José de Souza Andrade Neto, MD, PhD[1*], Vera Lucia Fernandes de Azevedo, MD, PhD[2], Italo Lopes and Carvalho, MD[3], Reinaldo da Silva Santos Junior, MD, MsC[4], Paulo do Nascimento Junior, MD, PhD[5] and Norma Sueli Pinheiro Modolo, MD, PhD[5]

[1]Department of Anesthesiology, Medical School, State University of the Southwest of Bahia, UESB, Bahia, Brazil

[2]Santo Antonio Hospital, Salvador, Bahia, Brazil

[3]Department of Anesthesiology, General Hospital of Vitoria da Conquista, Bahia, Brazil

[4]Department of Intensive Care Medicine, Medical School, Santa Izabel Hospital, Santa Casa de Misericórdia da Bahia, Bahia, Brazil

[5]Department of Anesthesiology, Botucatu School of Medicine, University of São Paulo State, UNESP, Botucatu, São Paulo, Brazil

*Corresponding author: José de Souza Andrade Neto, MD, PhD, Assistant Professor, Medical Doctor, Ph.D, Department of Anesthesiology, Medical School, UESB- Univ. Estadual do Sudoeste da Bahia, Brazil, Email: neto.jsa@hotmail.com

Check for updates

Research Article

Serum cystatin C as an early marker of Acute Kidney Injury in elderly patients after surgery for femur fracture. An observational study

Abstract

Background: Acute kidney injury (AKI) is prevalent in hospitalized patients, primarily in patients undergoing major surgical procedures. AKI is associated with increased morbimortality, and patients would benefit from a very early diagnosis that would allow implementation of specific therapeutic or additional prophylactic measures. The present study evaluated serum cystatin C as an early predictor of AKI in elderly patients during the postoperative period.

Methods: Fifty-nine patients, aged 60 years or older undergoing correction of femur fracture under spinal anaesthesia, were prospectively evaluated up to 48 hours after surgery. Serum cystatin C was measured immediately after surgery and four (early marker) and 24 hours after surgery. The diagnosis of AKI was based on creatinine values up to 48 hours after surgery (Kidney Disease Improving Global Outcomes, KDIGO), and the impact of serum cystatin C on the diagnosis of AKI was evaluated four hours after surgery.

Results: Twenty-one patients (35.6%) were diagnosed with AKI. The values of serum cystatin C [median (1st - 3rd quartiles)] at four hours were 1.24 (1.00 - 1.49) and 0.90 (0.78 - 1.15) mg.L⁻¹ for patients with and without AKI, respectively (p = 0.003). The best serum cystatin C cut-off value at four hours was 0.92 mg.L⁻¹, with negative and positive predictive values equal to 95% and 50%, respectively, a sensitivity of 94%, a specificity of 51%, and an accuracy (area under the curve) of 75% (95% confidence interval: 61% to 86%).

Conclusions: Serum cystatin C exhibited good accuracy (75%) for the diagnosis of AKI and elevated the potential identification of patients with lower chances of presenting AKI at a cut-off value of 0.92 mg.L⁻¹ four hours after femur fracture repair under spinal anaesthesia.

Abbreviations

AKI: Acute Kidney Injury; ASA: American Society of Anesthesiologists; KDIGO: Kidney Disease Improving Global Outcomes; ROC: Receiver Operating Characteristic

Introduction

Acute kidney injury (AKI) is a highly prevalent condition that occurs in 18 to 47% of surgical patients, primarily patients undergoing cardiovascular surgeries [1–3]. It has been reported that 5 to 7% of all hospitalized patients develop AKI, and greater than 30% of these patients are in intensive care units [4]. Recent studies found even higher numbers when considering a more sensitive classification of AKI scoring system, the Kidney Disease Improving Global Outcomes (KDIGO), which found an overall incidence of 23% in hospitalized patients [5].

AKI is an independent risk factor for mortality, and it reaches rates of 70% when renal replacement therapy is needed [6,7]. AKI also increases the length of hospital stay and hospital costs [8]. Considering the increased morbimortality, AKI should be identified as soon as possible during the postoperative period. Creatinine and urine output are used extensively to evaluate the glomerular filtration rate in clinical settings. However, creatinine fails in several aspects to diagnose AKI, and it is an insensitive marker for acute changes in glomerular filtration rate [9,10]. Diuresis is a nonspecific marker for AKI, and the inability to concentrate urine may lead to a dissociation between urine production and kidney function [11]. Patients in critical care conditions may exhibit periods of oliguria that are not followed by AKI [12], and the correct measurement of urinary output may also be a problem [13].

Cystatin C was investigated because of the scarcity of early

and accurate markers for AKI. All nucleated cells in the human body produce cystatin C protein at a constant rate. Cystatin C is freely filtered by the glomerulus and completely degraded by renal tubular cells. Its serum concentration rises particularly with a decrease in glomerular filtration rate [14,15]. In a meta-analysis, cystatin C appears to be a promising marker for the early evaluation of kidney function in patients at risk of kidney injury [16].

