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Urea urinaria, balance de nitrógeno y mortalidad en pacientes críticos: un estudio de cohorte prospectivo

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ABSTRACT

Introduction: nitrogen balance (NB) is the difference between nitrogen ingested and excreted, however its value as a prognostic marker in critically ill patients has yet to be determined. This study aimed to evaluate the association between NB, urinary parameters, and adverse outcomes among ICU patients.

Methods: NB, urinary urea (UUE) and creatinine (UCE) excretion were recorded in the first week of ICU. The primary outcome was ICU mortality, and secondary outcomes were time on mechanical ventilation (MV), ICU and hospital length of stay and hospital mortality.

Results: a total of 127 patients were included (58 ± 16 years, 87.4 % clinical admissions). Negative NB was observed in 77.2 % patients in the first and 47.2 % patients in the second measurement, with a protein intake of 40 (25-58) vs 86 (64-107) g/day. The ICU and hospital mortality rates were 22.0 % and 30.7 %. There was no

identified cut-off point for sensibility and specificity in the ROC curves for NB and urinary parameters regarding ICU and hospital mortality.
Conclusions: NB, UUE, or UCE were not associated with ICU or hospital mortality in our study. Further research is needed to evaluate the practical value of NB as a prognostic marker in ICU patients.

Keywords: Intensive care units. Critical care. Nitrogen balance. Parenteral nutrition. Enteral nutrition. Mechanical ventilation.

RESUMEN

Introducción: el balance de nitrógeno (BN) representa la diferencia entre el nitrógeno consumido y el eliminado; sin embargo, su valor como marcador pronóstico en pacientes críticos todavía no se ha establecido. El propósito de esta investigación fue analizar la asociación entre BN, parámetros urinarios y resultados adversos en pacientes de UCI.
Métodos: se registraron el BN y la excreción de urea urinaria (UUE) y la creatinina (UCE) durante la primera semana de UCI. El objetivo primario fue la mortalidad en UCI y los objetivos secundarios incluyen el tiempo en ventilación mecánica (VM), la duración de la estancia en UCI y hospitalaria y la mortalidad hospitalaria.
Resultados: se incluyeron un total de 127 pacientes (58 ± 16 años, 87,4 % de admisiones clínicas). Se observó BN negativo en el 77,2 % de los pacientes en la primera evaluación y en el 47,2 % de los pacientes en la segunda, con una ingesta proteica de 40 (25-58) en comparación con 86 (64-107) g/día, respectivamente. Las tasas de mortalidad en la UCI y en el hospital fueron del 22,0 % y del 30,7 %. No se identificó ningún punto de corte para la sensibilidad y la especificidad en las curvas ROC para BN y parámetros urinarios en relación con la mortalidad en la UCI y en el hospital.
Conclusiones: BN, UUE o UCE no se asociaron con la mortalidad en la UCI o en el hospital. Es necesario realizar más estudios para valorar

el impacto práctico de BN como indicador pronóstico en pacientes de la UCI.

Palabras clave: Unidades de cuidados intensivos. Resultados de cuidados críticos. Balance de nitrógeno. Nutrición parenteral. Nutrición enteral. Ventilación mecánica.

INTRODUCTION

Critically ill patients exhibit an elevated catabolic rate, primarily attributed to systemic inflammatory cytokines and anabolic resistance during the acute phase response (1). The resulting imbalance of protein turnover – suppression of protein synthesis and stimulus to protein breakdown - leads to muscle mass loss. Within the first ten days of intensive care unit (ICU) stay, loss of muscle mass can reach up to 20 %, particularly among patients with a higher severity of illness (1,2).

Ensuring adequate protein supply is challenging in the critical care setting. Protein requirements vary among individuals and may fluctuate daily during the acute phase of critical illness (3). The concept of nitrogen balance (NB) is that the difference between nitrogen intake (protein delivered) and loss (urinary urea excretion) it reflects the gain or loss of total body protein (4-7). Studies suggest that appropriate nutritional support, particularly in terms of protein supply, might improve NB and, therefore, contribute to better outcomes in critically ill patients (5,6,8).

Based on expert opinion, guidelines recommend achieving neutral or positive NB, and a consensus about classification, cut-off points, and frequency is lacking (5). Carrying out NB is also time-consuming and costly, which must be taken into account when considering its routine use.

Even though an attractive strategy to optimize protein delivery, NB has been sparsely assessed as a prognostic tool in the ICU (9-11). Given the limited and heterogeneous data regarding NB and urinary parameters in relation to mortality and ICU outcomes, we conducted a prospective, observational, single-center study to evaluate whether NB in the first week of ICU stay was associated with clinically meaningful outcomes.

MATERIAL AND METHODS

Study design and participants

Adult patients admitted to the ICU of a tertiary teaching center in Southern Brazil were prospectively and non-consecutively enrolled between March 2019 and May 2022. Data collection was interrupted between April 2020 and May 2021 owing to the SARS-CoV-2 outbreak. Exclusion criteria were renal failure (creatinine > 2 mg/dL, glomerular filtration rate < 30 mL/min, or renal replacement therapy), liver failure (bilirubin > 3 times the reference value), diarrhea (liquid feces > 3 times a day), pregnancy, palliative care, neurological diseases with pronounced loss of muscle mass, burn patients, BMI < 18.5 and ≥ 40.0 kg/m², oral intake in the first 24-hour urinary measurement, and COVID-19 infection within two months before ICU admission (for patients admitted between June 2021 and May 2022). Patients were followed up to hospital discharge or death, whichever occurred first.

