CLINICS

CLINICAL SCIENCE

Nutritional parameters are associated with mortality in acute kidney injury

Marina Nogueira Berbel,* Cassiana Regina de Góes, André Luis Balbi, Daniela Ponce

Botucatu School of Medicine, UNESP, Internal Medicine, Botucatu/SP, Brazil.

OBJECTIVE: The objective of this study was to perform a nutritional assessment of acute kidney injury patients and to identify the relationship between nutritional markers and outcomes.

METHOD: This was a prospective and observational study. Patients who were hospitalized at the Hospital of Botucatu School of Medicine were evaluated between January 2009 and December 2011. We evaluated a total of 133 patients with a clinical diagnosis of acute kidney injury and a clinical presentation suggestive of acute tubular necrosis. We explored the associations between clinical, laboratory and nutritional markers and in-hospital mortality. Multivariable logistic regression was used to adjust for confounding and selection bias.

RESULTS: Non-survivor patients were older (67 ± 14 *vs.* 59 ± 16 years) and exhibited a higher prevalence of sepsis (57.1 *vs.* 21.4%) and higher Acute Tubular Necrosis-Individual Severity Scores (0.60 ± 0.22 *vs.* 0.41 ± 0.21) than did survivor patients. Based on the multivariable analysis, laboratorial parameters such as blood urea nitrogen and C-reactive protein were associated with a higher risk of death (OR: 1.013, $p = 0.0052$; OR: 1.050, $p = 0.01$, respectively), and nutritional parameters such as low calorie intake, higher levels of edema, lower resistance based on bioelectrical impedance analysis and a more negative nitrogen balance were significantly associated with a higher risk of death (OR: 0.950, $p = 0.01$; OR: 1.138, $p = 0.03$; OR: 0.995, $p = 0.03$; OR: 0.934, $p = 0.04$, respectively).

CONCLUSIONS: In acute kidney injury patients, a nutritional assessment seems to identify nutritional markers that are associated with outcome. In this study, a low caloric intake, higher C-reactive protein levels, the presence of edema, a lower resistance measured during a bioelectrical impedance analysis and a lower nitrogen balance were significantly associated with risk of death in acute kidney injury patients.

KEYWORDS: Acute Kidney Injury; Anthropometry; Nitrogen Balance; Nutrition; Nutrition Assessment.

Bebel MN, Góes CR, Balbi AL, Ponce D. Nutritional parameters are associated with mortality in acute kidney injury. Clinics. 2014;69(7):476-482.

Received for publication on September 26, 2013; **First review completed on** October 29, 2013; **Accepted for publication on** January 13, 2014

E-mail: mnberbel@yahoo.com.br

*corresponding author

Tel.: 55 14 97885993

INTRODUCTION

Acute kidney injury (AKI) is a common clinical complication, particularly in intensive care units (ICUs). It affects approximately 5% of patients requiring renal replacement therapy (RRT), with mortality rates as high as approximately 60% (1). Clinical conditions such as age, mechanical ventilation requirement, vasopressors and septic shock are conditions that significantly contribute to an increased in-hospital mortality rate in these patients (2).

Nutritional and metabolic factors, such as hypercatabolism and pro-oxidative and proinflammatory states also predispose these patients to higher mortality rates (3).

Although it is known that AKI affects the metabolism of all macronutrients and causes important consequences for the nutritional status and prognosis of AKI patients, a clear understanding of the changes and their associations with important clinical prognostic factors remains elusive.

Laboratory parameters such as prealbumin, albumin, IGF-1 and cholesterol are described as risk factors for increased mortality (4-7). The presence of pre-existing severe malnutrition is also associated with a higher incidence of complications, longer hospital length of stay and increased mortality in AKI patients (8). Nitrogen balance, which is a marker of the extent of hypercatabolism and is the main nutritional problem in these patients, also showed a significant association with mortality in this population (9-10).

However, there are still few data available on the nutritional status of this population or the existence of an association between nutritional markers and important clinical outcomes.

The goals of this study were to compare the clinical, laboratory and nutritional characteristics of surviving and non-surviving AKI patients who were evaluated in a Brazilian teaching hospital and to generate a hypothesis

No potential conflict of interest was reported.

DOI: 10.6061/clinics/2014(07)06

regarding the relationship between nutritional markers and outcomes.

METHODS

Ethics statement

The authors declare that this work was approved by the research ethics committee of Botucatu School of Medicine University Hospital. Participants provided their written informed consent to participate in this study. The ethics committee approved this consent procedure.

This was a prospective and observational study performed from January 2009 to December 2011. A total of 133 patients with a clinical diagnosis of AKI and a clinical presentation suggestive of acute tubular necrosis (ATN) who were admitted to Botucatu School of Medicine University Hospital, São Paulo, Brazil were included. Patients were required to have a minimum of 7 days of follow up by the nephrology and nutrition team.