The use of cystatin C in the identification of acute kidney injury remains controversial [17]. The superior performance of cystatin C, rather than creatinine, as a marker of the glomerular filtration rate allowed a reclassification of renal function to better and worse scores, which resulted in a better correlation with the risk of death [18]. Cystatin C exhibited better accuracy than creatinine in the identification of acute kidney dysfunction in the intensive care setting [19], and it was an early marker of AKI [20,21]. However, similarity between these two markers was observed, even for the early detection of AKI [22,23].

Advanced age is a major risk factor for developing AKI [2]. Ageing causes a progressive decrease in renal mass and in the number of glomeruli, and it also causes tubulointerstitial fibrosis, which is more pronounced when associated with prevalent diseases in the elderly, such as hypertension, diabetes mellitus, chronic kidney disease, atherosclerosis and congestive heart failure [24-27]. The limitations of creatinine in demonstrating impairments in glomerular filtration in the elderly are known. Therefore, cystatin C may be a better marker than creatinine for the identification of AKI in older patients, primarily because of its non-dependency on muscle mass [28,29]. Cystatin C exhibited similar performance to creatinine as a marker of glomerular filtration rate in a study of 48 patients over 85 years old [30].

We hypothesized that cystatin C was a better marker than creatinine as an early marker of AKI in elderly patients undergoing major surgery. The present study evaluated the accuracy of serum cystatin C as an early predictor of AKI in elderly patients who underwent femoral fracture repair under spinal anaesthesia.

Materials and Methods

Participants and eligibility criteria

The present study was registered in the *Plataforma Brasil* (www.saude.gov.br/plataformabrasil) under CAAE 15062014.0.0000.5411 after approval of the Ethics Committee of the General Hospital of Vitória da Conquista, Bahia, Brazil. The study was performed according to the STROBE statement. This prospective cohort study was performed from February 1 to July 31, 2014. Sixty-six patients, both sexes, aged 60 years or older, in physical state 1 or 2 according to the American Society of Anesthesiologists, who were scheduled for elective femur fracture repair under spinal anaesthesia were recruited. Exclusion criteria were serum creatinine values > 2 mg.dL⁻¹, patients under renal replacement therapy, the presence of any degree of thyroid disease, the use of steroids and any condition contraindicated for spinal anaesthesia. All participants provided written informed consent.

Interventions

Patients fasted for 8 to 10 hours and received no preanaesthetic medication. Patients were referred to the operating room and monitored using a three-lead electrocardiogram, non-invasive blood pressure and pulse oximetry. An intravenous line was established using a 20G or 18G peripheral catheter, and lactated Ringer's solution was administered at 10 mL.kg⁻¹.h⁻¹.

Spinal anaesthesia was performed using a 25G Quincke needle at intervertebral spaces L_2-L_3 or L_3-L_4 via a midline approach with the patients seated, and 12.5 to 15 mg of isobaric bupivacaine hydrochloride plus 60 µg morphine was injected. Patients were lightly sedated according to the anaesthesiologist's judgement, and oxygen was provided via a nasal catheter at 2-3 L.min⁻¹. All patients received antibiotic prophylaxis of 2 g cephalothin. Additional boluses of crystalloids were administered according to the anaesthesiologist's judgement, and packed red blood cells were administered when haemoglobin values were less than 9 g.dL⁻¹. Arterial hypotension was considered as a systolic blood pressure lower than 90 mmHg or a 40% decrease in relation to the baseline value, and it was treated with etilefrine hydrochloride or metaraminol bitartrate. Atropine was administered when the heart rate fell below 50 beats.min⁻¹. Tramadol (100 mg intravenously (IV)) and ondansetron (8 mg, IV) were provided prophylactically for postoperative analgesia and nausea and vomiting, respectively. Urinary catheterization was not routinely performed, and diuresis was not measured. Patients remained in the recovery area at the end of surgery and were sent to the ward after partial or complete recovery from motor and sensory blocks, according to the anaesthesiologist's judgement.

Measurements and outcomes

A venous blood sample was collected at hospital admission for serum creatinine measurement. Venous blood samples were collected immediately at the end of surgery and four and 24 hours after the end of surgery in different tubes for determinations of serum cystatin C and serum creatinine values. An additional blood sample was collected 48 hours after surgery for serum creatinine measurement. All samples were 2 ml of venous blood collected in tubes containing ethylenediaminetetraacetic acid (EDTA). Samples for serum cystatin C measurement were centrifuged for serum separation, and sera were stored at -170 °C for subsequent analysis. Samples were analysed using enzyme-linked immunosorbent assay (ELISA) and a Cystatin C Kit (Human, product number ALX-850-292 Enzo Life Sciences, Farmingdale, NY, USA). Samples for the measurement of serum creatinine were transported to a laboratory and analysed using the Creatinine K 016 kit (Labtest, Belo Horizonte, MG, Brazil) based on the Jaffé reaction.

