Clinical Nutrition ESPEN 63 (2024) 944–951

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Analysis of metabolic alterations as 30 days intensive care mortality predictors for patients undergoing continuous renal replacement therapy

Vaidas Vicka [a, b, *], Alvita Vickiene [c, b], Sigute Miskinyte [a, b], Ieva Bartuseviciene [a, b], Ingrida Lisauskiene [a, b], Mindaugas Serpytis [a, b], Donata Ringaitiene [a, b], Jurate Sipylaite [a, b]

[a] Clinic of Anaesthesiology and Intensive Care, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[b] Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania
[c] Clinic of Gastroenterology, Nephro-Urology and Surgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

ARTICLE INFO

Article history:
Received 25 December 2023
Accepted 23 August 2024

Keywords:
AKI
CRRT
Metabolism
Amino acids
Energy expenditure

SUMMARY

Background: Acute kidney injury patients on continuous renal replacement therapy are subjected to alterations in metabolism, which in turn are associated with worse clinical outcome and mortality. The aim of this study is to determine which metabolism indicators can be used as independent predictors of 30 days intensive care unit (ICU) mortality.

Methods: This was a prospective observational study on critical care patients on renal replacement therapy. Integrated approach of metabolism evaluation was used, combining the energy expenditure measured by indirect calorimetry, bioelectrical impedance provided fat free mass index (FFMI), amino acid and glucose concentrations. ICU mortality was defined as all cause 30 days mortality. Regression analysis was conducted to determine the conventional and metabolism associated predictors of mortality.

Results: The study was conducted between the 2021 March and 2022 October. 60 high mortality risk patients (APACHE II of 22.98 ± 7.87, 97% on vasopressors, 100% on mechanical ventilation) were included during the period of the study. The rate of 30 days ICU mortality was 50% (n = 30). Differences across survivors and non-survivors in metabolic predictors were noted in energy expenditure (kcal/kg/day) (19.79 ± 5.55 vs 10.04 ± 3.97 p = 0.013), amino acid concentrations (mmol/L) (2.40 ± 1.06 vs 1.87 ± 0.90 p = 0.040) and glucose concentrations (mmol/L) (7.89 ± 1.90 vs 10.04 ± 3.97 p = 0.010). No differences were noted in FFMI (23.38 ± 4.25 vs 21.95 ± 3.08 p = 0.158). In the final linear regression analysis model, lower energy expenditure (exp(B) = 0.852 CI95%: 0.741–0.979 p = 0.024) and higher glucose (exp(B) = 1.360 CI95%: 1.013–1.824 p = 0.041) remained as independent predictors of the higher mortality.

Conclusion: The results of the study imply strong association between the metabolic alterations and ICU outcome. Our findings suggest that lower systemic amino acid concentration, lower energy expenditure and higher systemic glucose concentration are predictive of 30 days ICU mortality.

1. Introduction

Acute kidney injury (AKI) is reported in up to 60% of intensive care unit (ICU) patients [1]. Approximately 5–10% of AKI cases in critically ill patients are severe and require continuous renal replacement therapy (CRRT) [2]. These patients are recognized for the increased risk of death with mortality rates of 30–70% [3–5]. These patients usually have altered body composition and metabolism with lower protein reserves, indicated by lower fat free mass, lower amino acid concentration and hyperglycaemia [6–8]. In addition, during CRRT various nutrients and other micro molecules are removed through the haemodiafilter and “dialytrauma” is induced which may further alter metabolism [9,10]. Furthermore, citrate, which is the preferred anticoagulant for CCRT, has direct impact on the metabolism through interaction with the Krebs cycle

* Corresponding author. Vilnius University Hospital Santaros Klinikos, Vileisio str 9-18, Vilnius, Lithuania.
E-mail address: Vaidas.vicka@santa.lt (V. Vicka).

https://doi.org/10.1016/j.clnesp.2024.08.021

[11,12]. Therefore, it is important to identify these body composition and metabolic changes in critically ill patients requiring CRRT to individualize the treatment, allocate the resources and effect the clinical outcome.

The metabolism of critical care patients has been studied for more than a century, but the heterogeneity of the critically ill patient population, the varying duration and severity of the acute phase of illness and many confounding factors have hindered progress in the field. However, to be able to move toward individualized treatment and development of precision intensive care medicine, tools to monitor individual patient needs are needed. Yet, only a handful of biochemical indicators of metabolic function and nutrition, most notably glucose, urea, lactate and oxygen utilization in addition to measurement of energy expenditure are available at the bedside [13]. Someindicators are available to objectify the metabolic reserves of the patients before the critical state, i.e.the bioelectrical impedance analysis provided fat free mass index (FFMI), or phase angle, which classically have been used to determine the body composition and state of the nutrition rather than reserves of the patients, but have emerging application areas [14]. However, there are currently no recommendations on an integrated approach to evaluate the metabolism indicators of critically ill patients.

Metabolic alterations in critical care are different for each patient, so an individualized and integrated approach should be implemented to evaluate them. For example, indirect calorimetry is considered the gold standard to measure energy expenditure (EE) and caloric needs in individual critically ill patients at bedside, and its use is strongly recommended by the recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [15](16). However, EE is influenced by many individual and iatrogenic factors and different metabolic phases of critical illness and convalescence [17]. Furthermore, EE is increased by the muscle mass of the patient, increasing the oxygen demand with no pathological sequelae. In contrast, higher fat free mass may be indicative of better nutrition status, metabolic state and reserves of the patient [16]. However, even if the higher fat free mass is present, it may not be effectively mobilized from the tissues in form of amino acids during acute phase and in turn may not be used for gluconeogenesis and adaptive metabolic response to injurious stimuli. This maladaptive response is governed by anabolic downregulation, insulin resistance and overall catabolic shift in the tissues [18]. These metabolic shifts are difficult to evaluate at the bedside, and where are almost no studies simultaneously evaluating these different global and biochemical metabolism indicators.