The primary outcome was ICU mortality. Secondary outcomes were hospital mortality, duration of MV, and ICU and hospital length of stay (LOS).

Procedures

Sociodemographic data were obtained from the electronic medical records. Patients were classified as clinical or surgical according to their admission diagnosis. Disease severity was evaluated using the Simplified Acute Physiology Score 3 (SAPS 3), Sequential Organ Failure Assessment Score (SOFA), and Acute Physiology and Chronic

Health Evaluation II (APACHE II). Patients were further dichotomized according to SAPS 3 points into low risk (< 60 points) and high risk of mortality (> 60 points).

Nutritional status was evaluated using the Nutritional Risk Screening 2002 (NRS-2002) and Nutrition Risk in the Critically Ill (NUTRIC) modified, and patients were classified as having a high nutritional risk when they scored ≥ 5 points.

The 24-hour urine collections were performed at two time points during the first week in the ICU: between days 1 and 2, and between days 5 and 7 of ICU admission. A third variable was calculated from the average of the values of the first and second 24-hour urinary urea excretion (UUE) and urinary creatinine excretion (UCE). Calorie and protein intake data were obtained from the patient's records in the same 24-hour period of urinary collection. The nutritional support route and needs, were determined by clinical staff, which performed adjustments in energy and protein requirements unaware of urinary measurements following the institutional protocol.

NB was calculated as following: Protein intake (g/day) / 6.25 - Urinary urea nitrogen (g/day) - 4 g/day (12). NB was classified as negative when nitrogen intake was less than excretion (< -4 g/day), positive when nitrogen intake was higher than excretion (> +4 g/day), and neutral or in equilibrium when nitrogen intake and excretion were the same (-4 to +4 g/day) (13). Patients who received oral nutrition therapy in the second urinary collection did not have NB calculated because of the impossibility of estimating nitrogen intake. The NB delta was the difference between the second and first NB.

All procedures were performed following the ethical standards of the National Research Committee and the 1964 Helsinki Declaration. This study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre (2019-0063). Informed consent was obtained from all patients.

Statistical analysis

Adopting a specificity of 86 % and sensitivity of 75 %, assuming 40 % of ICU mortality and considering 10 % of losses, 100 patients would be needed to determine the predictive performance of NB on ICU mortality (14,15).

Categorical variables were described as absolute and relative frequencies. Continuous variables were analyzed for normality using the Shapiro-Wilk test, with parametric variables defined as mean ± standard deviation and non-parametric variables as mean (interquartile range). Correlations between continuous variables were analyzed using Pearson or Spearman tests. Associations were analyzed using the chi-squared test. Comparisons between means of the two groups were performed using Student's t-test, and for medians, the Mann-Whitney test was used. To compare the means of three or more groups, analysis of variance (ANOVA) with Bonferroni's post-hoc test was used, whereas medians were compared using the Kruskal–Wallis test. To identify the risk factors associated with mortality in the ICU, multiple logistic regression analyses were performed. Receiver Operating Characteristic (ROC) curve was also performed to analyze sensibility, specificity, and accuracy of UUE, UCE, and NB regarding ICU and hospital outcomes. Differences were considered statistically significant at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY).

RESULTS

Population characteristics

Of the 1710 screened patients, 127 met the inclusion criteria, of which 100 completed two 24-hour urinary collections (Fig. 1). The main exclusion criteria were acute renal failure (56.5 %) and oral intake during the first 24-hour urinary measurement (36.1 %).

The baseline characteristics of the included patients were 58 ± 16 years, 52.8 % were elderly, 52.0 % male, 89.0 % were caucasian and 87.0 % were admitted to the ICU for clinical purposes (respiratory 32.3 %, neurological 30.7 %, cardiovascular 7.9 %, sepsis 7.9 %). The most common comorbidities were hypertension (42.5 %), diabetes (26.0 %), neoplasia (23.6 %), and chronic obstructive pulmonary disease (13.4 %) (Table I).

Regarding severity and prognosis scores, 79 (62.2 %) patients had a SAPS 3 ≥ 60 points, and 54 (42.5 %) had a SOFA score of > 3 organ dysfunctions. The ICU and hospital mortality rates were 28 (22 %) and 39 (30.7 %), respectively.

Nutritional and anthropometric characteristics

High nutritional risk according to the NRS-2002 and NUTRIC modified was identified in 30 % and 48 % of patients, respectively. Regarding to standard nutritional evaluation, 24 % of the patients had obesity and 24 % had a calf circumference < 31 cm.

Among the evaluated patients, 84.3 % received early nutritional therapy. In the first evaluation, enteral nutrition was the most prevalent nutritional support (77 %), followed by nil per os support (16 %). A small proportion of patients were on parenteral nutrition (6 %), and only one patient received both interventions (1 %). Comparing the first and second assessments, an increase in calorie and protein intake was observed, as well as an improvement in NB (p < 0.01) (Table II).

Patients undergoing parenteral nutrition in the first evaluation received greater calorie (1482 ± 500 kcal/day vs. 779 ± 381 kcal/day, p < 0.05) and protein (88 ± 28 g/day vs. 39 ± 21 g/day, p < 0.05) supply than those receiving enteral nutrition. NB in the parenteral nutrition group was less negative 0.5 (-6.4 to 2.4) g/day compared to -7.4 (-10.5 to -4.1) g/day in the enteral nutrition group (p < 0.05).