The primary outcome was the incidence of AKI from serum creatinine measurements and its correlation with serum cystatin C values at four hours (early marker). The values of serum cystatin C 24 hours after surgery and the delta values from the end of the surgery to four and 24 hours after surgery were also analysed. The definition of AKI was based on the preoperative values of serum creatinine compared to its values

at 24 and 48 hours. The KDIGO classification was used [31]. Briefly, an absolute increase in serum creatinine greater than or equal to 0.3 mg.dL^{-1} or a percentage increase in serum creatinine greater than or equal to 50% (1.5-fold from baseline) within 48 hours indicated AKI.

We evaluated the values of serum creatinine at the end of surgery and four, 24 and 48 hours after surgery, as well as different postoperative delta values. The correlation between the values of serum cystatin C and serum creatinine and the relative risk of AKI according to serum cystatin C values were also analysed. We calculated the best cut-off value of serum cystatin C four hours after surgery, as well as its accuracy, sensitivity, specificity, and positive and negative predictive values related to the occurrence of AKI.

Statistical analysis

The sample size calculation, considering the estimated incidence of AKI equal to 25% with an accuracy (area under curve) equal to 0.8, a power of 90% and an alpha equal to 0.05, based on the formula proposed by Hanley and McNeil [32], indicated that a minimum of 48 patients would be necessary to detect differences between the accuracy of two different markers.

Numerical values are reported as the mean and standard deviation or median and interquartile range, according to the presented distribution of data. Evaluation of normality was performed using graphical analysis, values of skewness and kurtosis, and Kolmogorov-Smirnov and Shapiro-Wilk tests. The homogeneity of variance was evaluated using Levene's test. Student's t-test for independent samples and a factor analysis of variance (ANOVA one-way) were used for variables with a normal distribution. The Mann-Whitney test was used for the variables with an asymmetric distribution. The association between serum concentrations of creatinine and cystatin C were examined using the Spearman correlation. Categorical variables are presented as totals and relative frequencies and compared using the chi-square test or Fisher's exact test (when frequencies were lower than five). The association between serum cystatin C at different times (independent variable) and AKI (dependent variable) were examined using Poisson's regression model. Solid models were calculated to estimate the relative risk and the 95% confidence intervals. The receiver operating characteristic (ROC) curve was calculated to evaluate the accuracy of cystatin C as a diagnostic test for AKI. The optimal cut-off point was selected according to the Youden criterion. The significance level adopted was 5%. The data were analysed using IBM SPSS Statistics for Windows, Version 21.0, 2012 (Armonk, NY: IBM Corp) and MedCalc Statistical Software, version 14.8.1, 2014 (MedCalc Software bvba, Ostend, Belgium).

Results

Serum cystatin C was analysed in 59 of the 66 patients eligible for the study. Seven patients were excluded: one patient had clinical signs of sepsis in the operating room and had the surgery postponed; four patients were lost to follow-up after being transferred to another hospital; and two patients were missing data (blood sample not collected).

Table 1 shows the demographic and clinical data of the 59 patients and their distribution according to the presence or absence of AKI. Twenty-one patients (35.6%) developed postoperative AKI.

Table 2 shows the perioperative values of serum creatinine and cystatin C concentrations of all patients and according to the presence or absence of AKI. The postoperative delta values are also shown. Values of serum creatinine were significantly higher ($p < 0.05$) in patients who presented AKI at 24 and 48 hours, but not four hours, after the end of surgery. The delta values of serum creatinine were also significantly higher ($p < 0.05$) at 24 and 48 hours, but not in the first four hours, after surgery. However, serum cystatin C was significantly higher ($p < 0.05$) four hours after surgery when AKI was present. Delta values from the end of surgery to four hours were also significantly higher ($p < 0.05$) when AKI was present. Values of serum cystatin C remained significantly elevated ($p < 0.05$) for 24 hours after surgery in this group of patients.

Table 1: Baseline patient characteristics and intraoperative data. Data are presented as the means (standard deviation) or numbers (%). ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; KDIGO, Kidney Disease: Improving Global Outcomes, classification of acute kidney injury.

