



Influence of variation of the serum creatinine on outcomes of patient with acute kidney injury

Influência da variação da creatinina sérica no desfecho do paciente com lesão renal aguda

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Objective: to identify the influence of variations on serum creatinine on outcomes of patients with acute kidney failure. **Methods:** observational and prospective study. Eighty-five patients which evolved with renal impairment composed the sample. The data was extracted from medical records and reported in a questionnaire created previously. It was considered values $p \leq 0.05$ as significant. **Results:** most of patients were male gender (51.8%) and elder (66 ± 14 years). The reduction of kidney function occurred in different graduation, considering that 35.3% evolved with risk to kidney injury (stage 1) and lower percentage (14.1%) was more severely affected (stage 2 and 3), respectively. During follow-up, the clearance creatinine progressively increased showing recovery of kidney function. Patients with renal injury or failure (stage 2 or 3) evolved more frequently to death ($p=0,027$). **Conclusion:** variations on serum creatinine may exacerbate the patient outcomes over hospitalization period. **Descriptors:** Acute Kidney Injury; Creatinine; Mortality.

Objetivo: identificar a influência de variações na creatinina sérica sobre o desfecho dos pacientes com lesão renal aguda. **Métodos:** estudo observacional prospectivo. A amostra foi composta de 85 pacientes que evoluíram com comprometimento renal. Os dados foram extraídos do prontuário e registrados em questionário construído previamente. Valores com $p \leq 0,05$ foram considerados significativos. **Resultados:** a maioria dos pacientes era do sexo masculino (51,8%) e idosos (66 ± 14 anos). A redução da função renal ocorreu em graduações diferentes, haja vista que 35,3% evoluiu com risco para lesão renal (estágio 1) e um menor percentual (14,1%) foi acometido mais gravemente (estágios 2 e 3), respectivamente. O *clearance* de creatinina aumentou progressivamente revelando recuperação da função renal ao longo do acompanhamento. Pacientes com lesão ou falência renal (estágios 2 ou 3) evoluíram mais frequentemente ao óbito ($p=0,027$). **Conclusão:** variações na creatinina sérica podem agravar o desfecho do paciente ao longo do período de internação. **Descritores:** Lesão Renal Aguda; Creatinina; Mortalidade.

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Introduction

The hospital acute kidney injury is a multifactorial syndrome related with multiples etiologies and risk factors. The current diagnostic systems of kidney injury is based on detection high level of serum creatinine, on decrease of urine production, in the necessity of renal replacement therapy or combination of these factors⁽¹⁾.

In general, this syndrome is a complication founded in hospitalized patients and it is an independent risk factor to chronic kidney disease and for mortality increase⁽²⁾. The classification Kidney Disease Improving Global Outcomes (KDIGO) is the most actual consensus that define acute kidney injury as abrupt reduction (less than 48 hours) of renal function recognized by absolute increase of serum creatinine (sCr) equivalent to ≥ 26.5 micromols/L ($\geq 0,3$ mg/dL) or increase of 1.5 time in relation to its basal value, recognized as that occurred in 7 days, or even by reduction of urinary output (oliguria reported with volume < 0.5 mL/kg/hour per > 6 hours)⁽³⁾.

Despite the serum creatinine being recognized as the marker more used for evaluation of renal function, it suffers influence of factors like muscle mass, hypercatabolism and drugs, so can overestimate or underestimate the glomerular filtration rate⁽⁴⁾. Increases almost imperceptible on serum creatinine during hospitalization period are associated with short-term mortality, progression for chronic kidney disease and accelerated progression to end-stage renal disease, but still to higher risk to long term mortality, including in those patients with partial renal recovery⁽²⁾. However, it is considered the marker more used in clinical practice to identification of renal dysfunction, even delayed, considering that, generally its increasing occurs after renal function decline⁽⁵⁾.

In the general context, the acute kidney injury is one the most worrying complications in hospitalized patients, due its potential predisposition to unfavorable outcomes such as chronicity of renal impairment and mortality. It affects millions of patients worldwi-

de, and it is responsible for prolonging the hospitalization stay and, sometimes the necessity of admission in the intensive care unit, increasing cost related to care and the progression rate to chronic kidney disease, leading to poor quality of life⁽⁶⁾. Despite recent advances in treatment modalities, the incidence of acute kidney injury continues to rise, and represent 0.3% of the general population, 18.0% of hospitalized patients and reach 60.0% those critically ill⁽⁶⁾. Early recognition of risk to develop degrees, still that milder this syndrome, is relevant, since because even the milder forms injury can evolve with grave consequences⁽⁶⁾.