In the second evaluation, 79 % were on enteral nutrition, 7 % on parenteral nutrition, 11 % with oral feeding, one patient received both

nutritional therapies and two patients were on *nil per os*. Calorie (1435 ± 514 kcal/day vs. 1355 ± 481 kcal/day, $p = 0.60$), protein (90 ± 33 kcal/day vs. 85 ± 34 kcal/day, $p = 0.67$) intake, and NB -3.6 (-4.2 to 2.9) vs -2.8 (-9.2 to 1.3) g/day ($p = 0.49$) were similar for parenteral and enteral nutrition, respectively.

Urinary parameters

Among the included patients, 81 % started the first urine collection on day 1, and 82 % had the second measurement initiated on day 5. Table II shows the comparison between the first and second urinary collections. There was an increase in UUE, calorie, and protein intake, and a decrease in UCE and serum creatinine between collections 1 and 2. NB showed improvement between both collections. At both time points, a significant positive correlation was observed between UUE, UCE, and anthropometric parameters (weight, BMI, and calf circumference) (Supplementary Table I). Comparing according to disease severity, patients with SAPS > 60 points had higher UUE (26.1 ± 11.5 vs. 22.4 ± 10.7 g/day) and lower UCE (1046 ± 455 vs. 954 ± 436 mg/day) when compared to patients with lower scores, although no statistically significant difference was observed.

In the first collection, negative NB was observed in 77 % of the patients. Individuals with negative NB had higher 24-hour UUE, UCE and BMI; and lower protein and calorie intake than patients with positive NB. NB showed a significant negative correlation with anthropometric parameters (Supplementary Table I). In the second measurement, 47.2 % of patients had negative NB. The negative NB group revealed patients with higher excretion of urinary parameters, such as 24-hour UUE, and UCE.

Analyzing the groups according to the NB classification, individuals with negative NB had higher calf circumference values, higher UUE and UCE, but lower protein-calorie intake than the group with positive NB in both urinary measurements (Table I). Comparing NB delta groups, no difference was observed regarding primary and secondary

outcomes, and also no correlation was found between NB delta and clinical parameters.

Outcomes

The ROC curve performances for urinary parameters and NB could not discriminate ICU and hospital outcomes. There was no cut-off point for sensibility or specificity identified in the ROC curve for UUE and UCE regarding mortality in ICU or hospital both in the first and second urinary collections (Supplementary Fig. 1 and Fig. 2). NB evaluations were not discriminatory regarding mortality in the ICU and hospital, considering the area under the curve (Supplementary Fig. 3).

Regarding hospital outcomes, patients who were discharged from the hospital had higher UCE values, both in the first [961 (765 to 1426) vs. 771 (585 to 1048) mg/day, $p < 0.05$] and second [929 (715 to 1267) vs. 683 (516 to 1000 mg/day, $p < 0.05$] collections when compared to non-survivors. No correlation was found between 24-hour UUE and UCE concerning mechanical ventilation (MV) time, and LOS in ICU or hospital. Neither urinary parameters nor NB were associated with ICU mortality in any of the evaluations (Table III).

DISCUSSION

In our study, we found no association between NB or UUE measured at two different time points in the first week of ICU stay and ICU or in-hospital mortality. However, we observed higher urinary creatinine levels in hospital survivors during both periods. Also, UUE and UCE were positively correlated with anthropometric parameters, as weight, BMI and calf circumference. Considering that UCE is influenced by the amount of muscle mass, these results may be related to the fact that individuals with greater UCE may have a greater proportion of muscle mass. To our knowledge, this is the first study to evaluate UUE, UCE and NB in the first week of ICU as prognostic markers of mortality.

Critically ill patients experience high muscle wasting, which is

associated with ICU morbidity and mortality (2,16-18). Some studies suggest that protein supply should not necessarily be high in all phases of critical illness, but should be offered in smaller amounts in the early acute phase and progressively increased in the late acute phase (19,20).

Although NB is the gold standard for guiding protein intake in the latest ESPEN guidelines, several pitfalls are associated with its use. First, it takes a great deal of time to collect, and urinary collections can be lost, reducing the exam's accuracy. Second, NB requires a detailed registry of all patient nutrition during the urine collection period. Third, only a minority of critically ill patients were eligible for the NB calculation, due to loss of kidney function.

A recent systematic review and meta-analysis suggested that the improvement in NB is associated with reduced ICU mortality. This systematic review included patients with severe renal dysfunction, however the observed results may reflect the association between NB and renal function recovery (21). On the other hand, a cohort study of 234 critically ill patients whose NB was evaluated at different times during hospitalization (ICU days 1, 5, and 10) found no association between NB and ICU mortality (11).

Two recent studies evaluated the predictive value of urinary parameters and NB in patients with severe SARS-CoV-2 infection. Leyderman et al. found no significant predictive value for urinary nitrogen excretion and revealed a non-significant area under the curve for worse outcomes in the ICU. Dupuis et al. evaluated the trajectory of NB in COVID patients and stated that NB was higher in survivors (9,22).

Regarding UUE, it is known that its excretion is influenced by the phase of critical illness, increasing progressively throughout the first week of ICU stay (22,23). Additionally, protein supply can also affect UUE by increasing its excretion as protein intake increases (24,25). However, the literature needs studies assessing the effectiveness of

UUE as a predictor of outcomes in the ICU. In our research, UUE was not associated with improved ICU outcomes.

Serum creatinine reflects muscle mass reserve and can be used as a predictor of mortality in ICU (26-28). UCE can show a daily reduction of ≥ 1 % in chronically critically ill patients (≥ 31 days) (23). A retrospective cohort of 11,291 critically ill patients showed that low baseline serum creatinine level was associated with increased mortality in the ICU, even after adjustment for potential confounders (28). In another study, Hessels et al. (2018) analyzed UCE in 6,151 critically ill patients within the first three days of ICU admission and found that patients in the lowest UCE quintile had a higher risk of short- and long-term mortality than patients in the highest UCE quintile, adjusted for confounders (29). In our study, the survivors had higher urinary creatinine levels than those who died.