Therefore, the aim of this article is to determine which metabolism indicators are independent predictors of 30 days ICU mortality in AKI patients undergoing CRRT.

2. Methods

2.1. Patients

This was a prospective observational study on high mortality risk critical care patients on renal replacement therapy, conducted in tertiary reference university hospital. The selection criteria were applied to form a representable critical care cohort of patients, likely to have alterations in metabolism due to acute kidney injury and CRRT. Furthermore, emphasis on systemic inflammatory syndrome was made, by enriching the selection criteria with SEPSIS-3 and SIRS definition. The selection criteria are presented in the Table 1. AKI was defined by KDIGO criteria, using both creatinine and urine cut-offs. The patients were enrolled to the study within 24 h of CRRT initiation.

Sample size of the study was calculated to predict a difference of at least 20% in mortality, with expected mortality of the cohort to be at least 50%. Study sample was calculated to be 47, a final amount was set at 60 to compensate for possible alterations in different variability of the metabolism indicators, not yet extensively reported in the literature.

Ethical approval (No 2021/2-1306-784) was gained from the Vilnius Regional Biomedical Research Ethics Committee to conduct the study. All methods were performed in accordance with the relevant guidelines and regulations and the Declaration of Helsinki. Informed consent was obtained from the legal representatives of all the participants.

2.2. Metabolism indicators

2.2.1. Indirect calorimetry

Indirect calorimetry was chosen as a general indicator of overall oxidative process in the organism. Indirect calorimetry was performed with integrated module in the mechanical ventilation device (GE Carescape R860, Germany Holding GmbH). The measurement was started after enrollment to the study and continued for 24 h. Steady state conditions were required to include the measurement in the analysis, Weir equation was used by the device to calculate the energy expenditure.

Recommendations of the manufacturer and ESPEN were used. The main variables recorded were average 24 h energy expenditure and respiratory quotient. The energy expenditure was further indexed by the weight of the patient. The amount of CO2 lost through the CRRT machine was not accounted for, regarding the MECCIAS trial provided little clinical importance with less than 3% of bicarbonate being affected by the treatment. Furthermore, basal metabolic rate was calculated using the Harris-Benedict equation.

2.2.2. Body composition

To evaluate the main protein and amino acid reserves bioelectrical impedance analysis (BIA) was used. BIA was planned to be performed to all the patients. An InBody 72 S10 device (Biospace, Seoul, Korea) was used, following the instructions provided by the European Society for Clinical Nutrition and Metabolism. Patients assumed a lying posture for 10 min. Analysis was done in a supine position with arms abducted 15 from the trunk and legs spread apart at shoulder width. The analysis was performed using eight electrodes placed on both hands (on thumb and middle finger) and between the patient's anklebones and heels. BIA provides resistance and reactance measured using different frequency currents, which provide estimations of the fat mass, fatfree mass, total body water, and intracellular body water of the patient. The raw data of resistance and reactance are used to calculate the PA. This is done using the measurements of the 50 kHz electric current. The measurements were done after enrollment to the study. The fat-free mass was further indexed by the height of the patient (FFMI).

2.2.3. Amino acid concentration

To evaluate the concentration of the circulating amino acids calorimetric assay was used. Only total serum amino acid concentration was measured. The samples were gathered after enrollment to the study. All samples were diluted 5 times by mixing 20 μl of blood with 80 μl of working buffer solution from the kit. Subsequently, the diluted samples were thermally inactivated by heating at 90 °C for 15 min. After thermal inactivation, the samples were left to reach room temperature and centrifuged for 15 min at 15000×*g* to remove the precipitate. The concentration of L-amino acids was measured according to the supplier's technical bulletin (Sigma-Alrich product code MAK002-1 KT). Briefly, 50 μl of sample was placed in the well of a 96-well plate and mixed with 50 μl of the

Table 1
Selection criteria of the study.

Inclusion criteria	Exclusion criteria
Start of continuous renal replacement therapy because of AKI	Expected lethal outcome in <48 h
Mechanical ventilation	Age <18 y
SEPSIS-3 criteria:	
- low blood pressure (SBP ≤100 mmHg),	
- high respiratory rate (≥22 breaths per min), or	
- altered mentation (Glasgow coma scale <15) (quick SOFA))	
SIRS criteria:	
- tachycardia (heart rate >90 beats/min),	
- tachypnea (respiratory rate >20 breaths/min),	
- fever or hypothermia (temperature >38 or <36 °C),	
- leukocytosis, leukopenia, or bandemia (white blood cells >1200/mm3, <4000/mm3 or bandemia ≥10%)	

master mix (composed of working buffer solution, enzyme mixture, and a probe) and incubated at 37 °C for 30 min. After incubation, the absorbance at 570 nm wavelength was measured, compared to the blank, and the concentration of L-amino acids was calculated according to the calibration curve. The calibration curve was also obtained by mixing 50 μl of standard amino acid solutions (0, 0.16, 0.32, 0.48, 0.64, 0.8 mM) with 50 μl of the master mix.

2.2.4. Glucose concentrations

Glucose concentration was measured from the arterial blood samples with the ABG analyzer (The RAPIDPoint® 500e System, Siemens Healthcare GmbH ©). The glucose was measured 3 times per day, the average glucose is reported.