The acquisition of better comprehension about survivors' clinical history with hospital renal injury, at greater risk for progressive chronic kidney disease and death is vital importance for public health. Scientific evidences have showed that milder forms of renal injury, that not require dialysis are associated to short and long-term mortality⁽⁷⁻⁸⁾.

The recognition of risk at progressive chronic kidney disease in survivors of acute kidney injury and his risk factors can be an indicator for better directions of prevention strategies, in long term. Therefore, this study has as objective to identify the influence of variations on serum creatinine (sCr) on outcomes of patients with acute kidney injury.

Methods

Observational and prospective study carried out in a large public hospital of the Federal District, Brazil. Two hundred ninety four patients were followed, from these, 85 that evolved with renal impairment and necessity of treatment during eight months at general medical clinic were chosen. For data collect, it was used a questionnaire with patient's clinical and laboratory data, from 2017, January 15th to 2018, March 10th.

The inclusion criteria were: absent of previous history of acute kidney injury according criteria Kidney Disease Improving Global Outcome (KDIGO)⁽³⁾, age ≥ 18 years and admission over 48 hours. Patients

with chronic kidney disease, in maintenance dialysis or peritoneal dialysis and kidney transplant were excluded.

The laboratory parameters, urea, creatinine, sodium, serum potassium and estimated creatinine clearance (CKD-epi) measured during admission on medical clinic were extracted from medical records. When the value of serum creatinine was not available on admission, it was used his lower value, during hospitalization, as the reference of patient⁽⁹⁾. The demographic and clinical data included age of patient, gender, admission data, discharge, comorbidities coexisting, which all were extracted from patient's medical records or were identified during admission.

The burden of comorbidities was estimated by Charlson Comorbidity Index. This index incorporate 17 different medical conditions, and it made possible to evaluate the impact caused by comorbidities, as well as predict mortality through score that varies from 0 points for that person with lower severity and 6 points for that with higher severity (moribund)⁽¹⁰⁾.

The acute kidney injury was defined as increase of serum creatinine $\geq 0,3\text{mg/dL}$ in 48 hours or increase from 1.5 to 1.9 times of his initial value/baseline within seven days, according to KDIGO classification⁽³⁾, that establishes three dysfunction stages: stage 1 (risk), stage 2 (renal injury) and stage 3 (renal failure), according to the impairment of renal function always adopting the worst value of serum creatinine.

The patients were divided in two groups based in their status survival, being considered the mortality of patient into medium of 30 days of the identification of acute kidney injury.

Results were showed by descriptive statistic such as mean and standard deviation, median and percentile 25 and 75. The Mann-Whitney test was used for comparison of the two groups. The χ^2 test was used to compare both groups with categorical variables (nominals) by means of Statistical Package for the Social Sciences program version 23. Considering values of $p \leq 0.05$ as significant statistically.

The study protocol was approved by Ethic

Committee in research of the Secretary of Health of Federal District, under number 1.398.837 (CAAE: 51576215.8.0000.5553), and free and informed consent was obtained with patients included in the study or by main responsible relative, following the ethics standards required for researches with human being.

Results

Eighty-five patients were followed-up, from these, most were male gender 44 (51.8%) and elderly (66 ± 14 years), with body mass index and creatinine clearance of admission without alterations, 24.8 kg/m^2 and 65 mL/min , respectively. The race/color skin most frequent was black/brown 59 (69.4%), as well as marital status, married 26 (30.6%). Most of patients, although conscious 62 (72.9%) was bedridden 50 (58.8%)

Arterial hypertension 60 (70.6%), renal dysfunction 53 (62.5%), diabetes mellitus 49 (57.6%) and heart diseases 45 (52.9%) represented the most frequent comorbidities, even so more than half of patients were discharged 48 (56.5%), paradoxically, a lower percentage evolved to death 21 (24.7%). The higher incidence of discharge was based on Charlson Comorbidity Index (CCI) <4 (lower severity) identified in 53 (62.3%) of patients' total. In the same time, from 46 patients (54.1%) in worst clinical condition, 39 (45.9%) showed CCI ≥ 4 (greater severity).

In general, 60 (70.6%) patients used at least two classes of antibiotic during hospitalization on the medical clinic unit. In addition, the most of patients 54 (63.5%) used furosemide, and 46 (54.1%) were kept in ambient air, that is to say, without necessity of oxygen support. Blood transfusion was necessary for eight (9.4%) patients.