The diagnosis of AKI was based on serum creatinine levels, as proposed by the Acute Kidney Injury Network (AKIN) (1). Patients under 18 years old with AKI of other etiologies, those requiring chronic renal replacement therapy (dialysis or transplantation) and those with a history of severe chronic kidney disease (baseline serum creatinine >4 mg per 100 ml) were excluded. AKI patients were followed prospectively from the day of the first nephrology evaluation until nephrology discharge. The clinical characteristics were recorded on the first day and the laboratory and nutritional characteristics were recorded on the first day and every 7 days during the hospital stay.

For the classification of CKD stage, the baseline serum creatinine was defined as the lowest serum creatinine value in the last 6 months before AKI or, for patients without this measurement, the lowest value achieved during hospitalization in the absence of dialysis. Patients with CKD were considered to have stage 2 of the disease.

Nutritional assessment protocol

The Nutritional Assessment was based on the SGA (Subjective Global Assessment), biochemical parameters, anthropometry and bioelectrical impedance analysis (BIA) and was performed daily or weekly from the first nephrology evaluation until recovery of kidney function or the patient's death (8).

On the first day, clinical characteristics were measured and an SGA was performed (9). Daily, blood urea nitrogen (BUN), serum creatinine, and protein and energy intake were measured, and the nitrogen balance (NB) was calculated based on the excess of urea nitrogen appearance (UNA) formula (3), as calculated below:

Nitrogen Balance = dietetic nitrogen intake – ureic nitrogen appearance

Dietetic nitrogen (g/day) = dietetic protein (g/day)/6.25

Ureic nitrogen appearance (gN/day) = (UUN × V) + (BUN2 – BUN1) × 0.6 × BW (kg) + (BW2–BW1) × BUN2/100

For patients on dialysis, nitrogen losses through the dialysate were added to the UNA using the following formula:

Dialysate urea nitrogen (gN) x dialysate volume (l)

The rate of catabolism was calculated daily according to the net protein breakdown (13):

UNA × 6.25/body weight (kg)

Anthropometry and BIA were performed once a week. Ambulatory patients were weighed on a digital scale, whereas the weight of non-ambulatory patients was obtained using a bed scale. Arm circumference and triceps skin-fold thickness (TST) were also evaluated. BIA was performed using the single frequency equipment *Biodynamics model 450*. It provided results including resistance (ohms), reactance (ohms) and phase angle (°). In patients who were treated with hemodialysis, BIA was performed 30 minutes after the end of the session.

Albumin (g/dl), transferrin (g/dl), prealbumin (g/dl), total cholesterol (mg/dl), total lymphocyte count ($mm/^3$), phosphorus (mg/dl), potassium (mmol/l) and C reactive protein (CRP) serum levels (mg/dl) were measured once a week.

Statistical analysis

AKI patients were divided into two groups, survivors and non-survivors, and the study variables were compared between the groups. The results are presented as the mean and s.d. or the median, according to normality characteristics for each variable, with a 5% ($p<0.05$) significance level. The *t*-test was used to compare parametric variables of clinical, laboratory and nutritional data. For non-parametric variables, the *Mann-Whitney test* was used.

Statistical analyses were conducted using SAS version 9.2 for Windows

Variables with significant univariate associations ($p<0.20$) were candidates for the multivariable analysis. Multivariable logistic regression was performed using stepwise variable selection. Variables that were not selected by the automated procedure were added back into the models individually to evaluate them for residual confounding, and covariate and propensity score adjustments were used to adjust for baseline differences.

RESULTS

A total of 133 AKI patients were followed and the mortality rate of this group was 26.3%. Table 1 shows the baseline clinical characteristics of the studied patients. Non-surviving patients were older and exhibited more ICU admissions, a higher prevalence of sepsis and more severe ATN-ISS. They also showed a less favorable nutritional status based on a subjective global assessment in the first assessment.

Based on the characterization of the CKD stages, 12% of the patients were in stage 2, 6% were in stage 3A, 9.7% were in stage 3B and 8.2% were in stage 4.

In tables 2 and 3, the results are shown according to the baseline (first day) and the final assessment (last day for each patient) and were compared between survivors and non-survivors. The initial assessment was performed on day 1 and the final assessment was performed during the last week (considering that the patients were evaluated at the same time points: day 1, 7, 14, 21, 28…).

Table 2 shows the laboratory data of the survivors and non-survivors. At the final assessment, non-survivors showed significantly lower levels of albumin [(2.4 (2-2.9)

Table 1 - Clinical characteristics of the acute kidney injury patients according to survival.