Variable	All patients n = 59	Acute Kidney Injury	
		Yes n = 21 (35.6%)	No n = 38 (64.4%)
Age (years)	79.5 ± 9.9	80.5 ± 9.6	78.7 ± 10.0
60-69 years	13 (22.0)	3 (14.3)	10 (26.3)
70-79 years	17 (28.8)	10 (47.6)	7 (18.4)
80-89 years	22 (37.3)	5 (23.8)	17 (44.7)
≥ 90 years	7 (11.9)	3 (14.3)	4 (10.5)
Female	37 (62.7)	15 (71.4)	22 (57.9)
Weight (kg)	60.0 ± 12.7	63.3 ± 10.5	60.3 ± 14.2
ASA (1/2)	8 (13.6)/ 51 (86.4)	1 (4.8)/20 (95.2)	7 (18.4)/31 (81.6)
Hypertension	32 (54.2)	16 (76.2)	16 (42.1)
Diabetes	7 (11.9)	2 (9.5)	5 (13.1)
Stroke	4 (6.8)	3 (14.2)	1 (2.6)
COPD	4 (6.8)	1 (4.8)	3 (7.9)
Congestive heart failure	2 (3.4)	1 (4.8)	1 (2.6)
Myocardial infarction	1 (1.7)	1 (4.8)	0
Dementia	2 (3.4)	1 (4.8)	1 (2.6)
Epilepsy	1 (1.7)	1 (4.8)	0
Parkinson disease	1 (1.7)	0	1 (2.6)
Alcoholism	1 (1.7)	0	1 (2.6)
Preoperative haemoglobin (g.dL^{-1})	9.7 ± 1.7	10.0 ± 1.8	9.6 ± 1.7
Length of surgery (minutes)	101 ± 42.4	112.8 ± 40.0	96.2 ± 42.9
Intraoperative crystalloid (ml)	1669.6 ± 694.3	1812.5 ± 543.9	1612.5 ± 744.5
Packed red blood cells (ml)	347.1 ± 87.9	318.6 ± 32.9	397.0 ± 135.6
KDIGO 1		14 (66.7)	
KDIGO 2		7 (33.3)	

Table 3 presents the correlations between the values of serum cystatin C and serum creatinine. The best correlations were observed for serum cystatin C at four hours with serum creatinine at four and 24 hours, as well as serum cystatin C at 24 hours and serum creatinine at 24 hours.

Table 4 presents the relative risks of AKI according to serum cystatin C values at the end of surgery and four and 24 hours after surgery, as well as the delta values from the first four hours and from the end of surgery to 24 hours. The higher values were observed at the 4-hour measurement and the delta from the end of surgery to four hours after surgery. Regression estimated that every increase of one unit ($1 \ mg.L^{-1}$) in serum cystatin C at four hours increased the risk of occurrence of AKI 4.80 times.

The highest relative risk of AKI was measured from serum cystatin C values four hours after surgery. Table 5 shows an analysis of the accuracy (area under the ROC curve) of these values. The best cut-off value for serum cystatin C was 0.92 $mg.L^{-1}$, which provided very high sensitivity (94%) and a negative predictive value (95%).

Discussion

The present study demonstrated a high incidence of AKI (35.6%) in elderly patients undergoing femur fracture repair under spinal anaesthesia. The RIFLE classification in patients aged 65 years or older who had undergone surgical correction

Table 3: Coefficients of the correlation between serum creatinine and serum cystatin C calculated for the different moments of blood sampling.

Serum creatinine	Serum cystatin C		
	0 (end of surgery)	4	24
	Hours after surgery		
Preoperative	0.305†	0.453‡	0.443‡
Hours after surgery			
0 (end of surgery)	0.186	0.359‡	0.169
4	0.427‡	0.573*	0.455‡
24	0.355‡	0.613*	0.625*
48	0.387‡	0.481‡	0.541*

†$p < 0.05$; ‡$p < 0.01$; *$p < 0.001$.

Table 4: Relative risk of acute kidney injury, according to postoperative serum cystatin C (hours after surgery) and based on each increase of $1 \ mg.L^{-1}$.

Variable	Relative risk	95% confidence interval	p value
Cystatin C, 0 hours (end of surgery)	2.29	1.09 - 4.84	0.030
Cystatin C, 4 hours	4.80	2.17 - 10.62	< 0.001
Cystatin C, 24 hours	3.12	1.95 - 4.99	< 0.001
Delta Cystatin, 0 - 4 hours	3.76	0.88 - 16.03	0.073
Delta Cystatin C, 0 - 24 hours	3.29	1.17 - 9.28	0.024

Table 5: Parameters of performance for serum cystatin C as a biomarker of acute kidney injury when measured 4 hours after surgery. ROC, receiver operating characteristic; CI, confidence interval.

	Serum cystatin C measured 4 hours after surgery
Number of patients	59
Accuracy (area under ROC curve)	0.75 (95% CI: 0.61 - 0.86)
Cut-off point	0.92 $mg.L^{-1}$
Sensitivity	0.94
Specificity	0.51
Positive predictive value	0.50
Negative predictive value	0.95

Table 2: Preoperative and postoperative serum concentrations of creatinine and cystatin C. Values are medians (25% percentile - 75% percentile).