2.3. Evaluation of mortality

The predicted 30 days mortality in the cohort was 50%, according to the literature and hospital monitoring system for this type of patients. The mortality was defined as all cause 30 days mortality after the admission to the ICU. The mortality prediction scores APACHE II, SOFA and SAPS were used to calculate the standard mortality rate.

2.4. Statistical analysis

Descriptive analysis. Statistical analysis was carried out by the SPSS statistical software package version 23.0 (IBM/SPSS, Inc., Chicago, IL). Baseline characteristics were defined using descriptive statistics. Categorical variables were stated as an absolute number (n) and a relative frequency (%), and continuous variables were represented as a median (interquartile range) or as a mean (±SD), depending on the normality of the distribution. The normality of the distribution was tested by the single sample Kolmogorov-Smirnov test. Statistical significance level was set at 0,05.

Evaluation of the metabolism indicators and mortality. All metabolism indicators (indexed energy expenditure, fat free mass index, amino acid concentrations and glucose concentrations) were regarded as linear variables, showing a normal distribution. Fat free mass was further stratified by gender.

Detection of possible mortality predictors. Independent sample-t test or Mann-Whitney test was used to determine the difference between the mean/median values in all conventional ICU mortality predictors. The predictors with different mean/median values for mortality were when entered in the regression analysis.

Regression analysis. Conventional factors and metabolic indicators were entered in the univariate regression analysis. Final multivariate regression model was built form the variables significant in the univariate analysis. The model was tested for accuracy and collinearity; a stepwise approach was selected.

3. Results

3.1. Description of the cohort

The study was conducted between the 2021 March and 2022 October. 60 patients were included during the period of the study. The description of the cohort is presented in the Table 2. The population was high ICU mortality risk population with actual mortality of 50% (n = 30).

Conventional predictors of the ICU mortality were evaluated and compared across the two groups of survivors and non-survivors. These results are presented in the Table 2. Amongst these predictors the differences were observed in therapeutic or surgical profile of the patients (23 (76.7%) vs 9 (30.0%), p = 0.001), arterial pH value (7.35 ± 0.11 vs 7.28 ± 0.11, p = 0.019) and oxygen saturation percetange (97.30 ± 1.7 vs. 95.8 ± 3.5, p = 0.046). Profile of the patients, oxygen saturation and arterial pH were entered into the regression analysis.

3.2. Metabolism indicators

3.2.1. Indirect calorimetry

The indirect calorimetry was successfully applied to 59 patients in the cohort, 1 was not eligible because of mechanical ventilation setup. The mean value of energy expenditure was 1560 ± 517 kcal/day, the mean indexed value was 18.13 ± 5.32 kcal/kg/day. The results are presented in Table 3 The energy expenditure was compared to the Harris-Benedict equation provided basal metabolic rate 1628.6 ± 311.0 kcal/day, providing a moderate correlation (R = 0.584, Beta = 0.854, P < 0.001). Majority of the patients had lower EE than predicted with Harris-Benedict equation (1579.97 ± 516.6 vs 1630.43 ± 313.4, P < 0.001), indicating slightly lower metabolism state. This was further evident than indexing the energy expenditure with basal metabolic rate, with the results of 0.97 ± 0.26. After conducting the analysis of mean values in two groups of survivors and non-survivors, the weight adjusted energy expenditure was selected for regression analysis.

3.2.2. Body composition: estimated fat free mass

Bioelectrical impedance was successfully performed for 59 patients, one patient was omitted due to loss of limb. The analysis showed overall acceptable body composition of the patients, with FFMI values on average higher than ESPEN provided cut-off values of FFMI for malnutrition (15 kg/m^2 for women and 17 kg/m^2 for men). The raw FFMI values were categorized by gender and presented by percentile groups. The cohort had low phase angle (mean values of 3.83 ± 1.11), which may be indicative either of poor cell vitality or fluid overload. Due to lack of reference values for standardization of phase angle no further analysis was conducted. The results are presented in the Table 3. After conducting the analysis of mean values in two groups of survivors and non-survivors, no

Table 2
Description of the cohort.

