CYSTATIN C AS AN EARLY MARKER OF CARDIORENAL SYNDROME TYPE 1 IN PATIENTS ADMITTED WITH ACUTE HEART FAILURE

Diwakar Manandhar,[1] Bikram Bir Bajracharya,[2] Nirajan Shah,[3] Asia Khanum,[4] Tanjima Parvin[5]

[1]Department of Nephrology, Nepal Medical College Teaching Hospital, Attarkhel, Gokarneshwor-8, Kathmandu, [2]Shaid Dharma Bhakta National Transplant Center, Dudhpati, Bhaktapur, [3]B&C Medical College Teaching Hospital and Research Center, Birtamode, Jhapa, Nepal, [4]Department of Nephrology, [5]Department of Cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

ABSTRACT

The development of acute renal dysfunction in patients with acute heart failure is known as cardiorenal syndrome (CRS) type 1. Cystatin C has emerged as an alternative to serum creatinine which helps to detect early deterioration of the renal function, and in turn help to initiate necessary interventions in management to prevent acute kidney injury (AKI). This is a prospective observational study which was conducted in the Department of Cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The blood sample of the patients was collected on the day of admission for serum cystatin C and serum creatinine, then serum creatinine was subsequently followed on days 2 and 7, to identify the development of cardiorenal syndrome type 1. Cardiorenal syndrome type 1 developed in 18 (35.3%) of 51 patients admitted to the CCU. Most of the patients were men and had a median age of 57.61±12.99 years. Patients who had developed AKI had a higher serum cystatin C level (1.58±0.191mg/L vs. 0.971±0.344 mg/L) and also revealed that the stage of severity of the KDIGO AKI was correlated with a higher serum cystatin C. Serum cystatin C was proven as a good early biomarker for the diagnosis of cardiorenal syndrome type 1.

KEYWORDS

Acute heart failure, cardiorenal syndrome, cystatin C

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CORRESPONDING AUTHOR

Dr. Diwakar Manandhar
Department of Nephrology,
Nepal Medical College Teaching Hospital,
Attarkhel, Gokarneshwor-8, Kathmandu, Nepal
Email: diwakar11107@gmail.com
Orcid No: https://orcid.org/0000-0002-4603-1895
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INTRODUCTION

Heart failure is a condition with high morbidity and mortality in which a great proportion of patients requiring hospitalization also present different degrees of renal dysfunction.[1] The condition produced by acute heart failure that triggers acute renal dysfunction is known as CRS type 1.[2] It occurs in 25-33% of patients hospitalized for acute heart failure.[3] The development of this syndrome may only have partial renal recovery and can cause permanent renal impairment and the need for dialysis. Its main causes are altered renal perfusion and neurohumoral disorders.[4] Worsening renal function during hospitalization for acute heart failure has been shown to be a poor prognostic factor,[5] with longer hospital stay and higher in-hospital and at follow-up mortality. The factors involved in the development of cardiorenal syndrome type 1 are: venous congestion, dysfunction of the sympathetic nervous system, anemia, activation of the renin angiotensin aldosterone system (RAAS), disruption of the hypothalamic-pituitary axis, and significant changes in immune and somatic cell signaling.[6] Renal impairment occurs as a result of renal hypoperfusion, which occurs as a consequence of reduced cardiac output and systemic arterial pressure. A sudden decrease of intravascular volume activates the renin angiotensin aldosterone system (RAAS), which leads to an increase in angiotensin II, which stimulates creation and release of endothelin 1 in kidneys, a strong profibrotic inflammatory and vasoactive peptide which plays an important role in most pathogenetic mechanisms of acute kidney injury.[7] Serum Creatinine is not a reliable indicator during acute changes in renal function[8] because the level can be within the normal range even in patients with 50% kidney damage.[9] With serum creatinine, despite established renal failure, in many occasions the diagnosis of CRS is delayed by 24-48 hours. Cystatin C is a protein that belongs to the cystatin super family of human cysteine protease inhibitors, which is composed of 12 proteins.[10] It is produced at a constant rate by nucleated cells. Due to its low molecular weight (13-kDa), cystatin C is removed from the bloodstream by glomerular filtration, reabsorbed, and catabolized by tubular epithelial cells.[11] Cystatin C is able to detect small reductions in GFR, enabling the early diagnosis of renal dysfunction.[12] Its concentration can increase even two days before the increment of serum creatinine concentration.[13]

MATERIALS AND METHODS

This is a prospective observational study carried out in the Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from September 2018 to August 2019. Patient included were those who got admitted in the CCU of age ≥18 years of both sexes with features of heart failure based on history, physical examination, and lab parameters with normal serum creatinine (<1.4 mg/dl).[14] Exclusion criteria: Coronary procedure including angiogram or PCI two days prior or five days after administration. Patients with short term surgical plan for valvular heart disease or coronary artery bypass graft, patients with chronic kidney disease, abnormal thyroid function, and acute infective state. Serum cystatin C was measured within the first 24 hours after admission along with serum creatinine and serum urea, electrolytes, serum calcium, and serum phosphate. Then serum creatinine will be followed on days 0, 2, and 7. Patients will be divided into two groups based on development of AKI or not. The alteration of serum creatinine will be compared in each group and correlated with serum cystatin C, and the outcome will be measured.