The present study has some limitations. Firstly, due to its observational design, we could not evaluate the impact of changing protein intake based on NB. Our strict recruitment criteria may limit the generalizability of our results, but we aimed to avoid bias, particularly associated with renal failure and the predictive value of NB. However, since limited data exists on the prognostic value of nitrogen parameters in the ICU, this study certainly helps fill a gap in the literature. Due to its clinical nature, we only evaluated clinical outcomes and not those associated with protein synthesis and breakdown. Our study was not designed to evaluate post-ICU sarcopenia, functional capacity, or long-term quality of life. Furthermore, outcomes in critically evaluations should go beyond “dead” or “alive”, since long-term quality of life is lower for critically ill patients compared to that an age- and gender-matched healthy population (30).

In conclusion, nitrogen metabolites, including UUE, UCE, and NB, were not associated with ICU or hospital mortality during the first week of ICU stay. Intervention trials might further shed light on the best moment to analyze NB in order to guide protein supply during critical

illness.

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Table I. Comparison between NB groups in the first and second urinary collection regarding anthropometric, nutritional and clinical variables

Variables	**Overall**	**1st 24-hour urinary collection (*n* = 127)**			**2nd 24-hour urinary collection (*n* = 100)**		
		Positive NB	**Negative NB**	***p*-value**	**Positive NB**	**Negative NB**	***p*-value**
Age, years	58 ± 16	55 ± 16	58 ± 16	0.36	63 ± 14	53 ± 15	< 0.05
Weight, kg	70.1 ± 15.2	62.2 ± 10.2	72.5 ± 15.7	< 0.01	67.8 ± 16.9	73.9 ± 15.8	0.08
BMI, kg/m²	26.4 ± 5.3	24.2 ± 3.7	27.0 ± 5.5	< 0.05	25.9 ± 5.5	27.4 ± 5.5	0.24
Calf circumference, cm	33 ± 4	31.5 ± 2.8	33.9 ± 4.2	< 0.01	32.2 ± 4.5	34.4 ± 4.1	< 0.05
UUE, g/day	-	14.1 ± 5.4	23.2 ± 9.8	< 0.01	21.3 ± 10.1	36.3 ± 15.4	< 0.01
UCE, mg/day	-	708 ± 180	1114 ± 476	< 0.01	783 ± 372	1167 ± 486	< 0.01
Protein intake, g/day	-	64 (44 to 71)	35 (21 to 49)	< 0.01	94 (72 to 108)	69 (44 to 104)	< 0.05
Calorie intake, g/day	-	1168 (869 to 1398)	704 (430 to 966)	< 0.01	1564 (1256 to 1742)	1242 (713 to 1657)	< 0.01
Charlson index, points	3 (2 to 5)	3 (2 to 5)	4 (2 to 5)	0.65	4 (3 to 6)	3 (2 to 4)	< 0.05
APACHE II, points	20 ± 5	20 ± 5	20 ± 5	0.93	22 ± 5	20 ± 6	0.09

SOFA on 1st day, points	6 ± 3	5 (3 to 7)	6 (4 to 8)	0.07	6 (3 to 8)	6 (4 to 8)	0.97
SAPS 3, points	65 ± 15	63 ± 13	65 ± 16	0.45	65 ± 14	64 ± 18	0.87
NRS-2002, points	4 (3 to 5)	4 ± 1	4 ± 1	0.34	4 ± 1	4 ± 1	0.06
NUTRIC, points	4 (3 to 5)	4 ± 2	4 ± 2	0.22	5 ± 2	4 ± 2	0.11
MV time, day	6 (4 to 10)	5 (3 to 7)	6 (4 to 11)	0.14	7 (4 to 12)	7 (5 to 11)	0.81
ICU LOS, days	9 (7 to 14)	9 (6 to 12)	10 (7 to 15)	0.19	11 (8 to 17)	12 (8 to 19)	0.66
Hospital LOS, days	24 (14 to 38)	23 (13 to 45)	24 (15 to 35)	0.79	26 (19 to 44)	25 (13 to 41)	0.27

APACHE: Acute Physiology and Chronic Health Evaluation; BMI: body mass index; ICU: intensive care unit; MV: mechanical ventilation; LOS: length of stay; NUTRIC: Nutrition Risk in The Critically Ill; NRS: Nutritional Risk Screening; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment Score.

Variables	**collection (*n* = 127)**	**collection (*n* = 100)**	***p*-value**
UUE, g/day	19 (14 to 27)	25 (15 to 36)	< 0.01
UCE, mg/day	905 (692 to 1305)	829 (607 to 1218)	< 0.01
Serum creatinine, mg/dL	0.9 (0.7 to 1.2)	0.7 (0.6 to 0.9)	< 0.01
Body temperature, °C	37.3 (36.8 to 37.7)	37.2 (36.8 to 37.8)	0.79
Energy, kcal/day	793 (496 to 1130)	1399 (1083 to 1731)	< 0.01
Energy, kcal/kg ABW	11 (7 to 18)	21 (15 to 25)	< 0.01
Protein intake, g/day	40 (25 to 58)	86 (64 to 107)	< 0.01
Protein intake, g/kg ABW	0.6 (0.4 to 0.9)	1.3 (1.0 to 1.5)	< 0.01
NB, g/day	-7.9 (-11.3 to -4.5)	-3.3 (8.9 to 1.3)	< 0.01

Negative NB, *n* (%)	98 (77.2)	42 (47.2)	0.05

ABW: actual body weight; NB: nitrogen balance; UCE: urinary creatinine excretion; UUE: urinary urea excretion. Data are expressed as *n* (%), mean ± SD or median (interquartile range). 2nd NB was calculated for 89 individuals.