	All group (n = 60)	Survivors (n = 30, 50%)	Non-survivors (n = 30, 50%)	P value
	Mean ± SD, Median [IQR], n (%)			
Demographics				
Age (years)	66.00 ± 12.91	65.0 ± 14.28	67.0 ± 11.54	0.553
Gender:				
Male	26 (43.3)	19 (55.6)	15 (44.1)	
Female	34 (56.7)	11 (42.3)	15 (50.0)	0.297
Height (cm)	170.87 ± 17.75	172.20 ± 8.31	169.53 ± 23.84	0.567
Weight (kg)	88.70 ± 22.38	86.80 ± 19.36	90.60 ± 25.23	0.516
Co-morbidities				
Arterial hypertension	47 (78.3)	23 (76.7)	24 (80.0)	0.754
Heart failure	33 (55.0)	16 (53.3)	17 (56.7)	0.795
Diabetes	15 (25.0)	6 (20.0)	9 (30.0)	0.371
Chronic kidney disease	19 (31.7)	12 (40.0)	7 (23.3)	0.165
Chronic obstructive pulmonary disease	1 (1.7)	0 (0)	1 (3.3)	0.313
Immunosuppression	3 (5.0)	0 (0)	3 (10.0)	0.237
Clinical evaluation				
Mean arterial blood pressure (mmHG)	75.1 ± 12.0	74.80 ± 11.9	75.4 ± 12.2	0.842
Oxygen saturation (%)	96.5 ± 2.9	97.30 ± 1.7	95.8 ± 3.5	0.046
Temperature (degrees Celsium)	36.2 ± 1.4	36.2 ± 1.3	35.8 ± 1.5	0.291
Heart rate (bpm)	85.5 ± 19.9	88.3 ± 20.3	82.6 ± 19.3	0.273
Laboratory				
Arterial pH (units)	7.32 ± 0.12	7.35 ± 0.11	7.28 ± 0.11	0.019
Haemoglobin (g/L)	105.8 ± 20.7	104.4 ± 19.5	107.4 ± 22.2	0.597
Lactate (mmol/L)	2.1 [1.5–2.88]	1.94 [1.3–2.5]	2.1 [1.52–3.50]	0.316
Sodium (mmol/L)	137.5 ± 5.2	138.4 ± 4.7	136.7 ± 6.00	0.217
Potassium (mmol/L)	4.36 ± 0.74	4.27 ± 0.68	4.45 ± 0.80	0.375
C-reactive protein (mg/L)	154.1 [108.5–248.4]	154.5 [114.2–259.5]	152.3 [89.9–249.2]	0.469
Procalcitonin (mcg/L)	4.63 [1.95–16.71]	4.7 [2.64–13.45]	4.21 [0.63–23.38]	0.786
Leukocytes (*10^9)	13.17 [9.3–17.21]	13.33 [9.9–17.60]	12.39 [8.76–17.48]	0.544
Creatinine (mcmol/L)	207 [162.5–311.5]	222 [156.5–307.8]	204 [171–395]	0.848
Urea (mmol/L)	17.55 [11.5–26.70]	13.95 [10.5–26.70]	20.7 [12.7–27.3]	0.122
Bilirubin (mg/L)	28.8 [16.9–68.9]	29,6 [17.1–57.40]	28.5 [13.1–81.3]	0.901
Severity indices				
APACHE II (points)	22.98 ± 7.87	21.56 ± 7.47	24.44 ± 8.13	0.162
SOFA (points)	12.25 ± 3.61	11.47 ± 3.67	13.10 ± 3.42	0.089
SAPS II (points)	51.59 ± 15.51	47.83 ± 14.03	56.10 ± 16.40	0.083
On vasopressors	58 (96.7)	28 (93.3)	30 (100)	0.150
Mean dose of noradrenaline (mcg/kg/min)	0.23 [0.1–0.39]	0.19 [0.1–0.32]	0.3 [0.1 0.46]	0.272
Source of the infection and primary pathology group				
Non-surgical profile[a]:	32 (53.3)	9 (30.0)	23 (76.7)	0.001
Cardiac	5 (15.6)			
Pulmonary	11 (34.4)			
Gastric	8 (25.0)			
Neurological	3 (5.0)			
Kidney	1 (3.3)			
Hematological	2 (3.3)			
Trauma	2 (3.3)			
Surgical profile[a]:	28 (46.7)	7 (23.3)	21 (70.0)	0.001
Trauma	4 (6.7)			
Abdominal	7 (11.7)			
Cardiac	14 (23.3)			
Angiological	3 (5.0)			
CRRT and Mechanical ventilation parameters				
Initial dose (mL/kg/h)	29.92 ± 8.82	28.28 ± 6.33	31.6 ± 10.61	0.150
CRRT start after ICU admission (day)	2.0 [1.0–5.75]	2.5 [2.0–5.0]	2.0 [1.0–6.0]	0.188
Loss of amino acid via CRRT (g/day)	14.50 ± 9.63	16.65 ± 10.77	12.19 ± 7.79	0.075
Modality:				
CVVHD	33 (55.0)	19 (63.6)	14 (46.7)	0.194
CVVH	7 (11.7)	4 (13.3)	4 (13.3)	0.565
CVVHDF	20 (33.3)	7 (50.0)	14 (46.7)	0.058
PEEP value	9.33 ± 3.45	9.27 ± 3.63	9.4 ± 3.60	0.883
FiO2 value	55.2 ± 17.56	52.57 ± 18.01	57.8 ± 17.00	0.249
PaO2/FiO2 ratio	195.6 [134.9–265.8]	212.5 [142.50–293.21]	189 [113–251]	0.158
Disease course and outcomes				
Days before ICU	6 [2–11]	6.5 [3.5–13.75]	5 [1.7–9]	0.170
Hospital stay (days)	25 [10–48]	48 [26.5–82.0]	11 [6.5–25.3]	<0.001
ICU stay (days)	13.5 [7–23]	17.0 [12.0–36.0]	7 [3–16.5]	<0.001

SD – standard deviation, IQR – interquartile range, SAPS – Simplified Acute Physiology Score, SOFA – Sequential Organ Failure Assessment, APACHE II – Acute Physiology and Chronic Health Evaluation, ICU – intensive care unit, CRRT – continuous renal replacement therapy, CVVH – continuous veno-venous hemofiltration, CVVHD – continuous veno-venous haemodialysis, CVVHDF – continuous veno-venous hemodiafiltration.

[a] Patients are aggregated into non-surgical and surgical profile because of low number in subgroups.

Table 3
Analysis of metabolism indicators.