Characteristics (%)	Survivors (n = 98)	Non-survivors (n = 35)	*p*
Male	72.2	58.3	0.29
Age (years)	59 ± 16	67 ± 14	0.01
Hospital wards:			
Clinics	68.4	68.6	0.85
Surgical	31.6	31.4	
Admission in [a]ICU	59.2	88.6	0.0031
Etiology of AKI:			
Ischemic	48	54.3	0.65
Nephrotoxic	20.4	2.9	0.03
Mixed	31.6	42.8	0.32
[b]DM	21.4	20	0.94
Hypertension	37.7	42.8	0.74
Sepsis	21.4	57.1	0.0002
CKD	25.5	17.1	0.44
Oliguria	20.4	25.7	0.68
Initial serum creatinine (mg/dl)	4.3 (2.9-6.25)	3.4 (2.50-4.85)	0.03
Classification for AKI:			
AKIN 1	10.2	11.4	0.91
AKIN 2	42,8	37,1	0,70
AKIN 3	43,9	45,7	0,99
Dialysis	53.1	71.4	0.09
Hemodialysis	36.7	54.3	0.11
Peritoneal Dialysis	16.3	17.1	0.91
[d]ATN-ISS	0.41 ± 0.21	0.60 ± 0.22	<0.0001
Days of hospitalization	26.3 ± 15.9	24.6 ± 11.2	0.97
Days of nephrologic and nutritional evaluation	13 (7-21)	14 (9-18)	0.52
Days of hospital stay before nutritional evaluation	6 (3-13)	9 (3.5-12)	0.95
Malnutrition by [e]SGA:			
Well nourished (Class A)	47	20	0.0095
Moderately malnourished (Class B)	36.7	60	0.02
Severely malnourished (Class C)	16.3	20	0.81
Type of diet			
Oral	45.9	17.1	0.0051
Enteral	45.9	60	0.22
Parenteral	8.2	22.9	0.04

a) ICU: intensive care unit.
b) DM: diabetes mellitus.
c) CKD: chronic kidney disease.
d) ATN-ISS: Acute Tubular Necrosis-Individual Severity Score.
e) SGA: Subjective Global Assessment.

vs. 2.0 (1.8-2.6), $p = 0.04$)], transferrin [(1.37(1.05-1.8) *vs.* 1.02(0.88-1.35), $p = 0.009$)], and cholesterol [(127.5 (102.8-158.3) *vs.* 108 (86-139), $p = 0.05$)] compared with survivors. Furthermore, all parameters were below normal values. Lower levels of initial creatinine [(3.4 (2.5-4.85)×4.3 (2.9-6.25), $p = 0.03$)] and higher levels of BUN [(49.5(41.3-79.6) *vs.* 40.4(23.7-55.1), $p = 0.002$] and CRP [(7.2 (3.3-21.9) *vs.* 15.3 (5.9-27.7), $p = 0.03$)] at the final assessment were also observed in the non-surviving patients.

Nutritional data are presented in table 3. Non-survivors had higher measures of arm circumference (31.6 ± 6.21 *vs.* 29.3 ± 4.95, $p = 0.03$) at the final assessment, in addition to higher estimated edema [(5(1-10.9) *vs.* 1.4(0-4.35), $p = 0.002$)]. Based on the BIA analysis, the non-survivors had lower values of phase angle [(4.6(3.5-5.25) *vs.* 5.1(4.08-6.43), $p = 0.04$)], resistance [(323 ± 105.6 *vs.* 410.9 ± 126.5, $p = 0.002$)], and reactance [(19.4(17.5-34.6) *vs.* 40.1(24.5-53.3), $p = 0.001$)] at the final assessment. Non-survivors presented lower calorie (7.2(2.15-14.8) *vs.* 12.9(5.6-22.3), $p = 0.01$)] and protein intake [(0.3(0.09-0.628) *vs.* 0.54(0.24-0.99), $p = 0.02$)] at the initial assessment, as well as major catabolism, as shown by a more negative nitrogen balance [(-3.56(-6.96 – 2.56) *vs.* -1.32(-2.84-5.10), $p = 0.004$)].

A total of 22 factors met the criteria for inclusion in the multivariable analysis, and in-hospital mortality was significantly associated with older age (OR: 1.038, CI: 1.004-1.072, $p = 0.02$), the presence of sepsis (OR: 1.710, CI: 0.103-0.815, $p = 0.02$), and higher ATN-ISS (OR: 1.029, CI: 1.007-1.052, $p = 0.01$). Increased levels of BUN (OR: 1.013, CI: 1.004-1.023, $p = 0.005$) and CRP (OR: 1.050, CI: 1.011-1.092, $p = 0.01$), initial lower caloric intake (OR: 0.950, CI: 0.910-0.991, $p = 0.02$), higher levels of edema (OR: 1.138, CI: 1.012-1.280, $p = 0.03$), increased resistance based on BIA (OR: 0.995, CI: 0.991-1.000, $p = 0.03$), and a more negative nitrogen balance (OR: 0.934, CI: 0.872-1.000, $p = 0.04$) were also associated with an increased risk of death, as shown in table 4.

Table 5 shows some of the criteria for a malnutrition diagnosis proposed by the International Society of Renal Nutrition and Metabolism (ISRNM). According to those guidelines, only a cholesterol level <100 mg/dl suggested a trend toward worse nutritional status at the final assessment.