Hospitalization time (period from admission to discharge from medical clinic) was 49 ± 46 days. In the general context, a majority of patients 30 (35.3%) evolved with risk for kidney injury (stage 1) condition of lower severity expressed by KDIGO classification and 12 (14.1%) in stages 2 and 3, in other words, con-

dition of medium and high severity, respectively.

It is observed that, over the follow-up period, it was identified improvement of kidney function of patients, recognized by progressive variation of creatinine clearance (crCl). Considering that initially, in other words, in the first seven days of hospitalization in the medical clinic, this clearance reached the average minimum value 51 mL/min, but on the discharge of sector, this value increased to 62 mL/min and after discharge achieved 80±43 mL/min (Table 1).

Table 1 – Creatinine Clearance (crCl) in different follow-up period of patients admitted in the medical clinic unit

Follow-up period	Creatinine Clearance (mL/min)	
	Mean± standard deviation	Median (25-75)
7 days	51±33	40 (27-68)
Discharge	62±39	48 (30-99)
1 month after discharge	80±43	83 (31-120)

There was significant relation between kidney function and outcomes (p=0.027). The results show that patients with injury or kidney failure (greater severity stages) have greater chance to not survive (Table 2).

Table 2 – Relation between kidney function and the outcomes (death)

Kidney function	Survivor	Nonsurvivor	p*
	n(%)	n(%)	
Normal or risk (lower severity)	50 (82.0)	11 (21.9)	0.027
Injury or kidney failure (greater severity)	14 (58.3)	10 (41.7)	

*χ² Test (likelihood ratio)

The findings of Table 3 indicate, in general, that not being conscious during hospitalization in the medical clinic was significant for the occurrence of death (p<0.001), as well as to be black/brown(p=0.037), to show diastolic arterial pressure altered (p=0.035) and to have advancing age(p=0.023).

Table 3 – Relation between demographics, clinical aspects and outcomes (death) of patients hospitalized in the medical clinic unit in the period of 30 days after identification of kidney dysfunction

Demographics/clinical aspects	Survivor		Nonsurvivor		P
	Yes n(%)	No n(%)	Yes n(%)	No n(%)	
Male gender	30 (54.5)	25 (45.5)	13 (46.4)	15 (53.6)	0.487
Black or brown race	40 (72.7)	15 (27.3)	18 (64.3)	10 (35.7)	0.037
No consciousness	7 (12.7)	48 (87.3)	15 (53.6)	13 (46.4)	<0.001*
Systolic blood pressure altered	35 (63.6)	20 (36.4)	14 (50.0)	14 (50.0)	0.049
Dyastolic blood pressure altered	22 (40.0)	33 (60.0)	18 (64.3)	10 (35.7)	0.035
Kidney dysfunction	30 (54.5)	25 (45.5)	22 (78.6)	6 (21.4)	0.028*
Injury or failure	8 (14.5)	47 (85.5)	15 (53.6)	13 (46.4)	<0.001*
Age (years); Median (Percentile 25-75)	65 (55 – 74)		72 (60 – 79)		0.023**
Time in Medical Clinic (days); Median (Percentile 25-75)	33 (20 – 82)		25 (15 – 42)		0.042

*χ² Test (likelihood ratio); **Mann-Whitney test; Time in medical clinic = discharge date – Admission date medical clinic; Systolic pressure altered when <90 or >140mmHg; Diastolic pressure altered when <60 or >100mmHg

Discussion

The difficulties found during this study are associated to the lack of dosage of biologic markers that subsidize the follow-up of patients hospitalized in medical clinic, and also the fact the study had been developed in a unique center.

This study identified the influence of variations on the serum creatinine (sCr) on outcomes of patients with acute kidney injury. The results showed that depending of this variation the outcomes could be aggravated.

Clinically, the acute kidney injury is a renal syndrome of broad spectrum of manifestations ranging from tubular stress (subclinical) to oligoanuric renal failure, and infers a significant risk for short and long-term mortality⁽¹¹⁾. The hospital acquired kidney dysfunction occurs mainly in patients of risk, due to a combination of hypovolemia/hypotension, sepsis

and nephrotoxins, particularly in those elderly and in critical condition. Using the actual criteria of diagnostic and graduation, the acute kidney injury occurs in more than half of patients treated in the intensive care unit⁽¹²⁾.