	All group (n = 60)	Survivors (n = 30, 50%)	Non-survivors (n = 30, 50%)	P value
	Mean ± SD, Median [IQR], n (%)			
Indirect calorimetry				
Energy expenditure (kcal/day)	1560 ± 517	1689.3 ± 478.4	1466.9 ± 538.3	0.099
Energy expenditure (kcal/kg/day)	18.13 ± 5.32	19.79 ± 5.55	10.04 ± 3.97	0.013
Respiratory quotient (units)	0.76 ± 0.15	0.76 ± 0.16	0.76 ± 0.14	0.920
EE expenditure/Basal metabolic rate	0.97 ± 0.26	1.04 ± 0.25	0.89 ± 0.25	0.024
Bioelectrical impedance				
Fat free mass index (kg/m^2)	22.67 ± 3.74	23.38 ± 4.25	21.95 ± 3.08	0.158
Extracellular water (liters)	21.34 ± 4.62	22.14 ± 5.42	20.58 ± 3.58	0.214
Intracellular water (liters)	29.61 ± 5.89	30.36 ± 6.13	28.86 ± 5.64	0.345
Total body water (liters)	50.26 ± 11.33	51.10 ± 13.38	49.40 ± 9.00	0.580
Phase angle (degrees)	3.83 ± 1.11	3.91 ± 0.86	3.77 ± 1.32	0.633
Amino acids				
Amino acids (mmol/L)	2.14 ± 1.01	2.40 ± 1.06	1.87 ± 0.90	0.040
Glucose				
Glucose (mmol/L)	8.94 ± 3.26	7.89 ± 1.90	10.04 ± 3.97	0.010

bioelectrical impedance analysis provided variables were selected for the regression analysis.

3.2.3. Amino acid concentrations

Analysis of amino acid concentrations was successful for 59 patients in the cohort, one patient was omitted because of measured values outside the calibration curve. The whole blood samples were centrifuged, and the serum was separated from the sample. The amino acid concentration was measured in the serum. The results are presented in the Table 3, for both linear and categorized variables. Mean values of the circulating amino acids were 2.14 ± 1.01 mmol/L, which is concordance to reported values in the literature. Amino acid concentrations were different in survivors and non-survivor groups (2.40 ± 1.06 vs. 1.87 ± 0.90 p = 0.040), these values of the amino acids were entered into the regression analysis.

Furthermore, loss of amino acid was measured, reporting the average of 14.5 g of amino acid lost per day. Amino acid loss was calculated by using samples from the effluent fluid, taken after the initiation of CRRT. The samples were taken during the first 24 h of the CRRT procedure, the sampling was done from the effluent line of the extracorporeal circuit. During the period of 24 h the parameters of the CRRT machine were not changed. Individual net volume in liters of effluent fluid during the 24 h period was calculated. The individual moles of amino acids lost were calculated and by employing the average molecular weight of an amino acid of 110Da, converted into grams lost per 24 h. The formula for grams lost per 24 h is as follows: *Amino acids* (*molL*)*effluent*Volume*(*L*) *effluent *Molecular weight* (110 g/mol) *amino acids*. Further analysis was conducted to eliminate confounding effect of the type of the CRRT on amino acid concentration (7.15 ± 2.54 g for CVVH, 11.92 ± 7.21 for CVVHD, 20.78 ± 11.40 for CVVHDF, p = 0.02) and possible effect of dose of CRRT (pre filter concentration of (2.14 ± 1.01 mmol/L vs post filter concentration of 1.70 ± 0.91 mmol/L, p < 0.001). Ultimately, neither CRRT dose, lost amino acid content or type of CRRT were different in survivors and non-survivors groups therefore were not included in the regression analysis.

3.2.4. Glucose concentrations

The average glucose concentration was 8.94 ± 3.26 mmol/L. The glucose was measured for the first 24 h in the study (4–6 measurements per 24 h). The results are presented in the Table 3, for both linear and categorized variables. There was a difference of mean glucose concentrations in survivors and non-survivors (7.89 ± 1.90 vs. 10.04 ± 3.97 p = 0.010), these values of the glucose were entered into the regression analysis. The glucose concentration of the dialysate/replacement fluid was 7.8 mmol/L.

3.3. Nutritional therapy

The majority of the patients enrolled in the study were on their 2nd day of ICU stay. Therefore, the nutritional therapy provided was low, 8.86 kcal/kg/day, that is about 50% of the indirect calorimetry value (Table 4). Proteins provided were 0.26 g/kg/day, a low value, also explainable by the early course of ICU stay. Glucose provided was 3.24 g/kg/day. As for the method of nutritional support, most of the patients had almost 50% of the calories provided from the propofol emulsion used for sedation. 8.69% (n = 10) of the patients had some parenteral supplementary nutrition apart from propofol. All the patients had some sort of enteral nutrition; however, the amount was only minimal and is not reported. There were no differences in survival and non-survival rates along all the parameters of nutritional support.

Table 4
Nutritional therapy.

	All group (n = 60)	Survivors (n = 30, 50%)	Non-survivors (n = 30, 50%)	P value
	Median IIQR], n (%)			
Nutritional therapy				
All Energy (kcal/kg/day)	8.86 [4.53–16.14]	11.04 [5.97–17.22]	8.51 [3.34–14.52]	0.531
Proteins (g/kg/day)	0.26 [0.00–0.58]	0.27 [0.10–0.83]	0.27 [0.0–0.43]	0.292
Porpofol calories (kcal/kg/day)	3.57 [2.15–4.71]	3.43 [1.83–4.69]	3.67 [2.71–4.66]	0.404
Glucose amount (g/kg/day)	3.24 [0.0–7.21]	4.32 [0.72–7.83]	3.14 [0.00–5.75]	0.239
Exogenous insulin (units/day)	0.00 [0.00–11.50]	0.0 [0.0–0.5]	0.0 [0.0–18.0]	0.058

Table 5
Regression analysis of mortality predictors.