A parallel analysis comparing all nutritional markers according to the severity of the AKI (AKIN 1 and 2 *vs.* AKIN 3) showed that patients in the AKIN 3 group presented a

Table 2 - Laboratory parameters at the initial and final assessments in the survivors and non-survivors.

Parameters	Assessment	Survivors	Non-survivors	*p*
BUN[a] (mg/dl)	Initial	73.8±30.50	77.8±29.63	0.52
	Final	40.4 (23.7-55.1)	49.5 (41.3- 79.6)	0.002
Creatinine (mg/dl)	Initial	4.3 (2.9-6.25)	3.4 (2.50-4.85)	0.03
	Final	2.1 (1.5-3.0)	2.6 (1.85-3.40)	0.06
Potassium (mmol/l)	Initial	4.3 (3.9-4.97)	4.3 (3.8 - 5.25)	0.83
	Final	4.0 (3.6-4.70)	4.0 (3.60-4.80)	0.57
Phosphorus (mg/dl)	Initial	5.2 (4.12-6.37)	5.35 (3.97-6.47)	0.84
	Final	3.75 (3.1-4.6)	4.35 (3.32-5.97)	0.04
Albumin (g/dl)	Initial	2.4 (2.0 – 2.8)	2.3 (1.7 – 2.7)	0.64
	Final	2.4 (2-2.9)	2.0 (1.8-2.6)	0.04
CRP[b] (mg/dl)	Initial	8.8 (5.6-25.7)	16.2(5.7-30.0)	0.52
	Final	7.2 (3.3-21.9)	15.3 (5.9-27.7)	0.03
TLC[c] (mm^3)	Initial	1126(855-1707)	1241 (737-1771)	0.93
	Final	1340(987-1695)	912(673-1750)	0.11
Cholesterol (mg/dl)	Initial	114.5 (84.7-153.5)	122 (85-146)	0.94
	Final	127.5 (102.8-158.3)	108(86-139)	0.05
Transferrin (g/dl)	Initial	1.35±0.51	1.19±0.65	0.08
	Final	1.37 (1.05-1.8)	1.02 (0.88-1.35)	0.009
Prealbumin (g/dl)	Initial	0.11 (0.08-0.14)	0.12 (0.06-0.19)	0.88
	Final	0.16 (0.09-0.20)	0.16 (0.09-0.25)	0.41

a) BUN: blood urea nitrogen.
b) CRP: C-reactive protein.
c) TLC: Total lymphocyte count.

lower BMI, with median values of 25 kg/m^2 (22-29.3) *vs.* 23.05 kg/m^2 (21.75 -26.20, respectively), $p = 0.021$, and TSF with values of 20 mm (14.6 -29.8) *vs.* 16.5 mm (11.1 -22), $p = 0.02$. Therefore, we can conclude that the severity of the AKI was associated with a reduction in body weight and body fat.

Table 3 - Nutritional parameters at the initial and final assessments in the survivors and non-survivors.

Parameters	Assessment	Survivors	Non-survivors	*p*
Dry weight (kg)	Initial	70 (62-80)	73(62-80)	0.87
	Final	69(58.6-76.5)	67(56.5-78)	0.96
BMI[a] (kg/m^2)	Initial	25.1(22.7-29)	24.4(22.5-28.2)	0.63
	Final	24.2(21.9-27.6)	24(21.7-27.8)	0.76
AC[b] (cm)	Initial	30.7(27.5-34)	31(27-34.5)	0.76
	Final	29.3±4.95	31.6±6.21	0.03
TSF[c] (mm)	Initial	22.8±11.5	21.5±9.11	0.6
	Final	19.1±9.51	20.5±9.08	0.49
AMC[d] (cm)	Initial	23.4±2.59	23.1±3.03	0.67
	Final	22.7±2.92	22.4±2.76	0.63
Edema (l)	Initial	3 (0-6)	3 (0-10)	0.37
	Final	1.4 (0-4.35)	5 (1-10.9)	0.002
Phase Angle (°)	Initial	5.2 (4.5-6.5)	4.75 (4.3-5.85)	0.21
	Final	5.1(4.08-6.43)	4.6(3.5-5.25)	0.04
Resistance (ohms)	Initial	323(264-444.1)	299.1(237.6-421.6)	0.44
	Final	410.9±126.5	323±105.6	0.0023
Reactance (ohms)	Initial	32.3(23.4-46.8)	26.2(20.1-38.7)	0.24
	Final	40.1(24.5-53.3)	19.4(17.5-34.6)	0.001
Calorie (kcal/kg/day)	Initial	12.9(5.6-22.3)	7.2(2.15-14.8)	0.01
	Final	23.9(18-29.9)	25.6(9.39-28.6)	0.24
Protein (g/kg/day)	Initial	0.54(0.24-0.99)	0.3(0.09-0.628)	0.02
	Final	1.13(0.78-1.4)	1.15(0.59-1.48)	0.95
UNA[e] (gN/day)	Initial	12.4(7.42-17.3)	12.6(6.55-23.3)	0.48
	Final	10.2(6.51-14.8)	11.1 (6.29-18.8)	0.69
NB[f] (gN/day)	Initial	-6(-11.1-0.16)	-3.76(-14.8-0.42)	0.47
	Final	-1.32(-2.84-5.10)	-3.56(-6.96 - 2.56)	0.004
Protein catabolism rate (g/kg/day)	Initial	0.99 (0.62-1.48)	1.37 (0.73-1.83)	0.16
	Final	0.86 (0.56-1.35)	1.00 (0.57-1.58)	0.23