Variable	All patients n = 59	Acute kidney injury		p value
		Yes n = 21 (35.6%)	No n = 38 (64.4%)	
	Serum creatinine ($mg.dL^{-1}$)			
Preoperative	0.80 (0.70 - 1.00)	0.85 (0.70 - 1.08)	0.80 (0.70 - 1.00)	0.691
	Hours after surgery			
0 (end of surgery)	0.73 (0.57 - 0.92)	0.73 (0.62 - 0.99)	0.67 (0.54 - 0.83)	0.139
4	0.78 (0.63 - 1.01)	0.89 (0.75 - 1.10)	0.75 (0.57 - 0.96)	0.051
24	0.90 (0.70 - 1.14)	1.16 (0.92 - 1.57)	0.79 (0.65 - 0.97)	< 0.001
48	0.90 (0.70 - 1.20)	1.35 (1.08 - 1.50)	0.80 (0.62 - 0.90)	< 0.001
Delta (hours after surgery)				
0 - 4	0.03 (-0.06 - 0.21)	0.05 (-0.0 2 - 0.24)	0.03 (-0.08 - 0.14)	0.308
0 - 24	0.14 (0.06 - 0.31)	0.31 (0.17 - 0.71)	0.11 (0.03 - 0.21)	0.001
0 - 48	0.20 (-0.01 - 0.38)	0.44 (0.30 - 0.78)	0.13 (-0.05 - 0.20)	< 0.001
4 - 24	0.12 (0.01 - 0.19)	0.20 (0.06 - 0.54)	0.09 (0.01 - 0.15)	0.019
4 - 48	0.08 (-0.04 - 0.44)	0.44 (0.18 - 0.51)	0.01 (-0.11 - 0.13)	< 0.001
	Serum cystatin C ($mg.L^{-1}$)			
Hours after surgery				
0 (end of surgery)	1.04 (0.87 - 1.24)	1.12 (0.89 - 1.35)	1.02 (0.83 - 1.16)	0.106
4	1.01 (0.83 - 1.29)	1.24 (1.00 - 1.49)	0.90 (0.78 - 1.15)	0.003
24	1.05 (0.86 - 1.32)	1.30 (1.14 - 1.52)	0.92 (0.83 - 1.16)	0.001
Delta (hours after surgery)				
0 - 4	-0.02 (-0.12 - 0.19)	0.18 (-0.09 - 0.29)	-0.05 (-0.16 - 0.12)	0.032
0 - 24	0.07 (-0.16 - 0.29)	0.26 (-0.08 - 0.49)	0.03 (-0.14 - 0.19)	0.015

of femur fracture found an incidence of 21% of AKI [33]. The current recommended criteria for the diagnosis of AKI, which considers a small increase in the values of serum creatinine, $0.3 \ mg.dL^{-1}$ within 48 hours, independent of baseline values, may have increased the sensitivity to detect AKI [34], but in-hospital mortality was not reduced [35,36]. Therefore, other criteria based on early markers of renal function should be considered, primarily when a high incidence of AKI is expected, to offer clinicians the opportunity to treat or provide additional preventive measures to control the injury progression.

Monitoring the glomerular filtration rate using an endogenous marker is the most practical method to evaluate renal function. Creatinine is routinely used to measure the glomerular filtration rate, but it fails in several aspects, primarily in the elderly, because creatinine is influenced by muscle mass. Cystatin C may be a better marker of the decline in the glomerular filtration rate that accompanies ageing [37]. The short half-life of cystatin C explains the earlier changes in its serum levels compared to creatinine [38]. However,

the results remain controversial. Cystatin C exhibited only a modest discriminatory capacity for predicting AKI (area under the curve: 0.68, 95% confidence interval: 0.58 to 0.78) when assessed two hours after the end of cardiopulmonary bypass [39]. Cystatin C exhibited worse accuracy than creatinine, with areas under the ROC curve equal to 0.48 and 0.80, when measured 12 hours after the use of contrast media for coronary angiography, for the purpose of early diagnosis of contrast-induced nephropathy [40]. We focused on the serum cystatin C values obtained four hours after the end of surgery and verified the elevated values in these patients who developed AKI. The variation in the values from the end of the surgery to four hours after the surgery was also elevated. The gross value of serum creatinine and its delta value for the same moments of evaluation were not significantly higher in the group of patients with AKI.

Cystatin C and creatinine were also positively correlated. Elevated cystatin C four hours after the end of the surgery reflected an increase in creatinine measured 24 and 48 hours after the surgery. Therefore, the 4-hour serum cystatin C measurement reflected creatinine values at least 20 hours in advance, which confirms its potential as an earlier marker for the decrease in renal function.

The high relative risk and statistical significance based on the values of serum cystatin C obtained four hours after the end of the surgery, overwhelming the relative risk from its delta value in the first four hours after surgery, indicates that a single measurement of serum cystatin C is sufficient to evaluate the risk of AKI, and serial measurements of this marker are unnecessary. A cut-off value of 10% for the increase in cystatin C within 24 hours exhibited a 100% negative predictive value for the detection of acute changes in renal function in patients with chronic kidney disease undergoing coronary and/or peripheral angiography and/or angioplasty [41]. This fact represents valuable clinical information and indicates an earlier detection of changes in renal function compared to creatinine values. The 24-hour interval may not be considered an early detection, and it remains dependent on serial measurements of cystatin C.