Table III. Comparison between patients who died and were discharged from ICU (n = 127)

Variables	**Death (n = 28)**	**Discharge (n = 99)**	***p*-value**
Age, years	61 ± 16	57 ± 16	0.151
Urinary urea, g/day*	23.2 ± 9.2	25.1 ± 11.9	0.475
Urinary creatinine, mg/day*	885 ± 430	1027 ± 446	0.168
NB, g/day	-6.9 (-9.9 to -2.6)	-5.8 (-10.6 to -2.3)	0.949
Weight, kg	68.2 ± 13.7	70.7 ± 15.6	0.443
BMI, kg/m²	26.6 ± 5.9	26.3 ± 5.1	0.834
Calf circumference, cm	32.6 ± 4.4	33.7 ± 3.9	0.260
Calorie intake, g/day	918 ± 452	1091 ± 398	0.252
Protein intake, kcal/day	55 ± 26	62 ± 26	0.055
Charlson index, points	4 (3 to 6)	3 (2 to 5)	< 0.05
APACHE II, points	23 ± 6	19 ± 5	< 0.05
SOFA on 1st day, points	7 (4 to 8)	6 (4 to 7)	0.082
SAPS 3, points	70 ± 20	63 ± 13	0.098
NRS-2002, points	4 ± 1	4 ± 1	0.050
NUTRIC, points	5 (4 to 6)	4 (3 to 5)	< 0.05
MV time, day	9 (6 to 14)	5 (3 to 9)	< 0.05
ICU LOS, days	11 (7 to 17)	9 (6 to 13)	0.080
Hospital LOS, days	15 (9 to 32)	25 (16 to 39)	< 0.05

APACHE: Acute Physiology and Chronic Health Evaluation; BMI: body mass index; ICU: intensive care unit; MV: mechanical ventilation; LOS: length of stay; NUTRIC: Nutrition Risk in The Critically Ill; NRS: Nutritional Risk

Screening; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment Score. Data are expressed as *n* (%), mean ± SD or median (interquartile range). *Mean between first and second measurements.

Supplementary Table I. Correlations between urinary parameters and NB with anthropometric, nutritional and clinical variables (*n* = 127)

Variables	**1st Urinary Urea, g/day**		**2nd Urinary Urea, g/day**		**1st Urinary Creatinine, g/day**		**2nd Urinary Creatinine, mg/dL**		**1st Nitrogen Balance, g/day**		**2nd Nitrogen Balance, g/day**	
	r	***p*-value**	***r***	***p*-value**	***r***	***p*-value**	***r***	***p*-value**	***r***	***p*-value**	***r***	***p*-value**
Weight, kg	0.361	< 0.01	0.514	< 0.01	0.654	< 0.01	0.696	< 0.01	-0.346	< 0.01	-0.185	0.08
BMI, kg/m²	0.228	< 0.05	0.360	< 0.01	0.451	< 0.01	0.508	< 0.01	-0.177	< 0.05	-0.074	0.49
Calf circumference, cm	0.285	< 0.01	0.454	< 0.01	0.678	< 0.01	0.714	< 0.01	-0.323	< 0.01	-0.197	0.07
Charlson index, points	-0.067	0.45	-0.264	< 0.01	-0.354	< 0.01	-0.419	< 0.01	0.038	0.67	0.247	< 0.05

APACHE II, points	-0.105	0.24	-0.176	0.08	-0.244	< 0.01	-0.227	< 0.05	-0.009	0.92	0.185	0.08
SOFA on 1st day, points	0.001	0.99	-0.091	0.37	-0.044	0.63	-0.081	0.42	-0.159	0.07	0.018	0.87
SAPS 3, points	-0.086	0.33	0.057	0.57	-0.305	< 0.01	-0.178	0.08	0.052	0.56	0.078	0.47
NRS-2002, points	-0.127	0.16	-0.282	< 0.01	-0.423	< 0.01	-0.392	< 0.01	0.210	< 0.05	0.237	< 0.05
NUTRIC, points	-0.044	0.62	-0.149	0.14	-0.327	< 0.01	-0.340	< 0.01	0.015	< 0.05	0.149	0.16
MV time, day	0.125	0.18	0.175	0.09	0.073	0.44	0.118	0.26	-0.098	0.29	0.078	0.49
ICU LOS, days	0.023	0.80	0.105	0.30	0.060	0.51	0.097	0.34	-0.094	0.29	0.008	0.94
Hospital LOS, days	0.004	0.96	0.041	0.69	-0.073	0.42	-0.053	0.60	0.051	0.57	0.155	0.15

APACHE: Acute Physiology and Chronic Health Evaluation; BMI: body mass index; ICU: intensive care unit; MV: mechanical ventilation; LOS: length of stay; NUTRIC: Nutrition Risk in The Critically Ill; NRS: Nutritional Risk Screening; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment Score.