a) BMI: body mass index.
b) AC: arm circumference.
c) TSF: triceps skinfold.
d) AMC: arm muscle circumference.
e) UNA: urea nitrogen appearance.
f) NB: nitrogen balance.

Table 4 - Multivariable analysis of the clinical, laboratory, and nutritional parameters associated with death.

	Multivariate analysis		
Parameters	**Odds Ratio**	**95% CI**	***p***
Clinical			
Age	1.038	1.004 – 1.072	0.02
Admission to ICU[a]	0.254	0.052 – 1.234	0.09
Ischemic AKI[b]	0.758	0.264 – 2.178	0.93
Nephrotoxic AKI	0.649	0.065 – 6.523	0.80
Sepsis	1.710	0.103 – 0.815	0.02
Dialysis	1.004	0.333 – 2.976	0.99
ATN-ISS[c]	1.029	1.007 – 1.052	0.01
Laboratory			
BUN[d]	1.013	1.004 – 1.023	0.005
Creatinine	0.939	0.645 – 1.367	0.74
Phosphorus	1.260	0.901 – 1.763	0.17
Albumin	0.436	0.124 – 1.528	0.19
CRP[e]	1.050	1.011 – 1.092	0.013
TLC[f]	1.000	0.999 – 1.001	0.51
Cholesterol	1.005	0.997 – 1.013	0.19
Transferrin	0.611	0.143 – 2.614	0.50
Nutritional			
Initial Calorie	0.950	0.910 – 0.991	0.02
AC[g]	0.961	0.850 – 1.086	0.52
Edema	1.138	1.012 – 1.280	0.03
Phase Angle	1.091	0.469 – 2.535	0.84
Resistance	0.995	0.991 – 1.000	0.04
Reactance	0.960	0.855 – 1.077	0.48
NB[h]	0.934	0.872 – 1.000	0.04

All laboratory and nutritional variables are from the final evaluation, except calories.
a) ICU: intensive care unit.
b) AKI: acute kidney injury.
c) ATN-ISS: Acute Tubular Necrosis-Individual Severity Score.
d) BUN: blood urea nitrogen.
e) CRP: reactive protein.
f) TLC: Total lymphocyte count.
g) AC: arm circumference.
h) NB: nitrogen balance.

DISCUSSION

This study shows that non-surviving patients had several markers of nutritional status that were below normal and that were significantly reduced compared with those of the survivors. In addition, parameters such as caloric intake, CRP, edema, resistance and nitrogen balance were independently associated with an increased risk of death.

We also observed that the non-surviving population exhibited a more severe clinical condition due to the longer duration of ICU stay, and the higher prevalence of sepsis and ATN-ISS.

The nutritional status of AKI patients is poorly described in the literature. Fiaccadori et al. (8) assessed 309 patients with AKI and identified the presence of malnutrition in 58% of patients, based on the Subjective Global Assessment (SGA). In our study, 60.2% of the patients exhibited malnutrition (moderate or severe). Even with the subjectivity of the physical method of evaluation, the prevalence of malnutrition was similar in both studies (11-12). Applying SGA, Fiaccadori identified an association between severe malnutrition and unfavorable prognosis (8). In this study, non-survivors presented no significant differences in terms of severe malnutrition but did show a higher incidence of moderate malnutrition.

Laboratory evaluation is a tool used in several diseases to monitor the metabolic response to nutritional support and to identify the reserves of energy substrates (14).

Serum creatinine is used as a marker of muscle mass in patients with chronic and acute kidney disease. Paradoxically, some studies have shown that higher levels of serum creatinine are associated with better survival of AKI patients (15). In this study, non-survivors had lower levels of creatinine in the first nutritional evaluation. The hypotheses for this result include negative factors such as the loss of muscle mass and hemodilution due to the presence of edema, which indicated the poor prognosis.

Visceral proteins, which are conventionally used as markers of nutritional status, are associated with mortality in AKI patients. The reduction in the concentration of these proteins may be associated with a decrease in their synthesis, which can be a consequence of the limited supply of energy and protein substrates commonly associated with malnutrition (14).