This study, although developed in admission unit, showed high percentage of renal dysfunction. However, in the other hand, showed predominance of the outcomes of discharge. This finding highlight for reduced severity identified in the most of patients signalized by lower value of the Charlson Comorbidity Index (lower than 4). Moreover, it was verified that throughout of follow-up in the medical clinic the creatinine clearance of patients was progressively increasing until discharge, situation favorable for recovery of renal function⁽¹⁰⁾. The Charlson Index can be beneficial, not only to predict risk to death due comorbidities, but to predict adverse outcome of kidney function of patients with acute kidney injury⁽¹³⁾. In those patients that evolved to death, the injury or renal failure had present primarily during follow-up, showing positive association ($p < 0.001$). Scientific evidence developed in clinic, a different scenario of intensive therapy, showed intra-hospital mortality incidence about 28.6%⁽¹⁴⁾ similar to the percentage found in this study, 24.7%.

The acute kidney injury growing in the last two decades can be reflected in changes in characteristics on hospitalized patients (elder population and greater burden of comorbidities), finding identified in this study, in which most of them were elderly (66 ± 14 years) and accumulated comorbidities such as diabetes mellitus, arterial hypertension and heart disease. Changes in the severity of the precipitant disease (sepsis and cardiovascular diseases) and own rising administration of contrast or exposure to nephrotoxins, also are included in this scenario⁽¹⁵⁾, being illustrated in this study by the use of antibiotics and furosemide. The elders (≥ 65 years) are particularly vulnerable to renal insults, resulting of structural and functional alterations related to age that predispose to decrease of glomerular filtration rate and alteration of

renal reserve⁽¹⁶⁾. The increasing of life expectancy in long term is commonly accompanied of chronic diseases such as hypertension, diabetes mellitus and cardiovascular diseases, reality showed in our study too.

Individuals with diabetes mellitus and arterial hypertension accumulate risk for development of acute kidney injury, considering the losses in the mechanism of self-regulation of renal blood flow, and consequent reduction of renal perfusion⁽¹⁷⁾. Moreover, it is knowing that the hypertension compromise the structure of nephron that hinder the removal of residues and excess of blood liquid, which predispose to acute kidney injury. The diabetes in turn, result in progressive increase of urinary albumin excretion, resulting in decline of glomerular filtration⁽¹⁸⁻¹⁹⁾.

Increasing efforts to improve the control of arterial blood pressure usually increase the number of medicine prescribed, leading to wider pulse pressure and to reduction of diastolic arterial pressure. Even with absence of established hypotension, decrease on arterial pressure in patients with renal self-regulation compromised, particularly in those with arterial hypertension and elders, may lead to an increase of risk for acute kidney injury⁽⁷⁾, as identified in this research.

The permanency of patient in the hospital was minimally estimated in 15 days, in contrast, the maximum was 82 days. Acute kidney injury is a problem to health resulting from different causes and is related to high mortality rates and long periods of hospital admission⁽⁸⁾, finding identified in the present study.

Patients with brown and black skin color evolve with greater frequency to renal compromise⁽⁷⁾ when compared those with white skin color, condition identified in our study too. Currently, the disparities observed between ethnics and racial groups are clearly influenced by genetic susceptibility, socioeconomic status, choice of life style and/or environmental exposition. Ethnic minority groups can be predisposed to microalbumine or macroalbumine, which is common in those individuals with diabetes mellitus⁽¹³⁾. However, there is a rising body of evidence suggesting that

individuals of certain ethnics and racial origins have more susceptibility to develop diabetes and her complications macro and microvascular such renal dysfunction, as described in the present study. Specially, evidence identified that patients with proteinuria and particularly those of ethnicity/race, from south Asia and black people present high risk to renal dysfunction and can be benefited with additional monitoring in a specialized clinic⁽²⁰⁾.

Conclusion

The study made possible to identify that variations in the serum creatinine can aggravate the outcomes of patient during hospitalization period. These variations were identified mainly in elderly people, black race, with conscious level compromise and arterial pressure altered.

In this direction, findings contribute to emphasize the importance of continuum vigilance of patients with this characteristics looking at reduction of incidence of acute kidney injury, and consequently, of mortality. The early identification and intervention of patients with acute kidney injury may also reduce the occurrence of chronic kidney disease.

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Collaborations

Silva HM e Magro MCS contributed on conception and project, analysis and interpretation of data. Duarte TTP contributed in article writing, critical and relevant review of intellectual content and approval of final version to be published.

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