In our study, patients who developed AKI exhibited a 0.18 mg.L^{-1} median increase in serum concentrations of cystatin C in the first four hours after surgery, unlike patients who did not develop AKI, who exhibited a decrease in serum cystatin C concentrations. Similarly, a median increase of 0.26 mg.L^{-1} of serum cystatin C was observed in patients who developed AKI at the 24-hour interval, and no significant changes were observed in patients who did not develop AKI. Despite this increase in delta values, the relative risk associated with the value of a single measurement of serum cystatin C four hours after the end of the surgery was higher than the associated delta values of these two intervals.

Analysis of the overall performance of serum cystatin C four hours after the end of surgery demonstrated an accuracy of 75% (95% confidence interval: 61% to 86%), which is considered good. A recent meta-analysis of 30 prospective cohort studies found that the overall accuracy of cystatin C for the identification of AKI was 89% (95% confidence interval: 86% to 91%) [42]. Subgroup analysis of the accuracy from measurements one to six hours after surgery resulted in values very similar to ours, 77% (95% confidence interval: 73% to 80%). However, in elderly patients undergoing cardiac surgery, composing a group of patients who have high incidence of AKI, serum cystatin C was no better than creatinine in the detection of AKI. Twenty-four hours after surgery, the area under the curve for creatinine was 66% (95% confidence interval: 55% to 76%) and for cystatin C, it was 71% (95% confidence interval: 61% to 81%) [43]. Cystatin C also failed to perform better in the estimation of the glomerular filtration rate compared with creatinine in the general population [44].

The values of serum cystatin C as a discriminatory diagnostic test for AKI four hours after the end of surgery exhibited a sensitivity equal to 94% in our study. This sensitivity is considered very good as a screening test, indicating a low number of false negatives. The negative predictive value was 95% at four hours, with a cut-off value equal to 0.92 mg. L^{-1}, which was the highest clinical relevance value. This result demonstrates that a single measurement of serum cystatin C four hours after the surgery, i.e., the renal insult, may be used as an important screening test when an early exclusion of AKI is desired. On the other hand, according to the results of this study, the low especificity of cystatin C may incorrectly diagnose 50% of patients without AKI as having this disease. Similarly, because of its low positive predictive value, a cystatin C above 0,92 mg.L^{-1} does not necessarily mean that the patients have AKI.

We selected a group of patients with no chronic renal disease and values of baseline serum creatinine below 2 mg.dL^{-1}. Patients with chronic renal failure may have elevated levels of serum cystatin C [45], and any analyses of acute changes in renal function with this marker would likely be impaired. However, patients with chronic renal disease are at increased risk of developing AKI. Therefore, the exclusion of patients with this important risk factor for AKI was a limitation of the study.

We conclude that serum cystatin C is an early marker of AKI when measured four hours after surgery for correction of femur fracture in elderly patients. The test exhibited good accuracy (75%), but the main clinical information is that a single blood sample collected four hours after surgery with a value of serum cystatin C lower than 0.92 mg.L^{-1} is discriminatory for the identification of patients with lower chances of presenting AKI.

Declarations

Ethics approval and consent to participate

This study was approved by

Ethics Committee: 5411 – UNESP- Faculdade de Medicina de Botucatu

Telephone: 55 14 3880-1609

E-mail: cep@fmb.unesp.br

Address: Chácara Butignolli, s/n, Rubião Junior, Botucatu, São Paulo, Brazil

The informed consent to participate in the study was obtained from patients (or their parent or legal guardian) and is under the custody of the author.

Availability of data and materials

The datasets used and analysed in the current study are available from the corresponding author on reasonable request.

Funding

This study was performed with the authors' own financing.

Authors' contributions

JSAN and NSPM conceived and designed the study. JSAN and VLFA performed the clinical phase of the study. JSAN, NSPM, RSSJ and PNJ analysed the data. JSAN, NSPM, ILC and PNJ wrote the paper. All the authors reviewed and approved the manuscript.