Albumin is classically associated with nutritional status in several diseases. Despite being influenced by hydration and inflammatory status, its low levels indicate nutritional impairment independent of such factors in AKI patients (6-7). In this study, non-surviving patients had a median albumin level of 2 g/dl, which is significantly lower than that in surviving patients. However, the higher CRP levels affected the application of albumin only as a nutritional marker.

Prealbumin is also influenced by non-nutritional factors such as inflammation, infection, liver diseases and changes in hydration status, which may be involved in the reduction of synthesis of this protein. In AKI patients, prealbumin levels below 11 mg/dL were associated with a reduced survival of approximately 45% at 90 days (4). In this study, non-surviving patients showed prealbumin levels lower than 0.11 g/dl throughout the assessment period. In our study, all patients had elevated levels of CRP and lower prealbumin levels (above 0.2 g/dl) during the assessment period.

Table 5 - Prevalence of protein-energy wasting (PEW) (malnutrition) based on the International Society of Nutrition and Renal Metabolism (ISRNM) diagnosis at the initial and final assessments.

PEW diagnosis	Assessment	Survivors (%)	Non-survivors (%)	*p*
Albumin <3.8 g/dl	Initial	96	97	0.784
	Final	94.7	100	0.411
Cholesterol <100 mg/dl	Initial	32.6	37.5	0.775
	Final	24.7	43.7	0.073
BMC <23 kg/m^2	Initial	29.3	24.2	0.737
	Final	35	42.4	0.576

Low levels of cholesterol have also been described as a predictor of complications and mortality. In patients with AKI, studies have shown that cholesterol levels have a significant association with survival. Obialo et al. (6) identified an approximately 50% reduction in survival in AKI patients with cholesterol levels below 150 mg/dL at admission. More recently, Guimarães et al. (7) studying 56 patients with AKI in the ICU showed that cholesterol levels below 96 mg/dL were significantly and independently associated with a reduced survival rate in these patients. The findings of the present study also showed reduced levels of cholesterol, especially in patients who died.

Transferrin is also affected by non-nutritional factors. In the present study, non-survivors showed significantly lower levels of transferrin at the final assessment, suggesting that this marker may be associated with death in this population.

Based on the multivariable analysis, only CRP and BUN were associated with death. Elevations in BUN can result from increased catabolism of structural proteins, increased amino acid turnover and negative NB (16). In the present study, non-survivors presented higher levels of BUN at the beginning of follow-up and such levels were associated with a higher risk of death.

To date, no study has shown that CRP is a predictor of mortality in AKI patients. Xie et al. reported that CRP is a possible predictor of mortality in AKI patients. However, based on the multivariate analysis, only the ratio of CRP/prealbumin remained associated with mortality (17). In our study, it was possible to show an association between CRP and a higher risk of death based on the final assessment.

It is important to note that it was difficult to perform the anthropometry measures on these patients. Given that 89% of all of the patients were in the ICU, this difficulty becomes more understandable. The lack of ambulation, decreased level of consciousness and important presence of edema were the main limiting factors. The main reason to discourage the use of these methods is the lack of reliability in the interpretation of the measurement results. It is known that AKI is responsible for various situations that negatively compromise the nutritional status of patients. Among these are insulin resistance, increased secretion of catabolic hormones, acidosis and the activation of catabolism and the loss of nutrients by dialysis. Considering the large number of causal factors that can exert a deleterious effect on nutritional status, the lack of a difference between the anthropometric parameters of the survivors and non-survivors at the final assessment is unexpected. This result suggests that, in fact, it is quite difficult to measure these parameters in practice because of the reduced accuracy of parameters such as weight, BMI, TSF and AMC in critically ill AKI patients. Based on the multivariable analysis, there was no association between anthropometric parameters and mortality, confirming that these parameters have reduced accuracy in critically ill AKI patients. Only edema was associated with higher mortality, suggesting that this clinical situation can significantly affect the use of anthropometric parameters in AKI patients.

Unlike mortality, we observed that the severity of the AKI according to AKIN classification was associated with loss of body fat and body mass at the final assessment, as evidenced by lower values of TSF and BMI, respectively. These data suggest that patients with more aggressive AKI may exhibit higher levels of nutritional impairment. Therefore, the nutritional assessment could be interpreted as a marker of AKI severity, which is associated with outcomes. BIA is a non-invasive, easy and low-cost method for body assessment. Its use in critically ill patients has limitations because these patients experience frequent changes in tissue hydration due to edema, ascites, serum therapy and the use of diuretics (18). However, some BIA parameters have been described as predictors of survival. Given the lack of validation supporting the use of predictive equations in acute situations, only independent parameters from these formulas, such as resistance, reactance and phase angle, were used in this study.