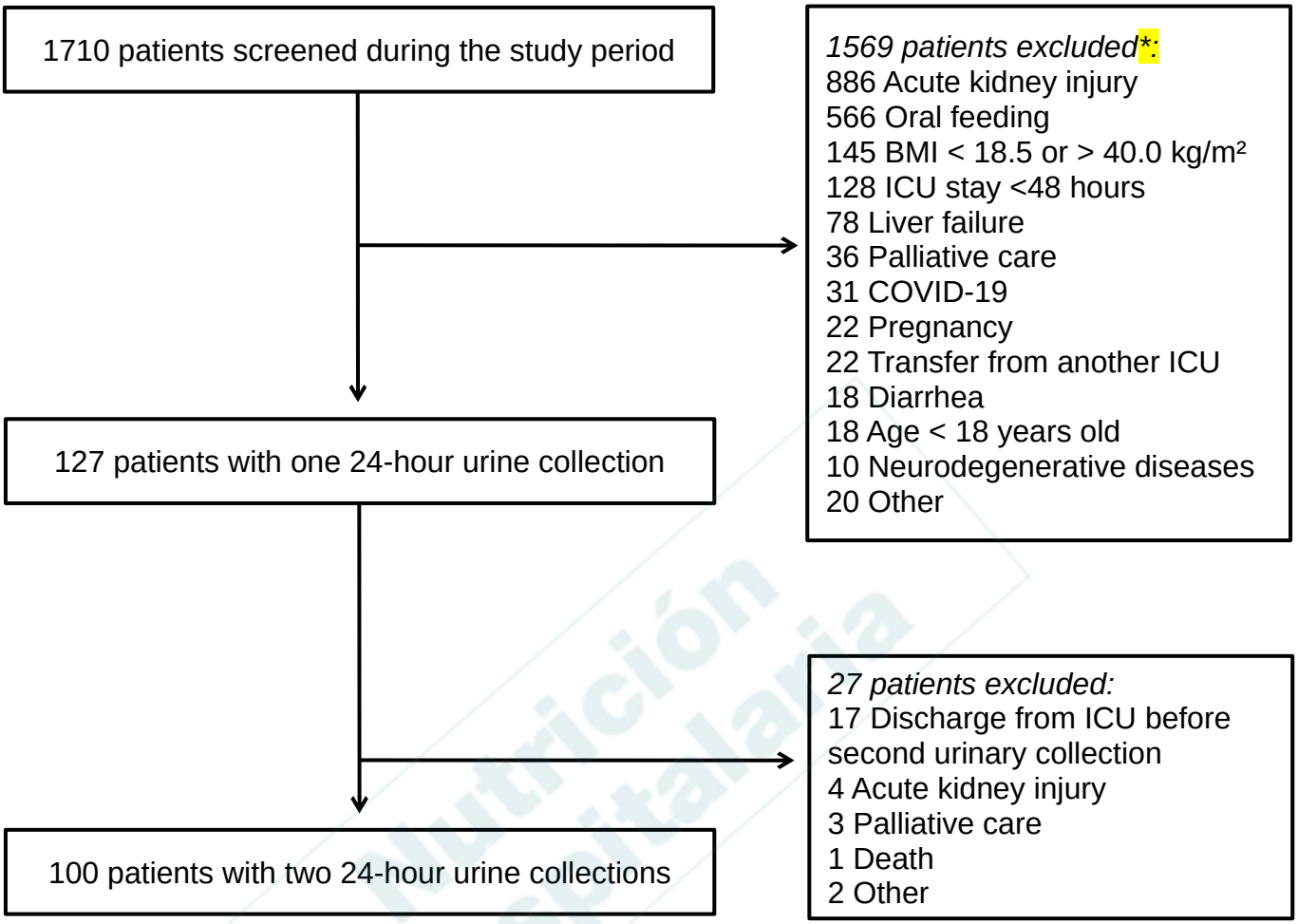
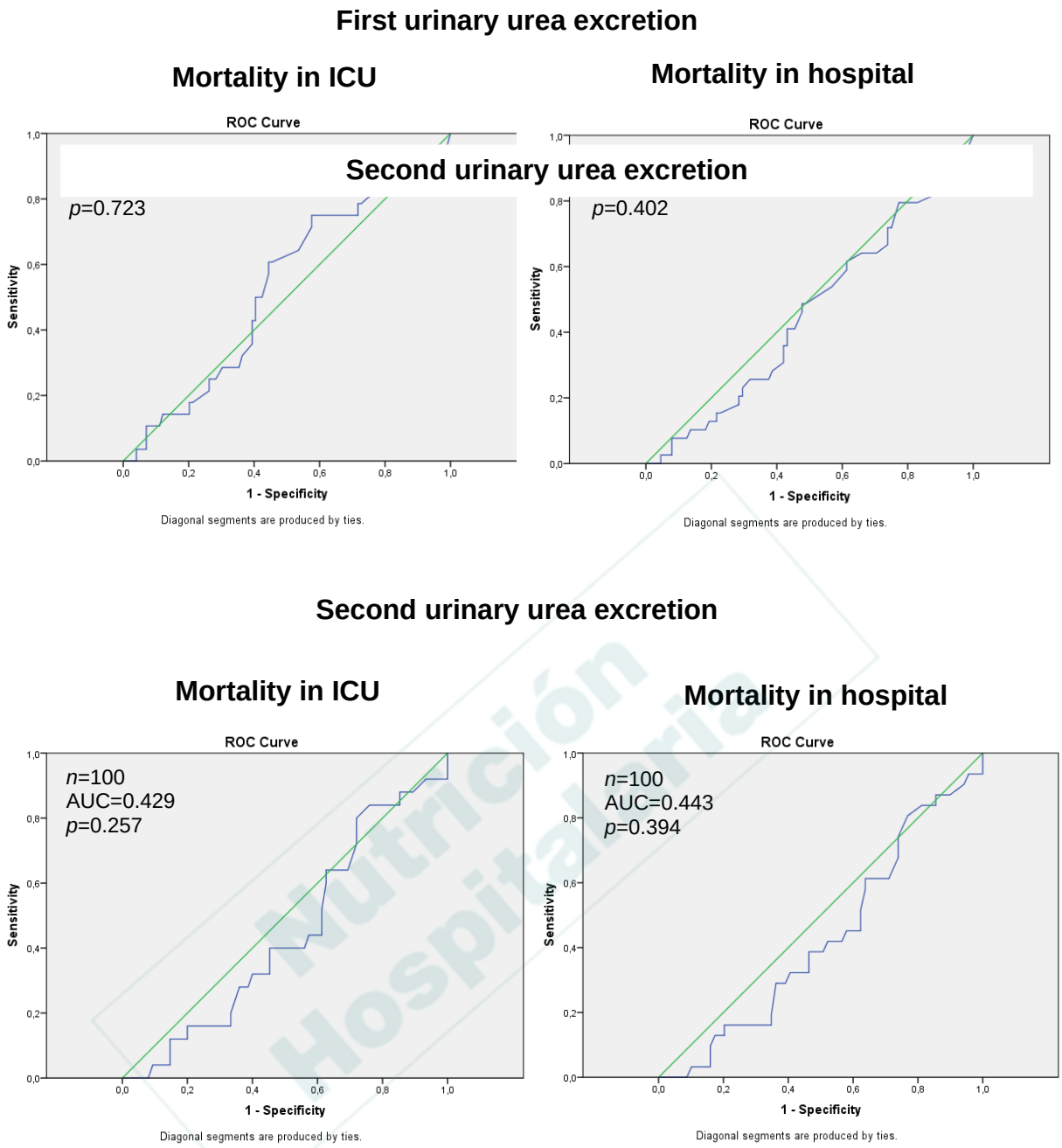
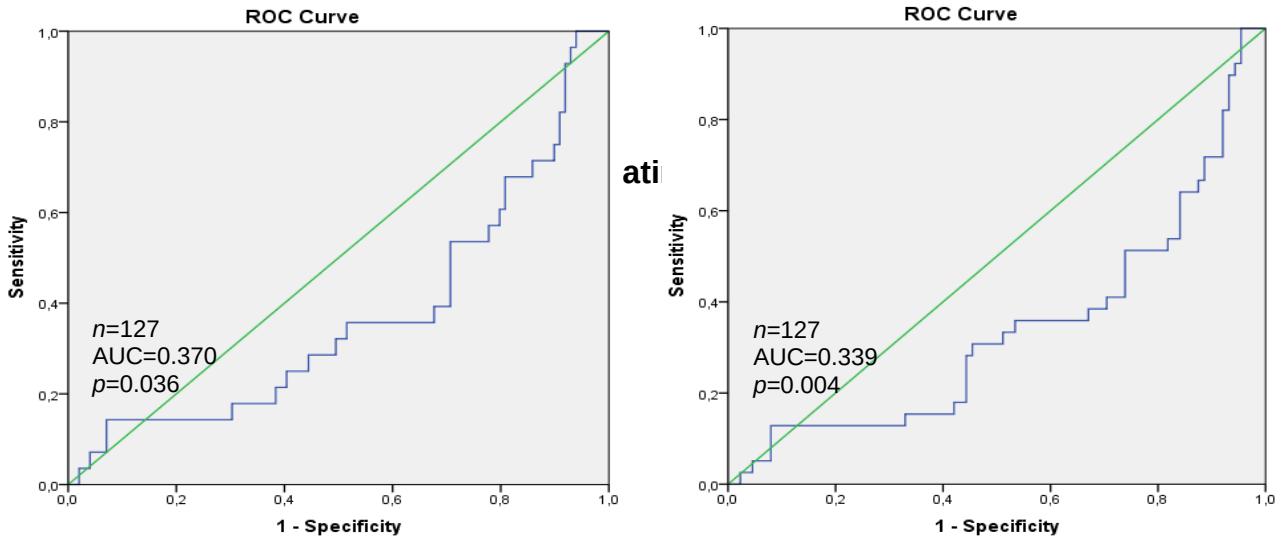