References

1. Carmichael P, Carmichael AR (2003) Acute renal failure in the surgical setting. ANZ J Surg 73: 144-153. **Link:** https://tinyurl.com/y4cjrd33

2. Calvert S, Shaw A (2012) Perioperative acute kidney injury. Perioper Med (Lond) 1: 6. **Link:** https://tinyurl.com/y57nb9tt

3. Thakar CV (2013) Perioperative acute kidney injury. Adv Chronic Kidney Dis 20: 67-75. **Link:** https://tinyurl.com/y43tfg68

4. Nash K, Hafeez A, Hou S (2002) Hospital-acquired renal insufficiency. Am J Kidney Dis 39: 930-936. **Link:** https://tinyurl.com/y59c5bep

5. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, et al (2013) World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol 8: 1482-1493. **Link:** https://tinyurl.com/yym9su5z

6. Hoste EA, Kellum JA (2007) Incidence, classification, and outcomes of acute kidney injury. Contrib Nephrol 156: 32-38. **Link:** https://tinyurl.com/y3ptwql9

7. Ympa YP, Sakr Y, Reinhart K, Vincent JL (2005) Has mortality from acute renal failure decreased? A systematic review of the literature. Am J Med 118: 827-832. **Link:** https://tinyurl.com/yym77chf

8. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, et al. (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294: 813-838. **Link:** https://tinyurl.com/yx9m3gxv

9. Levey AS, de Jong PE, Coresh J, El Nahas M, et al. (2011) The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 80: 17-28. **Link:** https://tinyurl.com/y5qqqn8v

10. Bagshaw SM, Gibney RT (2008) Conventional markers of kidney function. Crit Care Med 36: S152-S158. **Link:** https://tinyurl.com/y3uc6w3r

11. Ostermann M, Joannidis M (2016) Acute kidney injury 2016: diagnosis and diagnostic workup. Crit Care 20: 299. **Link:** https://tinyurl.com/y35r9pa2

12. Prowle JR, Liu YL, Licari E, Bagshaw SM, Egi M, et al. (2011) Oliguria as predictive biomarker of acute kidney injury in critically ill patients. Crit Care 15: R172. **Link:** https://tinyurl.com/y5o7gxch

13. Okusa MD, Jaber BL, Doran P, Duranteau J, Yang L, et al. (2013) Physiological biomarkers of acute kidney injury: a conceptual approach to improving outcomes. Contrib Nephrol 182: 65-81. **Link:** https://tinyurl.com/y5sn4p9j

14. Filler G, Bokenkamp A, Hofmann W, Le Bricon T, Martinez-Bru C, et al. (2005) Cystatin C as a marker of GFR--history, indications, and future research. Clin Biochem 38: 1-8. **Link:** https://tinyurl.com/y487a4d3

15. Seronie-Vivien S, Delanaye P, Pieroni L, Mariat C, Froissart M, et al. (2008) Cystatin C: current position and future prospects. Clin Chem Lab Med 46: 1664-1686. **Link:** https://tinyurl.com/y3hqhdhk

16. Zhang Z, Lu B, Sheng X, Jin N (2011) Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. Am J Kidney Dis 58: 356-365. **Link:** https://tinyurl.com/y6b2my7w

17. Bagshaw SM, Bellomo R (2010) Cystatin C in acute kidney injury. Curr Opin Crit Care 16: 533-539. **Link:** https://tinyurl.com/yy72tx73

18. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, et al. (2013) Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med 369: 932-943. **Link:** https://tinyurl.com/y6jn53pw

19. Villa P, Jimenez M, Soriano MC, Manzanares J, Casasnovas P (2005) Serum cystatin C concentration as a marker of acute renal dysfunction in critically ill patients. Crit Care 9: R139-R143. **Link:** https://tinyurl.com/yya3q4kh

20. Herget-Rosenthal S, Marggraf G, Husing J, Goring F, Pietruck F, et al. (2004) Early detection of acute renal failure by serum cystatin C. Kidney Int 66: 1115-1122. **Link:** https://tinyurl.com/y3y2zusv

21. Nejat M, Pickering JW, Walker RJ, Endre ZH (2010) Rapid detection of acute kidney injury by plasma cystatin C in the intensive care unit. Nephrol Dial Transplant 25: 3283-3289. **Link:** https://tinyurl.com/y6xupqz8

22. Sagheb MM, Namazi S, Geramizadeh B, Karimzadeh A, Oghazian MB, et al. (2014) Serum cystatin C as a marker of renal function in critically ill patients with normal serum creatinine. Nephrourol Mon 6: e15224. **Link:** https://tinyurl.com/y4bbw9yd

23. Bongiovanni C, Magrini L, Salerno G, Gori SC, Cardelli P, et al. (2015) Serum cystatin C for the diagnosis of acute kidney injury in patients admitted in the emergency department. Dis Markers 2015: 416059. **Link:** https://tinyurl.com/y3yy85zd

24. Kohli HS, Bhaskaran MC, Muthukumar T, Thennarasu K, Sud K, et al. (2000) Treatment-related acute renal failure in the elderly: a hospital-based prospective study. Nephrol Dial Transplant 15: 212-217. Link: https://tinyurl.com/y2reob4v

25. Lamb EJ, O'Riordan SE, Delaney MP (2003) Kidney function in older people: pathology, assessment and management. Clin Chim Acta 334: 25-40. **Link:** https://tinyurl.com/yyob63co

26. Short A, Cumming A (1999) ABC of intensive care. Renal support. BMJ 319: 41-44. **Link:** https://tinyurl.com/y3984kra

