CYSTATIN C AS A SURROGATE MARKER FOR EVALUATING GLOMERULAR FILTRATION RATE IN ACUTE KIDNEY INJURY

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ABSTRACT

BACKGROUND

The gold standard for measuring GFR has practical limitations in clinical practice; instead it is estimated by use of the serum concentration of endogenous filtration markers. The objective of this research was to compare serum cystatin C with serum creatinine for Estimating Glomerular Filtration Rate (eGFR) in acute kidney injury and to determine whether elevated serum cystatin C has an impact on mortality in the presence of kidney injury.

METHODS

This prospective observation study was carried out for 18 months in our institution. It included all indoor Acute Kidney Injury (AKI) patients more than 18 years, admitted in the Department of Medicine of our tertiary care centre. The renal function of the patients was evaluated by testing for serum creatinine and serum cystatin C. Serum creatinine based Cockcroft and Gault (CG) equation and Estimated GFR (e-GFR) with Modification of Diet in Renal Disease (MDRD) equation were compared with serum cystatin C based e-GFR Hoek and Larsson equations. All-cause mortality was ascertained by examination of death certificates, inpatient hospital records.

RESULTS

A total of 90 patients were enrolled during the study. The mean serum creatinine (mg/dL) 3.455±1.77, serum cystatin (mg/L) 2.932±1.13, and creatinine clearance (CG) 27.16±16.96, eGFR-MDRD (mL/min.) 24.94±17.95, eGFR-Larsson 31.60±17.36 and eGFR-Hoek 29.00±17.39. The correlation of the Larsson and Hoek cystatin C based GFR estimates (r= 0.94; p=<0.001) and MDRD and CG serum creatinine based GFR estimates (r=-0.93; p<0.001) were highly significant. In multiple logistic regression analysis which included age, serum creatinine and serum cystatin C as variables, only serum cystatin C (p=0. 046) was found to be a significant factor influencing mortality in acute kidney injury.

CONCLUSIONS

The present study suggests that the cystatin C-based prediction equation achieved a diagnostic performance that was at least as good as the creatinine based formulas. Serum cystatin C has superior diagnostic value than serum creatinine in influencing mortality in patients with acute kidney injury.

KEYWORDS

Cystatin C, Glomerular Filtration Rate, Acute Kidney Injury.

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INTRODUCTION

The gold standard for measuring GFR (e.g. Using insulin clearance, urinary clearance of exogenous radioactive markers (125I-iothalamate and 99 mTc-DTPA (Diethylenetriamine-Pentaacetate)), has practical limitations in clinical practice; instead it is estimated by use of the serum concentration of endogenous filtration markers. GFR is presently being monitored by serum creatinine concentration and calculated creatinine clearance using the Cockcroft and Gault equation (CG) or Modification of Diet in Renal Disease study (MDRD) equation.[1],[2],[3]

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The previous studies have suggested that serum cystatin C concentration is a better indicator of GFR than the serum creatinine concentration in patients with spine injury, liver cirrhosis, diabetes, mild-to-moderate impaired kidney function and in elderly patients.[4],[5],[6],[7],[8] The aim of this study was to compare serum cystatin C with serum creatinine for Estimating Glomerular Filtration Rate (eGFR) in acute kidney injury and to determine whether elevated serum cystatin C has an impact on mortality in the presence of kidney injury.

MATERIAL AND METHODS

This prospective observation study was approved by the ethics committee and was performed at our tertiary care centre from February 2013 to July 2014. The study included all indoor Acute Kidney Injury (AKI) patients more than 18 years, admitted in the Department of Medicine of our tertiary care centre. Patients with deranged thyroid function, chronic renal failure and on corticosteroid treatment were excluded from the study. The patients were followed up for 3 months after discharged from the hospital.

