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Original Research Article

A Prospective Comparison of Serum Cystatin C and Creatinine in the Early Diagnosis of Contrast-Induced Nephropathy in North-Eastern Nigeria

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Abstract: ***Aims:*** We aimed to compare the diagnostic efficacy of serum cystatin C (sCyC) for contrast induced nephropathy (CIN) in north-eastern Nigerians undergoing investigations requiring the administration of iodinated contrast media. ***Methods:*** In this prospective study of 150 patients undergoing investigations requiring the administration of iodinated contrast. The demographic, levels of sCr and cystatin c at baseline, 24, 48, 72hours and 3 months after the procedure were noted. Increase of 0.5 mg/dl or 25% from baseline sCr was used to define CIN and optimum cut off of sCyC for CIN diagnosis was obtained using Receiver Operating Characteristic (ROC) curve analysis. Sensitivity and specificity of sCyC for diagnosis of CIN was obtained using Receiver Operating Characteristic (ROC) curve analysis. ***Results:*** At 24 hours of contrast media (CM) exposure, Cystatin C at 24 hours had maximum sensitivity and specificity of 86.2% and 81.0% respectively indicating a good diagnostic efficacy for CIN, however, a rise in serum creatinine was not significant. The optimum cut off of sCyC for diagnosing CIN was found to be a rise of 10% from baseline (AUC – 0.867; sensitivity – 86.2%, specificity – 81.0%). ***Conclusion:*** We may conclude that a rise of 10% in sCyC at 24 h has a good sensitivity and specificity and is reliable in the early diagnosis of CIN.

Keywords: Contrast-Induced Nephropathy (CIN), Cystatin C (CyC / sCyC), Serum Creatinine (sCr), Early Diagnosis, Biomarker.

1. INTRODUCTION

Contrast induced nephropathy (CIN) is defined as acute elevation of serum creatinine >0.5 mg/dL above baseline or increase of serum creatinine >25%, within 48 to 72 hours after administration of contrast media (CM).[1] Serum creatinine is the clinical diagnostic standard, but it does not usually rise immediately after contrast exposure, thus most renal injury may not be detected early. In developed countries of the world CIN has become the third leading cause of hospital-acquired acute renal failure (ARF) after hypovolemia and surgical procedures. [2] With the increasing demand for radiological imaging in our clinical practice in Northern Nigeria and use of contrast media (low-osmolar contrast media, iso-osmolar contrast media, and high-osmolar contrast media) it is expected that the frequency of CIN will increase with corresponding increase in the number of patients with acute kidney injury (AKI) who may require dialysis with its attendant financial cost, morbidity and mortality, hence the need for more search for a means of early detection of CIN following contrast administration and subsequent intervention. Serum Cystatin C (sCyC) is considered to be a more reliable marker than sCr in evaluating the glomerular filtration rate (GFR) in patients with acute renal failure during the first 24–48 h [3]. Furthermore, growing evidence suggest that sCyC is a stronger predictor of clinical outcomes associated with CKD than sCr [4]. However, limited data exist on whether changes in sCyC are superior to sCr in detecting CIN and predicting long-term renal impairment

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and mortality after exposure to CM. In contrast to majority of the studies favouring sCyC as a marker of CIN over sCr, Ribichini *et al.,*[5] in 2012, performed first "head-to-head" comparison of both the markers and found that sCr had better diagnostic power for CIN as compared to sCyC. There is also a lacuna of research in the field of representative range of sCyC for particular ethnic group. In 2008, Darcy *et al.,* [6], showed that sCyC is significantly associated with race/ethnicity of the population and hence standardization of its cut-off for screening of patients with altered renal functions is of utmost important.

Contrast induced nephropathy accounts for 12% of all cases of hospital-acquired ARF in the developed countries. Okoye *et al.,*[7] in a study carried out in Benin, Nigeria to determine the frequency and risk factors of contrast induced nephropathy after contrast procedures reported the incidence of CIN to be 35.9%. Factors that increase the risk of CIN after contrast infusion are pre-existing renal insufficiency, diabetes mellitus, and nephrotoxic agents. Accumulating evidence implicating a combination of ischemic and toxic injury to the renal tubular cells in the pathogenesis of CIN has also been found [8-10].

Bosan *et al.,*[11] described in a study of the characteristics of AKI population indicated a high prevalence of AKI in hospital patients in Nigeria. However, it is not clear whether prior contrast exposure to radiocontrast agents is to be blamed for the observed high rate of AKI in this population. Fortunately, not all patients exposed to radiocontrast agents develop CIN. The fact that many patients exposed to radiocontrast agents never develop CIN suggests that some peculiarities or factors must be present that protects some subjects and renders others vulnerable to the risk of CIN. If these peculiarities and factors are identified in our population and their significance determined, it might be possible to prevent the development of CIN and consequently reduce the high rate of AKI in our setting. Therefore, this prospective study was aimed at determining the prevalence of CIN using serum creatinine, the short-term renal outcomes of patients who developed CIN within 2 weeks and 3 months as well as evaluating the risk factors associated with CIN in Maiduguri.