27. Goren O, Matot I (2015) Perioperative acute kidney injury. Br J Anaesth 115: ii3- ii 14. **Link:** https://tinyurl.com/yxpbfcxz

28. Fliser D, Ritz E (2001) Serum cystatin C concentration as a marker of renal dysfunction in the elderly. Am J Kidney Dis 37: 79-83. **Link:** https://tinyurl.com/yy7x3r74

29. Hojs R, Bevc S, Antolinc B, Gorenjak M, Puklavec L (2004) Serum cystatin C as an endogenous marker of renal function in the elderly. Int J Clin Pharmacol Res 24: 49-54. **Link:** https://tinyurl.com/y2ggede6

30. Van Den Noortgate NJ, Janssens WH, Delanghe JR, Afschrift MB, Lameire NH (2002) Serum cystatin C concentration compared with other markers of glomerular filtration rate in the old old. J Am Geriatr Soc 50: 1278-1282. **Link:** https://tinyurl.com/y3zpxt42

31. Work Group Membership (2012) Kidney Int Suppl (2011) 2: 2. **Link:** https://tinyurl.com/y2sbmon3

32. Hanley JA, McNeil BJ (1983) A method of comparing the areas under receiver

operating characteristic curves derived from the same cases. Radiology 148: 839-843. **Link:** https://tinyurl.com/yyhqxy9r

33. Azevedo VL, Silveira MA, Santos JN, Braz JR, Braz LG, et al. (2008) Postoperative renal function evaluation, through RIFLE criteria, of elderly patients who underwent femur fracture surgery under spinal anesthesia. Ren Fail 30: 485-490. **Link:** https://tinyurl.com/y3hgmqgd

34. Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, et al. (2015) The definition of acute kidney injury and its use in practice. Kidney Int 87: 62-73. **Link:** https://tinyurl.com/y23m4bpe

35. Bagshaw SM, George C, Bellomo R, Committe ADM (2008) A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. Nephrol Dial Transplant 23: 1569-1574. **Link:** https://tinyurl.com/y66bys5o

36. Robert AM, Kramer RS, Dacey LJ, Charlesworth DC, Leavitt BJ, et al. (2010) Cardiac surgery-associated acute kidney injury: a comparison of two consensus criteria. Ann Thorac Surg 90: 1939-1943. **Link:** https://tinyurl.com/yyltv6yo

37. Finney H, Bates CJ, Price CP (1999) Plasma cystatin C determinations in a healthy elderly population. Arch Gerontol Geriatr 29: 75-94. **Link:** https://tinyurl.com/y638ccx8

38. Sjostrom P, Tidman M, Jones I (2004) The shorter T1/2 of cystatin C explains the earlier change of its serum level compared to serum creatinine. Clin Nephrol 62: 241-242. **Link:** https://tinyurl.com/y45hb2km

39. Wald R, Liangos O, Perianayagam MC, Kolyada A, Herget-Rosenthal

S, et al. (2010) Plasma cystatin C and acute kidney injury after cardiopulmonary bypass. Clin J Am Soc Nephrol 5: 1373-1379. **Link:** https://tinyurl.com/y3fsabdy

40. Ribichini F, Gambaro G, Graziani MS, Pighi M, Pesarini G, et al. (2012) Comparison of serum creatinine and cystatin C for early diagnosis of contrast-induced nephropathy after coronary angiography and interventions. Clin Chem 58: 458-464. **Link:** https://tinyurl.com/y4542de7

41. Briguori C, Visconti G, Rivera NV, Focaccio A, Golia B, et al. (2010) Cystatin C and contrast-induced acute kidney injury. Circulation 121: 2117-2122. **Link:** https://tinyurl.com/y4nnnyv8

42. Yong Z, Pei X, Zhu B, Yuan H, Zhao W (2017) Predictive value of serum cystatin C for acute kidney injury in adults: a meta-analysis of prospective cohort trials. Sci Rep 7: 41012. **Link:** https://tinyurl.com/y4aou9nd

43. Ristikankare A, Poyhia R, Kuitunen A, Skrifvars M, Hammainen P, et al. (2010) Serum cystatin C in elderly cardiac surgery patients. Ann Thorac Surg 89: 689-694. **Link:** https://tinyurl.com/y3zwyfwc

44. Eriksen BO, Mathisen UD, Melsom T, Ingebretsen OC, Jenssen TG, et al. (2010) Cystatin C is not a better estimator of GFR than plasma creatinine in the general population. Kidney Int 78: 1305-1311. **Link:** https://tinyurl.com/yy4345jd

45. Wei L, Ye X, Pei X, Wu J, Zhao W (2015) Diagnostic accuracy of serum cystatin C in chronic kidney disease: a meta-analysis. Clin Nephrol 84: 86-94. Link: https://tinyurl.com/yxql9mgj