Acute kidney injury was defined as a serum creatinine level detected over normal range (>1.2 mg/dL) at presentation or showed increase of 50% or more from the baseline value. The renal function of the patients was evaluated by testing for serum creatinine and serum cystatin C. The serum cystatin C and serum creatinine values were measured simultaneously and analysed at the time of admission. Samples were assayed immediately or stored at -20°C. Cystatin C assay (Human Cystatin C ELISA kits; BioVendor LLC, Candler, NC, USA) employed the quantitative sandwich enzyme immunoassay assay (ELISA) with Microplates were pre-coated with monoclonal antibodies specific for cystatin C.

Serum creatinine was used to estimate creatinine clearance by Cockcroft and Gault (CG) equation and estimated GFR (e-GFR) with the four-variable Modification of Diet in Renal Disease (MDRD) equation.

1. e-GFR (MDRD) (mL/min/1.73m2) =186× (Serum creatinine) -1.154× (Age) -0.203× (0.742 if female).
2. e-GFR (CG)=[(140-Age) × Mass (in kg)] \[72 × Serum creatinine (in mg/dL).

GFR was calculated also according to cystatin C equations.

1. e-GFR (Hoek) (mL/min) =80. 35/serum cystatin C-4.32.
2. e-GFR (Larsson) (mL/min) =99. 43×serum cystatin C-1.583.

All-cause mortality was ascertained by examination of death certificates, inpatient hospital records.

Statistical Analysis

All statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean±SD or n (%). The results of comparing the correlation between two continuous variables were indicated by the correlation coefficient (r) using correlation analysis. Reference values were defined the maximum sum of sensitivity and specificity with over 0.6 of each value. The logistic regression test was performed to identify independent factors impacting mortality in acute kidney injury. A result was deemed statistically significant when p <0.05.

RESULTS

A total of 90 patients were enrolled during the study. There were 68 (75.6%) males and 22 (24.4%) females. The mean age (Years) was 48.89±14.4 (19-70), Weight (Kg) 60.3±12.0 (38-80), BMI (kg/m2) 21.69±2.7 (16-30), and Body Surface Area (m2) 1.64±0.2 (1.13-1.98). (Table 1). Among 90 patients, 52 patients required emergency hospitalization. The most common causes of AKI observed were diarrhoea 63 (70%) and sepsis 22 (24.4%). The mean Serum Creatinine (mg/dL) 3.455±1.77, Serum Cystatin (mg/L) 2.932±1.13 and creatinine clearance (CG) 27.16±16.96, eGFR-MDRD (mL/min) 24.94±17.95, eGFR-Larsson 31.60±17.36 and eGFR-Hoek 29.00±17.39 are shown in Table 1.

The correlation of the Larsson and Hoek cystatin C based GFR estimates (r=0.94; p=<0.001) and MDRD and CG serum creatinine based GFR estimates (r=-0.93; p <0.001) were highly significant. During the study, 12 (13%) patients expired and 11 (12%) patients were lost in the followup after discharged from the hospital. The death group exhibited higher average serum cystatin C (3.36±0.98 mg/L vs. 2.71±1.02 mg/L, p=0.043) as compared to the survival.

Whereas, serum creatinine in the death group was lower (2.41±0.82 mg/dL vs. 3.23±1.27 mg/dL, p=0.035) as compared to the survival group (Table 2). Multiple logistic regression analysis was performed to know the factors impacting mortality in patients with acute kidney injury. Among the variables which included age, serum creatinine, and serum cystatin C, only serum cystatin C (p=0.046) was found to be a significant factor influencing mortality in acute kidney injury (Table 3).