	Univariate regression			
	B	Exp(B)	95% CI for B	P value
General predictors				
Profile (non-surgical)	2.037	7.667	2.424–24.245	0.001
Arterial pH (units)	−5.660	0.003	0300–0.487	0.025
Arterial oxygen saturation (%)	−0.234	0.792	0.623–1.007	0.057
Metabolism indicators				
Energy expenditure (kcal/kg/day)	−0.138	0.871	0.776–0.979	0.020
Glucose (mmol/L)	0.254	1.290	1.044–1.594	0.019
Amino acids (mmol/L)	−0.569	0.566	0.324–0.989	0.046
Fat free mass index (kg/m^2)	n.s.			0.164
	Multivariate regression			
	B	Exp(B)	95% CI for B	P value
General predictors				
Profile (non-surgical)	2.348	10.462	2.591–42.246	0.001
Arterial pH (units)	n.s.			0.415
Metabolism indicators				
Energy expenditure (kcal/kg/day)	−0.160	0.852	0.741–0.979	0.024
Glucose (mmol/L)	0.307	1.360	1.013–1.824	0.041
Amino acids (mmol/L)	n.s.			0.119

In part A univariate regression analysis is presented. In part B multivariate regression analysis is presented. Abbreviations: n.s. – not significant, n.i. – not included.

3.4. 30 days mortality

The rate of 30 days mortality was 50% (n = 30). This rate was comparable to predicted rate with APACHE II score (predicated rate of 46%, standardized mortality = 1.09), SOFA score (predicated rate of 50%, standardized mortality = 1.0) and SAPS II score (predicated rate of 50%, standardized mortality = 1.0).

3.5. Regression analysis of 30 days mortality predictors

Regression analysis was performed in two parts. First part was univariate regression of all possible ICU mortality predictors, evident to be different in two groups: survivors and non-survivors, as reported in Table 2. The second part was multivariate regression analysis with forward selection method, the model was built form the statistically significant variables in the univariate regression. The results are presented in Table 5.

In the univariate regression model in general predictors group the non-surgical profile of the disease and the lower value of the pH was revealed to be predictors of the increased mortality. In the metabolic predictors group lower amino acid concentration, lower energy expenditure and higher glucose concentration were significant predictors of the increased mortality.

In the multivariate regression analysis non-surgical disease profile remained as the sole variable form the general predictors group. From the metabolism indicators lower energy expenditure and higher glucose remained as independent predictors of the higher mortality, even when adjusting for the non-surgical profile mortality effect. The result for the metabolic predictors is presented in the Fig. 1.

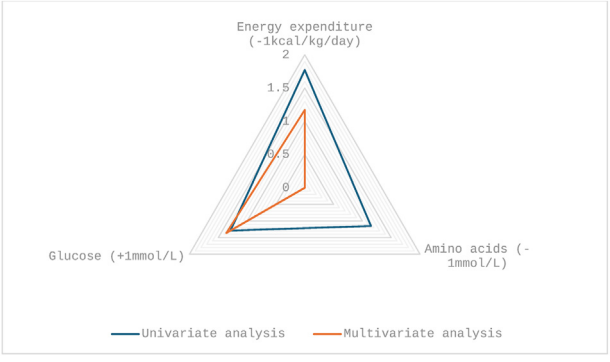

Fig. 1. Regression analysis results for metabolic indicators as predictors of 30 days mortality. Legends. The radar chart presents the standardized regression coefficients. Blue line indicates risk ratio of mortality for a unit change in predictor in univariate analysis, orange line in multivariate analysis. Fat free mass index was not included in the regression analysis. Amino acid concentration was not significant in the multivariate regression.

4. Discussion

4.1. General findings

We conducted the study of 60 high mortality risk ICU patients with AKI undergoing CRRT. Using novel technologies to evaluate the metabolism we demonstrated significant metabolic differences in the beginning of the critical state between survivors and non - survivors over a 30 days observation period. Alterations in energy expenditure, glucose and amino acid concentrations were shown to be significant predictors of mortality.

4.2. Energy expenditure and mortality

Indirect calorimetry (IC) is considered as the gold standard to measure energy expenditure in critically ill patients and its use has been strongly recommended by the recent European Society for Clinical Nutrition and Metabolism (ESPEN) and American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines [15,16,19,20]. The use of IC is increasing due to precise resting energy expenditure (REE) measurement, which in turn is used both for intensity of metabolic response evaluation and nutrition needs estimation. Metabolic response to critical illness is complex and has been a subject of research and debate for decades. The available evidence indicates numerous factors that may lead to significant daily variations in EE in and between intensive care unit patients [15,19,21]. It is believed that critical illness is accompanied by a hypermetabolic state related to the activation of various catabolic hormones and this situation results in elevated energy expenditure. However, hypermetabolism does not always characterize the initial phase of critical illness, as several studies show that during the first days, EE may fall to lower or near-baseline levels [22,23]. In our study, most of the patients were on their second day of ICU stay, usually marking a shift from Ebb phase to hypermetabolic phase of critical illness. Therefore, measured EE to REE ratio is 0.97, a result concordant to current evidence for patients ir early critical state [24]. Furthermore, lower EE may be indicative of low oxygenation capacity and micro molecule turnover, which may be indicative of loss of ability to synthetize the immune and structural cells, needed to overcome the injurious stimuli. In our study lower energy expenditure was independently and significantly associated with increased 30-day mortality.

4.3. Protein reserve, amino acid concentrations and mortality

The most reliable, well validated non-invasive and relatively inexpensive method of body composition assessment in general population is bioelectric impedance analysis (BIA), recommended by the ESPEN, ASPEN, as well as Global Leadership Initiative on Malnutrition (GLIM) [25]. One of the BIA parameters, fat-free mass, provides potential use in estimation of muscle mass, i.e. protein reserve. Critically ill patients with AKI on CRRT are often catabolic with rapid breakdown of the muscles in the tissues and in turn mobilization of amino acids to blood and liver for gluconeogenesis.

