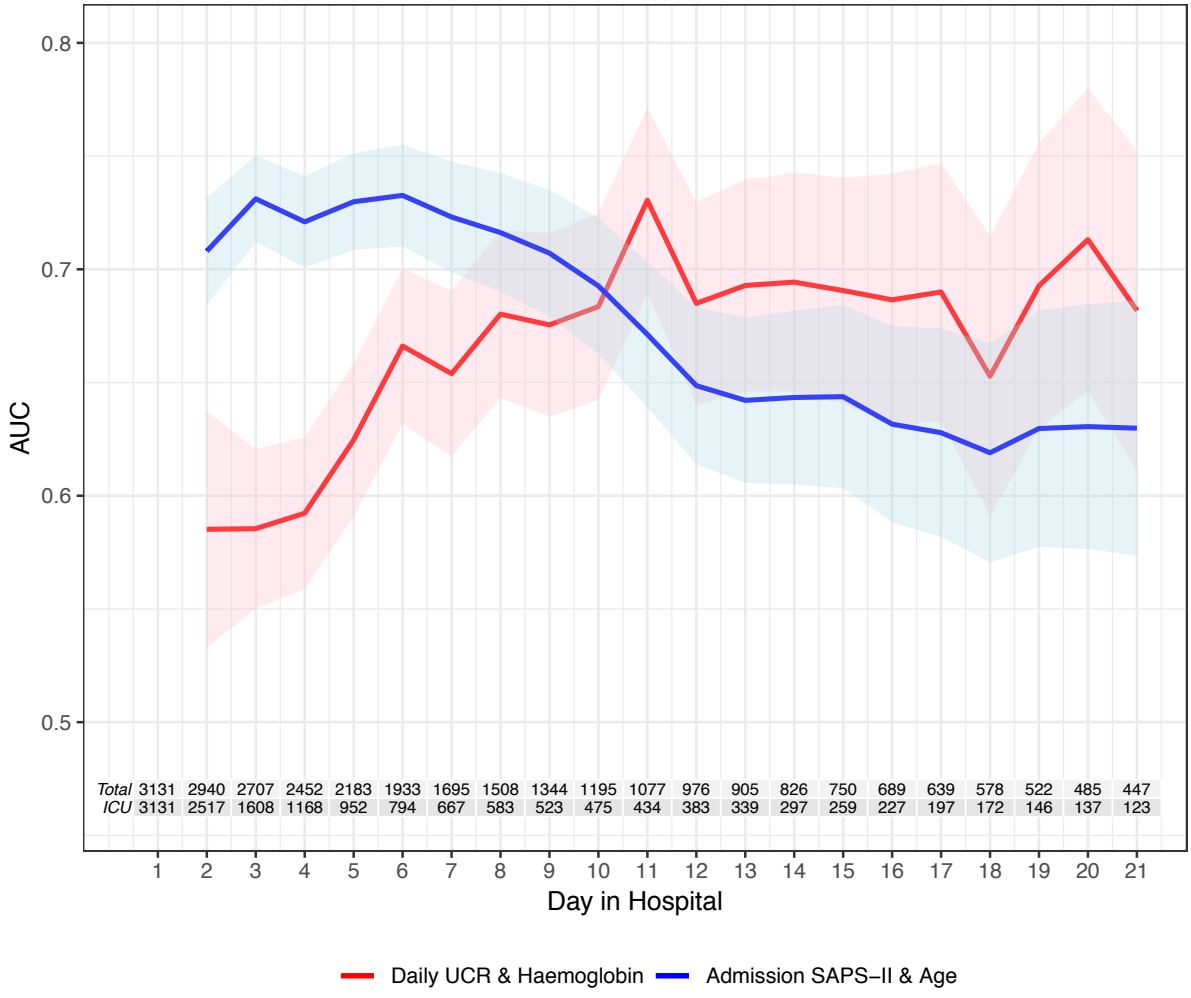


**Fig S13:** Discrimination of persistent need for intensive care from 3131 trauma-ICU patients in the MIMIC-III database (17 with no values for urea excluded). Patients in hospital with blood tests results available on each day were considered. For each day logistic regression models were constructed with persistent need for intensive care on that day as the dependent variable using i) initial illness severity and age (SAPS-II and Age) or ii) urea:creatinine ratio and haemoglobin concentration on that day as explanatory variables. Model AUC (c-statistics) with 95% continence intervals are plotted. Total numbers of patients with blood tests on each day and number of these still in ICU are appended. Model 'i' is superior to 'ii' on days 2-8, and thereafter model 'ii' performs as well or better (significantly better on day 11, 14,15,16 & 20 , Delong's test, $p<0.005$).



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