In this study, we performed a prospective study comparing changes in sCr and sCyC in patients requiring intravenous contrast exposure in north-eastern Nigeria. The purpose was to assess, whether the changes in sCyC at 24 h after CM exposure is a reliable index for early identification of CIN as compared to sCr levels.

2. METHODOLOGY

Consecutive patients who met the inclusion criteria were enrolled as they presented to the radiology department for imaging requiring the use of iodinated contrast media (CM). One hundred and fifty subjects were enrolled for the study. Of these subjects, we posited that some may develop CIN, while others will not. Analysis was done comparing those who developed CIN with those who did not.

Inclusion Criteria;

All patients undergoing contrast studies in Radiology Department of UMTH who are 18 years and above and have consented.

Exclusion Criteria Include;

- Failure to obtain consent from subjects/refusal of subjects to participate in the study
- Subjects with documented end stage renal disease or on maintenance hemodialysis
- Patients in any shock state or severe debilitation
- Subjects who have uncontrolled hyperthyroidism/ thyroid malignancies
- Subjects in heart failure New York Heart Association class III and IV
- Exposure to contrast in the last 24-48hours
- Nursing/pregnant subjects.
- History of hypersensitivity to contrast in the past
- Post renal transplant recipient

3. Sample Collection and Processing

Using standard phlebotomy technique, 10mls of venous blood was collected with a 10ml syringe and needle, and dispensed into a plain bottle. Blood was allowed to clot within 30 minutes and centrifuged for 10 minutes at 14000 rotations per minute. The serum was used to assay creatinine.

4. Statistical Analysis

Data entry and analysis were done using the IBM-SPSS (International Business Machines-Statistical Package for the Social Sciences) Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. Quantitative and qualitative variables were presented as tables and charts while Quantitative variables were summarized as means and standard deviation. Chi-square test was used to assess the association between qualitative variables and development of CIN, Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of sCyC (24 h). Two-sided p value ≤0.05 was considered to indicate statistical significance.

5. RESULTS

Sociodemographic Characteristics

The mean age of the study population was 49.20 ± 15.44 years, with a range of 23 to 75 years. The age group 50-59 years accounted for the highest percentage of subjects at 33.3% (50 subjects) while that of 60-69 years accounted for 20.7% (31 subjects) of the study subjects. Only 6 subjects in the age-range of 18-29 years were enrolled in the study.

Ninety-two (61.3%) subjects were male while 58 (38.7%) were female, with a male to female ratio of 1.58:1.

Most of the study subjects had tertiary education 67(44.6%), 22 subjects (14.7%) had secondary education, 40 subjects (26.7%) had no formal education, while 22 (14.7%) and 21 (14%) subjects had secondary and Islamic education respectively.

Subjects of Kanuri ethnicity accounted for the majority of participants (32.0% of the study subjects). Babur is the second majority (15.3) then followed by Hausa/Fulani (11.3%), Marghi (18%) and Shuwa (6%). Yoruba and Igbo constituted the least participants at 6% each. Other minority tribes accounted for 20% of the study subjects, including Igala, Tiv, Idoma, Nupe, Jaba, Egbira, and others.

The majority of the subjects were married accounting for 74.7% of the study subjects, 12% were widowed, 10.7% single and 2% separated. (Table 4.1)

Table 1: Socio-demographic Characteristics of Study Participants

Variable	Number of subjects (%)	Mean age ± SD (years)
Sex		
Male	92(61.3)	55.5 ± 10.7
Female	58 (38.7)	45.5 ± 13.3
Age Group (years)		
18-29	9(6.0)	
30-39	22 (14.7)	
40-49	27 (18.0)	
50-59	50(33.3)	
60-69	31(20.7)	
70-79	11(7.3)	
Marital Status		
Single	16 (10.7)	
Married	112 (74.7)	
Separated/Divorced	3 (2.0)	
Widowed	19 (12.7)	
Ethnicity		
Kanuri Babur Marghi Shuwa	48 (32.0) 23(15.3) 18 (12.0) 9(6.0)	
Hausa/Fulani	17(11.3)	
Igbo Yoruba	6 (4.0) 6 (4.0)	
Others	20 (13.3)	
Educational Status		
None Secondary Tertiary	40 (26.7) 22(14.7) 67(44.6)	
Islamic	21 (14.0)	

Comparison of Sociodemographic and clinical features between subjects who developed CIN and those without CIN

Table 2 compares the demographics and clinical features of the study subjects, it showed the total number of males and females that developed CIN and those that did not, it also showed the SBP, DBP, with their respective chi-square and P values. Screa, and Cysc at various hours are also on the table, the types of studies the patients had, route of contrast administration, osmolality and ionicity of contrast agents are also reflected on the table. All with their respective chi-square and P values.