This profound effect of AKI and CRRT on body composition results in significant depletion of lean body mass. ICU patients feature a loss of fat-free mass of up to 440 g/day, which is associated with increased morbidity and prolonged recovery [26]. However, the gluconeogenesis should be interpreted as adaptive mechanism to stress, and the extent of it is only indicative of the gravity of the critical state. Currently, there are no clinical interventions, apart of the treatment of the progenitor disease, directed towards reduction of the tissue catabolism. Thus, it seems that larger muscle mass reserve present in the tissues should enable the patient to adapt to stress more efficiently. However, based on the results of our study, the amount of the reserve is not important in context of failure to mobilize it in form of amino acids. We did not have aim to link amino acid concentration to FFMI in our study, however, we report a signal, that amino acid concentration, instead of FFMI is lower in non survivors and is predictive of mortality. This implies a more difficult mechanism of amino acid flux from the tissues, which should be investigated more with amino acid phenotyping and isotope marking, eluding the limiting factors of amino acid mobilization. Furthermore, BIA used for FFMI evaluation in our study may not be the most accurate methodology in critical care patients. BIA is criticized in critical care setting due to alterations in hydration state, reference equation inadequacy, shortage of large sample studies and technical impracticalities [27]. Thus, we cannot definitely make a conclusion in the study if FFMI has no link with mortality as a metabolic predictor, or this link is not consistent due to FFMI limitations in critical care setting.

4.4. Glucose concentration and mortality

Critical illness is associated with increased endogenous glucose production, hepatic and peripheral insulin resistance which results from activation of insulin counter regulatory hormones caused by stress. While thought to be an adaptive response to redirect resources towards the immune response and cell synthesis, it has been associated with severity of illness and significant morbidities as well as increased mortality in critical states. The target for glucose management in this population and its relationship with the patients' outcome is not clear, and results from literature are contrasting [28]. Some evidence states that hyperglycemia, with a threshold value of 10 mmol/L, relates to an increased risk of death and morbidity due to infection in ICU patients. A previous retrospective analysis of a heterogeneous group of critically ill patients in ICU revealed that mean and maximum glucose values were significantly higher among non survivors than among survivors for the entire group [29]. The results of our study suggest a difference of glucose concentration in survivors and non-survivors. This difference persisted as an independent predictor of mortality. If the increase in glucose would be evaluated in context of lower energy expenditure and lower amino acid concentration, which are combined results of our study, the more important mortality predictors would be lower energy expenditure and higher glucose concentration. This would fit into the concept of lower metabolic state and higher insulin resistance, indicative of low anabolic capacity which may further lead to loss of ability to synthetize the immune and structural cells, needed to overcome the injurious stimuli.

4.5. Limitations

Firstly, this is an observational study with a relatively small sample size. Also, this is a single-center study with no external validity. Thus, further large-scale investigations are needed to verify metabolic alterations as predictors of mortality of critically ill AKI patients with CRRT.

Secondly, there are some limitations of the techniques used to evaluate the metabolism in our study. Several mechanisms may potentially influence IC energy expenditure results [1] citrate, the preferred anticoagulant for CRRT, has a direct impact on the patient's metabolism through interaction with the Krebs cycle [2]; VCO2 measurements are influenced by CRRT because CO2 is exchanged during the blood purification process, even though the MECCIAS trial showed that this led to a change in REE of only 3% which makes a correction factor unnecessary [3]; amount of energy used to process the nutrients is not possible to be redacted form the overall energy expenditure, even though minimal nutrition was initiated during the first day of the trial according to general recommendations of ESPEN. Furthermore, there are some limitations to the use of bioelectrical impedance [1]: the patients upon start of the CRRT are usually fluid overloaded, which is also the case in our study, this may falsely decrease the fat-free mass [2]; the fat-free mass measured is standardized according to the gender and percentile cut-off points of the cohort, no population based nomograms are available for critical care patients. Furthermore, application oh BIA provided phase angle in critical care is also limited. Even though it has been shown as a predictor of clinical outcome in different settings lack of standardization and reference values in critical care limits the prognostic value of phase angle, as shown in our study [3] no follow up on later ICU days of bioelectrical impedance may be done, because of the fluid accumulation and shift to extracellular space – the reading would be biased.

Furthermore, we have no data about the endogenous insulin production and insulin concentration during the observation period, which limits our assumptions on insulin resistance. However, most current guidelines recommend to target blood glucose levels <10 mmol/L in critically ill patients which was also a target in our patient's group, at least controlling for the exogenous insulin part.

Finally, the authors note that there is difference in individual amino acid kinetics during critical illness, with possible different or no clinical effect. Indeed, the data is still lacking whether total blood amino acid concentrations can be used as a proxy for amino acid/protein reserves, with recent studies shift towards a more complex flux analysis (PMID: 33946038). In our opinion total L-amino acid concentration is not indicative of tissue reserve, but rather a dynamic marker of metabolic intensity, somewhat comparable with its kinetics to other micro molecules (glucose, etc.). More research is needed to determine what is the physiology behind a clear clinical association with survival. In this study total serum amino acid concentration was investigated, and thus no comments can be made on separate amino acid kinetics.

5. Conclusion

The results of the study imply strong association between the metabolic alterations and ICU outcome. Our findings suggest that lower systemic amino acid concentration, lower energy expenditure and higher systemic glucose concentration are predictive of 30 days ICU mortality.