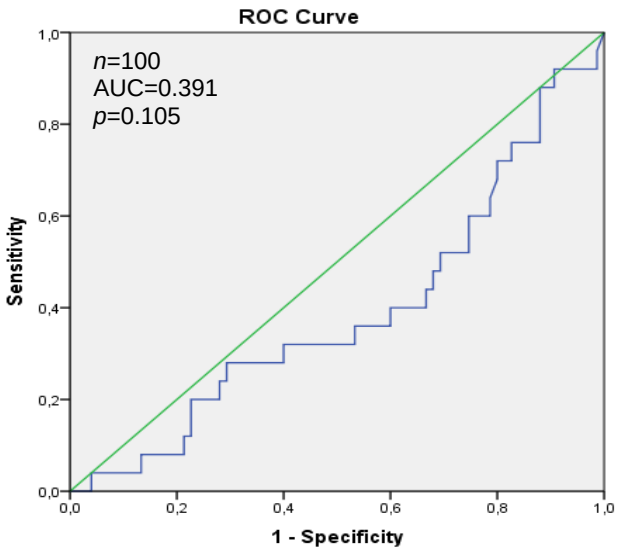
Figure 1. Flowchart of study inclusion (BMI: body mass index; ICU: intensive care unit. *Some patients can have more than one exclusion criteria).