The phase angle, being a direct measure of the stability of cells and being interpreted as an indicator of membrane integrity and a predictor of body cell mass, has assumed an important role as a prognostic indicator and predictor of survival in different pathologies (19). A study involving 3009 patients receiving chronic hemodialysis showed that phase angle values below 4.0 were associated with a significantly higher risk of death after one year of follow up (20). In the literature, there are no available data about these parameters in patients with AKI. In this study, patients who died had a median phase angle of 4.6, suggesting that such lower values may be associated with death in this population. These patients also showed reduced levels of resistance (323 ± 105.6 ohms) and reactance (median of 19.4 ohms) at the final assessment compared with survivors, suggesting the presence of unhealthy cell membranes and deficient integrity (21). Despite not accurately indicating the composition of body tissues, the parameters can be used as factors of poor prognosis for this group of patients. Furthermore, this study produced new data highlighting the protective effect of higher levels of resistance, which were significantly and independently associated with a lower risk of death.

When calories and protein supply were evaluated, both survivors and non-survivors received quantities below those recommended for hospitalized patients, critical or not; 44.1 and 82.9% (data not shown) of survivors and non-survivors, respectively, received enteral or parenteral nutrition upon initial admission, such that the low supply and slower progression is understandable and expected. Factors such as prolonged fasting, abdominal distension and absence of bowel, which are common in critically ill patients, justify the small volume and decreased nutrients of the initial diet administered to these patients. In this study, prolongation of the offered diet was associated with an increased risk of death.

Hypercatabolism is the main nutritional and metabolic feature of AKI and is closely related to the increased mortality in AKI patients. Factors such as insulin resistance, increased secretion of catabolic hormones, inflammatory response and nutrient loss through dialysis are among the main causes. By calculating the urea nitrogen appearance, it is possible to estimate the extent of protein catabolism in AKI patients (3). Patients on continuous renal replacement therapy present a rate of catabolism between 1.4 and 1.8 g/kg/day (22). In this study, there was no difference between the urea nitrogen appearance and the protein catabolism rate among survivors and non-survivors at any point during the evaluation.

NB is a reliable method to assess nitrogen losses and to classify the extent of catabolism. In this study, all patients improved from the negative NB at baseline, advancing to mild hypercatabolism during the course of the evaluation.

At the end of the assessment, however, non-survivors still had more negative NBs than did survivors.

NB has important associations with the clinical prognosis of AKI patients. Scheinkestel et al. (9) evaluated the protein needs of 50 critically ill AKI patients on continuous RRT and observed that a positive nitrogen balance was significantly associated with better prognosis in the ICU and hospital. In addition, each 1 g/day increase resulted in a 21% increase in the probability of survival. High-volume peritoneal dialysis patients also showed a significant association with survival. For each 1 g/day increase in NB, there was a 31% reduction in the risk of death in these patients (10). In the present study, a higher NB resulted in a reduction of approximately 7% in the risk of death.

Diagnosing protein-energy wasting (PEW) in AKI patients is difficult. However, the International Society of Renal and Nutrition Metabolism (ISRNM) proposed the utilization of several markers (23).

The authors selected some objective criteria, such as albumin<3.8 g/dl, cholesterol<100 mg/dl, and body mass index<23 kg/m^2 (23). Only low cholesterol suggested a trend toward a worse nutritional status at the final assessment. Although recommended by the ISRNM, it is important to emphasize the difficulty of relying on these isolated criteria as markers of nutritional status.

This study has some limitations, such as the use of nutritional parameters that are not very accurate but are conventional, meaning they are easy and cost-effective to implement. The reliability of SGA applied in critically ill patients has been questioned; however, the same evaluator performed the assessment, reducing the interobserver error. A BIA single-frequency measurement was applied. Multi-frequency BIA is indicated in critically ill patients, but that approach also has limitations. Furthermore, this work did not use parameters from the predictor equations. The evaluation of the dry weight is subjective. It is likely that there was more pronounced weight loss in these patients during the follow-up period. However, it is quite difficult to precisely estimate the correct weight due to the edema in this group of patients.

Despite the limitations outlined above, data from this study show that through nutritional assessment of AKI patients using laboratory methods, food intake, and catabolism, it was possible to identify parameters associated with death.

A low calorie intake, higher CRP levels, the presence of edema, a lower resistance based on bioelectrical impedance, and a lower nitrogen balance were significantly associated with a higher risk of death in AKI patients during the assessment period. Easy and simple nutritional methods can be applied in AKI patients and seem to identify markers associated with outcome.

AUTHOR CONTRIBUTIONS

Berbel MN was responsible for the data collection, interpretation of the results and manuscript writing. Góes CR contributed to the data collection. Ponce D and Balbi AL contributed to the conception and design of the study and manuscript writing.