Funding statement

This research was funded by Lithuanian research council as part of "Biosensor Platform for Fast, Cheap and Accurate Quantification of Amino Acids in Patients Undergoing Renal Replacement Therapy (DIALSENS)" (No. 01.2.2-LMT-K-718-01-0019).

Author contribution

VV, AV, SM and IB collected the data and prepared the original draft; VV conducted the analysis and supervised the study; DR and

JS created the design of the study and revised the manuscript; IL and MS revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The dataset used during the current study is available from the corresponding author on reasonable request according to the data protection policies.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

The authors of the study would like to thank all the patients who participated in the study. Also, the authors would like to express gratitude to the Vilnius University Life Sciences Centre for amino acid analysis and help with conducting the study.

References

[1] Hoste EAJ, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015 Aug;41(8):1411–23.
[2] Tolwani A. Continuous renal-replacement therapy for acute kidney injury. N Engl J Med 2012 Dec 27;367(26):2505–14.
[3] Liu KD, Himmelfarb J, Paganini E, Ikizler TA, Soroko SH, Mehta RL, et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. CJASN 2006 Sep;1(5):915–9.
[4] Saudan P, Niederberger M, De Seigneux S, Romand J, Pugin J, Perneger T, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006 Oct;70(7):1312–7.
[5] Uchino S. Acute renal failure in critically ill PatientsA multinational, multicenter study. JAMA 2005 Aug 17;294(7):813.
[6] Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr 2012 Aug;31(4):462–8.
[7] Thibault R, Makhlouf AM, Mulliez A, Cristina Gonzalez M, Kekstas G, Kozjek NR, et al. Fat-free mass at admission predicts 28-day mortality in intensive care unit patients: the international prospective observational study Phase Angle Project. Intensive Care Med 2016 Sep;42(9):1445–53.
[8] Zhou K. Glycemic targets in the ICU: a look back, and ahead. CCJM 2022 Apr;89(4):189–90.
[9] Btaiche IF, Mohammad RA, Alaniz C, Mueller BA. Amino acid requirements in critically ill patients with acute kidney injury treated with continuous renal replacement therapy. Pharmacotherapy 2008 May;28(5):600–13.
[10] Maynar Moliner J, Honore PM, Sánchez-Izquierdo Riera JA, Herrera Gutiérrez M, Spapen HD. Handling continuous renal replacement therapy-related adverse effects in intensive care unit patients: the dialytrauma concept. Blood Purif 2012;34(2):177–85.
[11] Jonckheer J, Spapen H, Malbrain MLNG, Oschima T, De Waele E. Energy expenditure and caloric targets during continuous renal replacement therapy under regional citrate anticoagulation. A viewpoint. Clin Nutr 2020 Feb;39(2):353–7.
[12] Schneider AG, Journois D, Rimmelé T. Complications of regional citrate anticoagulation: accumulation or overload? Crit Care 2017 Dec;21(1):281.
[13] Wernerman J, Christopher KB, Annane D, Casaer MP, Coopersmith CM, Deane AM, et al. Metabolic support in the critically ill: a consensus of 19. Crit Care 2019 Dec;23(1):318.
[14] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr 2004 Dec;23(6):1430–53.
[15] Delsoglio M, Achamrah N, Berger MM, Pichard C. Indirect calorimetry in clinical practice. JCM 2019 Sep 5;8(9):1387.
[16] Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019 Feb;38(1):48–79.
[17] Moonen HPFX, Beckers KJH, van Zanten ARH. Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations. j intensive care 2021 Dec;9(1):8.
[18] Lad H, Saumur TM, Herridge MS, Dos Santos CC, Mathur S, Batt J, et al. Intensive care unit-acquired weakness: not just another muscle atrophying condition. Int J Mol Sci [Internet] 2020 Nov 1;21(21):1–30 [cited 2024 Jun 4] Available from:/pmc/articles/PMC7660068/.
[19] Oshima T, Delsoglio M, Dupertuis YM, Singer P, De Waele E, Veraar C, et al. The clinical evaluation of the new indirect calorimeter developed by the ICALIC project. Clin Nutr 2020 Oct;39(10):3105–11.
[20] McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N. JPEN - J Parenter Enter Nutr 2016 Feb;40(2):159–211.
[21] Berger MM, Pichard C. Feeding should be individualized in the critically ill patients. Curr Opin Crit Care 2019 Aug;25(4):307–13.
[22] Singer M. Critical illness and flat batteries. Crit Care 2017 Dec;21(S3):309.
[23] Wischmeyer PE. Tailoring nutrition therapy to illness and recovery. Crit Care 2017 Dec;21(S3):316.
[24] Ndahimana D, Kim E-K. Energy requirements in critically ill patients. Clin Nutr Res [Internet] 2018;7(2):81 [cited 2024 Jun 4]Available from:/pmc/articles/PMC5921333/.
[25] Moonen HPFX, Van Zanten ARH. Bioelectric impedance analysis for body composition measurement and other potential clinical applications in critical illness. Curr Opin Crit Care 2021 Aug;27(4):344–53.
[26] Kyle U. Bioelectrical impedance analysis?part I: review of principles and methods. Clin Nutr 2004 Oct;23(5):1226–43.
[27] Myatchin I, Abraham P, Malbrain MLNG. Bio-electrical impedance analysis in critically ill patients: are we ready for prime time? J Clin Monit Comput [Internet] 2020 Jun 1;34(3):401 [cited 2024 Jun 4]Available from:/pmc/articles/PMC7223384/.
[28] Robba C, Bilotta F. Admission hyperglycemia and outcome in ICU patients with sepsis. J Thorac Dis 2016 Jul;8(7):E581–3.
[29] Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003 Dec;78(12):1471–8.