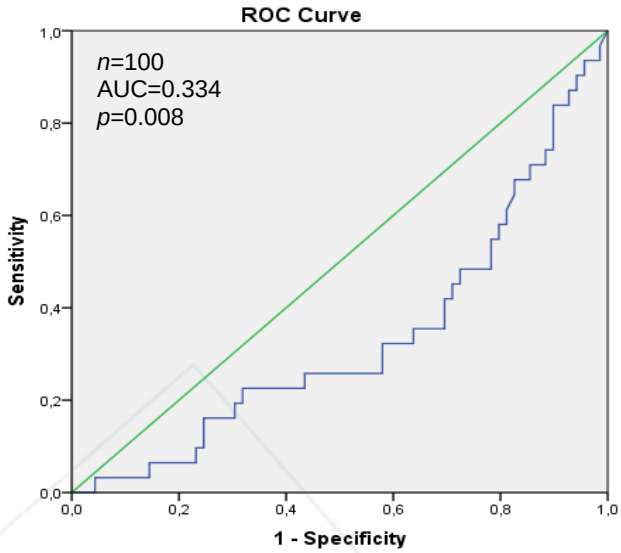
Supplementary Figure 1. The ROC curves performance for UUE as a discriminating factor for ICU and hospital mortality.



Mortality in ICU



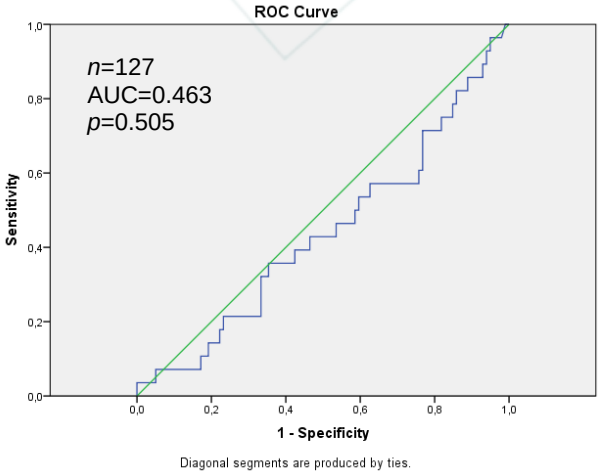
Mortality in hospital



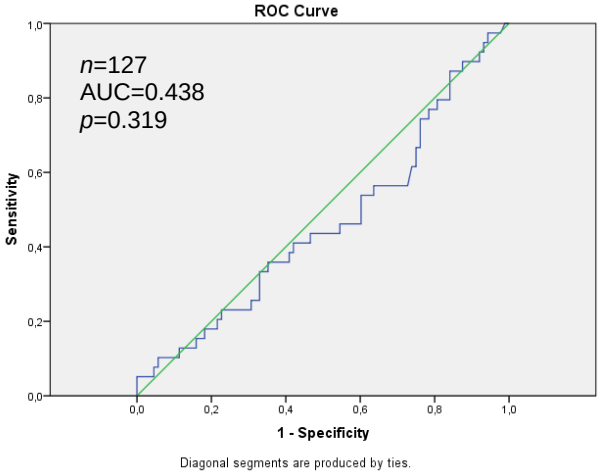
Supplementary Figure 2. The ROC curves performance for UCE as a discriminating factor for ICU and hospital mortality.

First nitrogen balance

Mortality in ICU

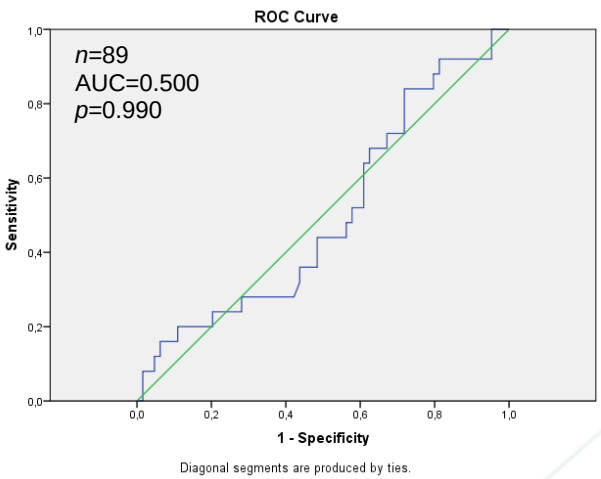


Mortality in hospital

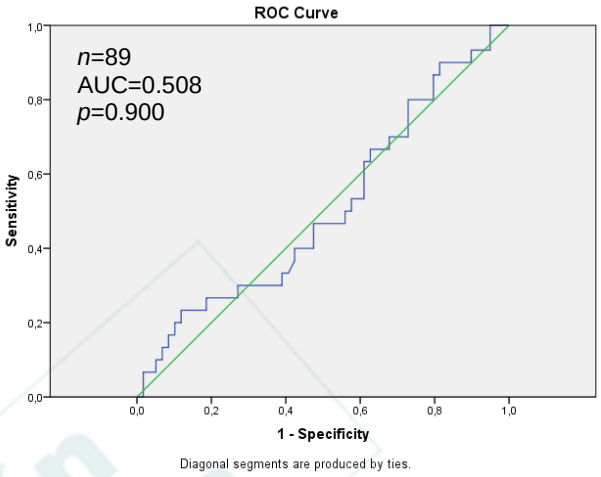


Second nitrogen balance

Mortality in ICU



Mortality in hospital



Supplementary Figure 3. The ROC curves performance for NB as a discriminating factor for ICU and hospital mortality.