REFERENCES

1. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network (AKIN): report of an intitiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):1-8.
2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute Renal Failure in critically ill patients. A multinational, multicenter study. JAMA. 2005;294(7):813-8, http://dx.doi.org/10.1001/jama.294.7.813.
3. Druml W. Nutritional support in acute renal failure. Handbook of Nutrition and the Kidney. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.pp.95-114.
4. Perez-Valdivieso JR, Bes-Rastrollo M, Monedero P, de Irala J, Lavilla FJ. Impact of prealbumin levels on mortality in patients with acute kidney injury: an observational cohort study. J Ren Nutr. 2008;18(3):262-8.
5. Chertow GM, Lazarus JM, Paganini EP, Allgren RL, Lafayette RA, Sayegh MH. Predictors of mortality and the provision of dialysis in patients with acute tubular necrosis. The Auriculin Anaritide Acute Renal Failure Study Group. J Am Soc Nephrol. 1998;9(4):692-8.
6. Obialo CL, Okonofua EC, Nzerue MC, Tayade AS, Riley LJ. Role of hypoalbuminemia and hypocholesterolemia as copredictors of mortality in acute renal failure. Kidney Int. 1999;56(3):1058-63, http://dx.doi.org/10.1046/j.1523-1755.1999.00622.x.
7. Guimarães SM, Lima EQ, Cipullo JP, Lobo SM, Burdmann EA. Low insulin growth factor-1 and hypocholesterolemia as mortality predictors in acute kidney injury in the intensive care unit. Crit Care Med. 2008;36(12):3165-70, http://dx.doi.org/10.1097/CCM.0b013e318186ab70.
8. Fiaccadori E, Lombardi M, Leonardi S, Rotelli CF, Tortorella G, Borghetti A. Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: a prospective cohort study. J Am Soc Nephrol. 1999;10(3):581-93.
9. Scheinkestel CD, Kar L, Marshall K, Bailey M, Davies A, Nyulasi I, et al. Prospective randomized trial to assess caloric and protein needs of critically ill. anuric. ventilated patients requiring continuous renal replacement therapy. Nutrition. 2003;19(11-12):909-16, http://dx.doi.org/10.1016/S0899-9007(03)00175-8.
10. Ponce D, Berbel MN, Regina de Góes, Almeida CT, Balbi AL. High-volume peritoneal dialysis in acute kidney injury: indications and limitations. Clin J Am Soc Nephrol. 2012;7(6):887-94, http://dx.doi.org/10.2215/CJN.11131111.
11. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? J Parenter Enteral Nutr. 1987;11(1):8-13, http://dx.doi.org/10.1177/014860718701100108.
12. Detsky AS, Smalley PS, Chang J. Is this patient malnourished? JAMA. 1994;271(1):54-8, http://dx.doi.org/10.1001/jama.1994.03510250070038.
13. Chima CS, Meyer L, Hummell C, Bosworth C, Heyka R, Paganini EP, et al. Protein catabolic rate in patients with acute renal failure on continuous arteriovenous hemofiltration and total parenteral nutrition. J Am Soc Nephrol. 1993;3(8):1516-21.
14. Raguso CA, Dupertuis YM, Pichard C. The role of visceral proteins in the nutricional assessment of intensive care unit patients. Curr Opin Clin Nutr Metab Care. 2003;6(2):211-6, http://dx.doi.org/10.1097/00075197-200303000-00010.
15. Cerdá J, Cerdá M, Kilcullen P, Prendergast J. In severe acute kidney injury, a higher serum creatinine is paradoxically associated with better patient survival. Nephrol Dial Transplant. 2007;22(10):2781-4, http://dx.doi.org/10.1093/ndt/gfm395.
16. Macedo E. Blood urea nitrogen beyond estimation os renal function. Crit Care Med. 2011;39(2):405-6, http://dx.doi.org/10.1097/CCM.0b013e318205c33a.
17. Xie Q, Zhou Y, Xu Z, Yang Y, Kuang D, Youh H et al. The ratio of CRP to prealbumin levels predict mortality in patients with hospital-acquired acute kidney injury. BMC Nephrol. 2011;12(30):1-8.
18. Barbosa-Silva MCG, Barros AJD. Bioelectric impedance individual characteristics as prognostic factos for post-operative complications. Clin Nutr. 2005;24(5):830-8, http://dx.doi.org/10.1016/j.clnu.2005.05.005.
19. Silva LMDL, Caruso L, Martini LA. Aplicação do ângulo de fase em situações clínicas. Rev Bras Nutr Clin. 2007;23(4):317-21.
20. Chertow GM, Jacobs DO, Lazarus MJ, Lew NL, Lowrie EG. Phase angle predicts survival in hemodialysis in patients. J Ren Nutr. 1997;7(4):204-7.
21. Pupim LCB, Ribeiro CB, Kent P, Ikizler TA. Atualização em diálise: Uso da impedância bioelétrica em pacientes em diálise. J Bras Nefrol. 2000;22(4):249-56.
22. Fiaccadori E, Cremaschi E, Regolisti G. Nutritional assessment and delivery in renal replacement therapy patients. Semin Dial 2011;24(2):169-75, http://dx.doi.org/10.1111/j.1525-139X.2011.00831.x.
23. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73(4):391-8, http://dx.doi.org/10.1038/sj.ki.5002585.