Statistical analysis: Computer-based statistical analysis were carried out with appropriate techniques and systems. All data were recorded systematically in pre-built data collection form. Quantitative data were expressed as mean and standard deviation and qualitative data were expressed as frequency distribution and percentage. Statistical analysis were performed by using Windows-based computer software with Statistical Packages for Social Sciences (SPSS-23) (SPSS Inc, Chicago, IL, USA). The association between categorical variables was performed using the chi-square test and continuous variables using the t test or the Mann-Whitney U test. For all statistical tests, we considered p value <0.05 as statistically significant.

Ethical implication: This protocol was approved by the Ethics Review Committee of BSMMU, Dhaka.

RESULTS

Total number of 51 patients were recruited among which 18 (35.8%) developed AKI and 33 (64.7%) did not. The mean age of the patient who developed AKI was 57.61±12.99 years and that of who did not develop AKI was 54.85±8.30. Patients who developed AKI were older than those who did not, but there was no significant statistical difference between the two groups.

Table 1: Baseline demographic characteristics of the study patients on day 0 (n=51)				
Demographic characteristics	**Total (n=51)**	**AKI (n=18)**	**No AKI (n=33)**	**P value**
BMI (kg/m^2)	25.6±3.92	26.21±4.46	25.33±3.63	0.451 ^
History of diabetes mellitus	37 (72.5%)	17 (94.4%)	20 (60.6%)	**0.010** *
History of hypertension	30 (58.8%)	12 (66.7%)	18 (54.5%)	0.401 *
Drugs history				
NSAIDs	10 (19.6%)	1 (5.6%)	9 (27.3%)	0.062 *
Aspirin	24 (47.1%)	8 (44.4%)	16 (48.5%)	0.782 *
ACE I/ARB	20 (39.2%)	7 (35%)	13 (65%)	0.972*
Systolic blood pressure (mmHg), Day 0	113.5±16.1	102.67±15.58	119.33±13.19	<0.001 ^
Diastolic blood pressure(mmHg), Day 0	71.5±13.4	63.89±10.02	75.64±13.3	0.002 ^
Mean arterial pressure (mmHg), Day 0	85.4±13.3	76.8±11.6	90.1±11.9	<0.001^

^Unpaired t-test was done for quantitative variables and * Chi-square test was done for qualitative variable

Table 2: Clinical parameters of the study subjects on day 0 (n=51)				
Investigations	**Total (n=51)**	**AKI (n=18)**	**No AKI (n=33)**	**P value**
Serum cystatin C (mg/L)	1.11±0.35	1.58±0.191	0.971±0.344	<0.001
S. creatinine (mg/dl)	1.10±0.16	1.14±0.14	1.08±0.17	0.103
Pro BNP (U/L)	1537.7±3015.4	1492.8±2329.9	1562.1±3364.7	0.938
Troponin I (ng/dl)	8.75±15.89	10.36±17.28	7.87±15.29	0.598
CPKMB (U/L)	39.28±34.65	33.43±24.66	42.47±39.03	0.379
Serum urea (mmol/L)	12.44±16.33	17.72±22.76	9.55±10.84	0.088
Hemoglobin (gm/dl)	11.56±1.87	10.27±1.23	12.27±1.80	<0.001
eGFR (ml/min/1.73^2)	69.71±12.78	65.83±9.4	71.83±13.9	0.024
S. sodium (mmol/l)	137.80±5.95	139.44±7.72	136.91±4.62	0.148
S. potassium (mmol/l)	4.17±0.81	3.99±0.87	4.26±0.78	0.262
S. calcium (mmol/l)	2.23±0.12	2.20±0.14	2.24±0.10	0.201
S. phosphate (mmol/l)	1.11±0.24	1.18±0.25	1.08±0.22	0.141
RBS (mmol/l)	12.02±3.83	13.23±3.01	11.35±4.11	0.094
Ejection fraction (%)	36.49±9.77	37.11±10.97	36.15±9.21	0.740

Males were predominantly affected more than females. Seventeen of 37 patients with diabetes mellitus had developed AKI which was statistically significant and had a lower blood pressure. Systolic blood pressure was 102.67±15.58 vs. 119.33±13.19 mmHg), diastolic blood pressure was (63.89±10.02 vs. 75.64±13.31 mmHg) and mean arterial pressure was (76.8±11.6 vs. 90.1±11.9 mmHg). Study subjects were more anemic (10.27±1.23 vs 12.27±1.80 g%) and had a higher baseline serum cystatin C value (1.58±0.191 vs. 0.971±0.344 mg/L) who

Table 3: Comparison of serum cystitin C between AKI and non-AKI patients (n=51)			
Variables	**AKI (n=18)**	**No AKI (n=33)**	**P value**
Serum cystatin C (mg/L)	1.58±0.191	0.971±0.344	<0.001