Patient Characteristics	n=90
Age (Years)	48.89±14.4 (19-70)
Male/Female	68/22
Weight (Kg)	60.3±12.0 (38-80)
BMI (Kg/m^2)	21.69±2.7 (16-30)
Body Surface Area (m^2)	1.64±0.2 (1.13-1.98)
Serum Creatinine (mg/dL)	3.45±1.8 (0.9-9.10)
Serum Cystatin (mg/L)	2.91±1.1 (0.88-5.20)
eGFR-CG (mL/min)	27.16±16.9(6.94-101.98)
eGFR-MDRD (mL/min)	24.95±17.9(4.8-105.5)
eGFR-Larsson (mL/min)	31.61±17.4(9.4-77.5)
eGFR-Hoek (mL/min)	29.00±17.4(11.13-86.99)

Table 1: Baseline Characteristic of all Patients

Data are shown as mean±standard deviation (SD).

	Status	n	Mean±SD	t	p
Serum creatinine (mg/dL)	Dead	12	2.41±0.82	-2.142	.035
	Alive	67	3.23±1.27		
Serum Cystatin C (mg/L)	Dead	12	3.36±0.98	2.056	.043
	Alive	67	2.71±1.02		
MDRD (mL/min)	Dead	12	32.14±13.64	1.751	.084
	Alive	67	24.02±14.97		
Cockcroft-Gault (mL/min)	Dead	12	37.82±15.06	3.073	.003
	Alive	67	25.38±12.52		
Hoek (mL/min)	Dead	12	22.17±7.03	-1.703	.093
	Alive	67	31.11±17.85		
Larsson (mL/min)	Dead	12	27.20±10.34	-1.280	.204
	Alive	67	33.72±17.05		

Table 2: GFR Markers according to Overall Mortality

	B	S.E.	Wald	df	p-value
Age Year	.024	.023	1.087	1	.297
Serum Cystatin C mg/L	-.646	.323	3.993	1	.046
Serum Creatinine mg/dL	.630	.465	1.833	1	.176
Constant	2.531	1.464	2.988	1	.084

Table 3: Multivariate Logistic Regression for Mortality using Age, Serum Cystatin C and Serum Creatinine

DISCUSSION

The CG and MDRD equations have been evaluated in numerous published studies and widely applied. However, the equations have some well-known limitations.[9] Therefore, new alternatives like creatinine-based CKD-EPI equation, cystatin C-based formulas and equations that uses both serum creatinine and serum cystatin C were developed.[2],[10],[11],[12],[13],[14] In our study, we compared the widely used creatinine-based equations and cystatin C-based equations in patients with AKI.

No difference between correlation coefficients of the creatinine based formulas and cystatin C formula was found. The results of the present study suggest that the cystatin C-based prediction equation, which requires just one variable, achieved a diagnostic performance that was at least as good as the creatinine based formulas using more variables. Rule et al, in a prospective study, concluded that the cystatin C formula is complementary to the serum creatinine-based equations or can be used in place of the serum creatinine-based equations.[15]

Cystatin C is also a marker of inflammation and like many other markers of inflammation its plasma concentration may be higher in patients with decreased renal clearance. There is mounting evidence, however, that cystatin C may be a predictor of adverse outcomes independent of renal function.[16] In the study by Koenig et al, the association of serum cystatin C with adverse outcome was independent of CRP and other factors known to influence cystatin C concentrations.[17] In the present study, both serum creatinine and serum cystatin C concentrations as measured during hospitalization were significantly higher for the group exhibiting mortality during the course of the study period.

The death group within the first three months had an average serum cystatin C level of 3.36 mg/L, while the survival group had an average level of 2.7 mg/L, thus yielding a significant difference (p=0.04). In multiple logistic regression analysis which included age, serum creatinine and serum cystatin C, only serum cystatin C was found to be a significant independent factor influencing mortality in acute kidney injury. This suggests that in patients with serum cystatin C concentrations of 3.36 mg/L or higher, there is a higher rate of mortality.

In conclusion, the results of the present study suggest that the cystatin C-based prediction equation achieved a diagnostic performance that was at least as good as the creatinine based formulas. Serum cystatin C has superior diagnostic value than serum creatinine in influencing mortality in patients with acute kidney injury.

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