Table 4: Comparison of Serum Cystatin C among different stages of AKI on day 0				
KDIGO stage n (%)	**Stage 1** 14 (77.7%)	**Stage 2** 1 (5.5%)	**Stage3** 3 (16.7%)	**P value**
Mean±SD(mg/L)	1.317±0.196	1.442±0.0	1.521±0.072	0.001

One-way ANOVA test was performed

Table 5: Sensitivity and specificity at different cutoff values of serum cystatin C in diagnosis of cardiorenal syndrome Type 1

Cystatin C cut-off value	Sensitivity	Specificity
1.202	88.9	72.7
1.236	83.3	72.7
1.255	**83.3**	**75.8**
1.275	77.8	75.8
1.284	77.8	78.8
1.295	72.2	78.8

developed AKI and were statistically significant (p<0.001). In the AKI group, it revealed that serum creatinine was increasing, 1.82±0.79 mg/dl on day 2 and 2.15±1.09 mg/dl on day 7, whereas the non-AKI group didn't show any significant increase in serum creatinine. Subjects who developed AKI presented with a higher level of serum cystatin C (1.58±0.191 vs. 0.971±0.344) which was statistically significant (p=<0.001). Most of the patients were in KDIGO AKI stage 1 which was 14 (77.7%), one (5.5%) was in stage 2 and three (16.66%) was in stage 3. Serum cystatin C at different stages were 1.317±0.196 mg/L in stage 1, 1.442±0.0mg/L in stage 2 and 1.521±0.072 mg/L in stage 3, which was statistically significant (p=0.001). The area under the curve (AUC) of serum cystatin C was 0.831 (95% CI 0.721-0.941). There was a strong correlation with serum creatinine on the day of admission who developed AKI.

DISCUSSION

Cardiorenal syndrome type 1 is a serious medical condition that develops in patients who present with acute heart failure. This study had a total of 51 study subjects, of which 35.3% had developed AKI. The majority were male (72.5%) and the age average age was 57.61±12.99 years, It was similar to other studies conducted Constantin *et al*,[18] Zhang *et al*,[19] Bongiovanni *et al*.[20] This can be explained by the fact that cardiovascular disease is found to be common in older male population groups,[15] Older patients have structural and functional changes with a decrease in the number of nephrons and a decrease in autoregulation capacity, along which there is accumulation of various comorbidities, which eventually leads to an increased susceptibility to AKI.[16] Patients enrolled in this study who developed AKI were relatively hypotensive. Their mean systolic blood pressure was 102.67±15.58 mm of Hg, the diastolic blood pressure was 63.89±10.02 mm of Hg and a mean arterial pressure was 76.8±11.6 mm of Hg. Similar finding was demonstrated by other studies including Hu *et al*.[21] If the mean arterial pressure of the patients decreased below the level to maintain normal renal function, there would be hypoperfusion of the kidney that leads to the development of AKI. GFR is normally autoregulated within an optimal mean arterial pressure but as the mean arterial pressure falls below 80 mm of Hg there would be a rapid decline of the renal function.[17] Hemoglobin was lower 10.27±1.23 gm/dl in the study subjects who developed AKI which was similar to other studies conducted by Han *et al*,[22] and Chen *et al*.[23] Patients who developed AKI are usually in a fluid overload state leading to hemodilution leading to decreased hemoglobin level. Anemia directly reduces the delivery of oxygen to the renal system leading to AKI. Serum cystatin C was found to be a good early marker for the diagnosis of cardiorenal syndrome type 1. Similar studies done by Berezin[24] and Bongiovanni *et al*[25] also showed serum cystatin C levels were higher on the day of admission who subsequently developed AKI. The mean value of serum cystatin C was found to be 1.58±0.91 mg/L in patients who subsequently developed AKI compared to 0.971±0.344 mg/L who didn't develop AKI with a p-value of <0.001. It was not dependent on the age, sex, race, body built, and nutritional status of the patient. Serum cystatin C is capable of the detection of a small reduction in GFR. The increase in serum creatinine occurs only when there is a decrease of greater than 50% in the glomerular ultrafiltration. Serum cystatin C would detect AKI 1-2 days earlier than serum creatinine. As serum cystatin C increases, there is a proportional increase in the severity of the KDIGO AKI stage. The level of serum cystatin C in 14 subjects who developed stage 1 was 1.317±0.196 mg/L, 1.442 mg/L had 1 subject in stage 2 and 1.521±0.072 mg/L had 3 patients in stage 3, as the severity of the glomerular ultrafiltration decreases there is accumulation of more cystatin C which is produced at a constant rate and hence will be proportional to the level of rise of serum creatinine. The conventionally used serum creatinine, when used to detect AKI lagged behind compared to serum cystatin C. Hence, serum cystatin C could be a valuable early biomarker to reflect the possibility of early detection of renal deterioration. Having said this Cystatin C does has its variability and should be cautiously interpreted in patients with advancing age, diabetes mellitus, hyperalbuminemia, thyroid disorders, steroid therapy, inflammatory conditions.[17]

Limitations: There are some limitations to the study. The sample size was small and the study was carried out in a limited time frame. The sample size was taken from one center, and hence it may not represent the whole population of the country.

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