Table 2: Comparison of demographic and clinical features between subjects who developed CIN and those without CIN

Variables	CIN n=45	No CIN n=105	Chi Square	P Value
Age **Sex, n(%)** Male Female SBP	55.61 ± 10.7 27(60.0) 18(40.0) 139.11±24.19	48.01±12.02 65(62.0) 40(38.0) 139.62±22.09	χ^2 =0.048 χ^2=0.00	0.009 p=0.826 p=0.971 0.900

DBP	81.56±19.42	82.38±16.49		0.791
RBG (baseline)	7.15±1.64	6.94±1.66		0.536
RBG (24hrs)	7.09±1.45	7.05±1.45		0.999
RBG (48hrs)	6.93±1.52	7.10±1.49		0.734
RBG (72hrs)	7.34±1.45	7.66±6.63		0.364
Scr (baseline)	118.93±30.44	124.81±29.78		0.272
Scr (24hrs)	128.27±27.23	125.70±34.23		0.657
Scr (48hrs)	234.97±163.84	120.20±34.06		0.000
Scr (72hrs)	331.80±247.05	117.94±27.79		0.000
Cys C (baseline)	1.28±0.48	1.34±1.57		0.800
Cys C (24hrs)	2.31±1.72	1.30±1.10		0.000
Cys C (48hrs)	3.22±2.88	1.22±0.69		0.000
Cys C (72hrs)	3.23±2.82	1.29±1.14		0.000
Types of study, n(%)				
IVU	20(44.4)	34(32.3)	χ^2=14.522	, p=0.013
CECT	12(26.6)	10(9.5)	χ^2=15.490	p=0.003
MCUG	7(15.5)	24(22.8)	χ^2=14.522	p=0.013
RCUG	0(0)	1(0.9)	χ^2=8.99	p=0.013
HSG	4(8.80)	15(14.2)	χ^2=150	p=0.023
Barium Study	2(4.40)	21(20.0)	χ^2=11.522	p=0.113
Route of administration, n(%)				
Intravenous other routes	32(71.1)	44(41.9)		0.002
Osmolality of contrast, n(%)	13(28.9)	61(58.1)		0.600
Hyper-osmolar	20(44.4)	34(32.3)	χ^2=1.990	p=0.160
Hypo-osmolar	25(55.6)	71(67.7)	χ^2=1.976	p=0.013

Abbreviations: CIN (contrast-induced nephropathy), Scr (serum creatinine) Cys C (cystatin C)

Sensitivity and Specificity of Cystatin and Creatinine

Receiver operating characteristic curve analysis showed that Cystatin C at 24 hours had maximum sensitivity and specificity of 86.2% and 81.0% respectively indicating a good diagnostic efficacy for CIN. The area under the curve (AUC) for Cystatin C is 0.967 which is slightly higher than AUC for serum creatinine at 24 hours (0.748). The optimum cut off for Cystatin C based on sensitivity and specificity is 10% (Table 3). The comparison of diagnostic power of Cystatin C (24hours) and serum creatinine (24hours) are presented in Figures 1 and 2.

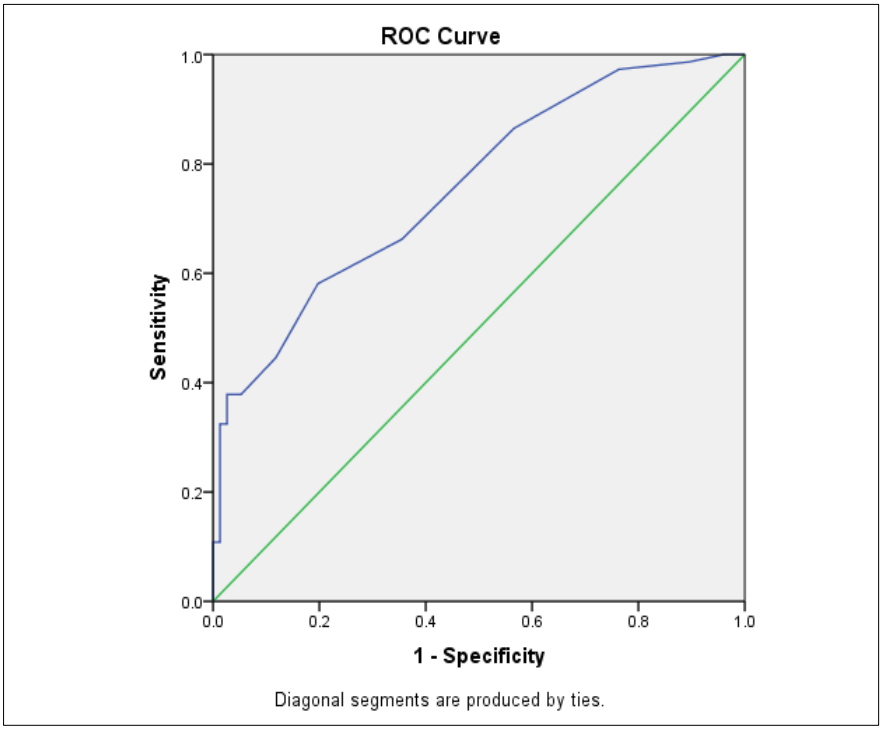

Figure 1: ROC for Cystatin C (24hours)

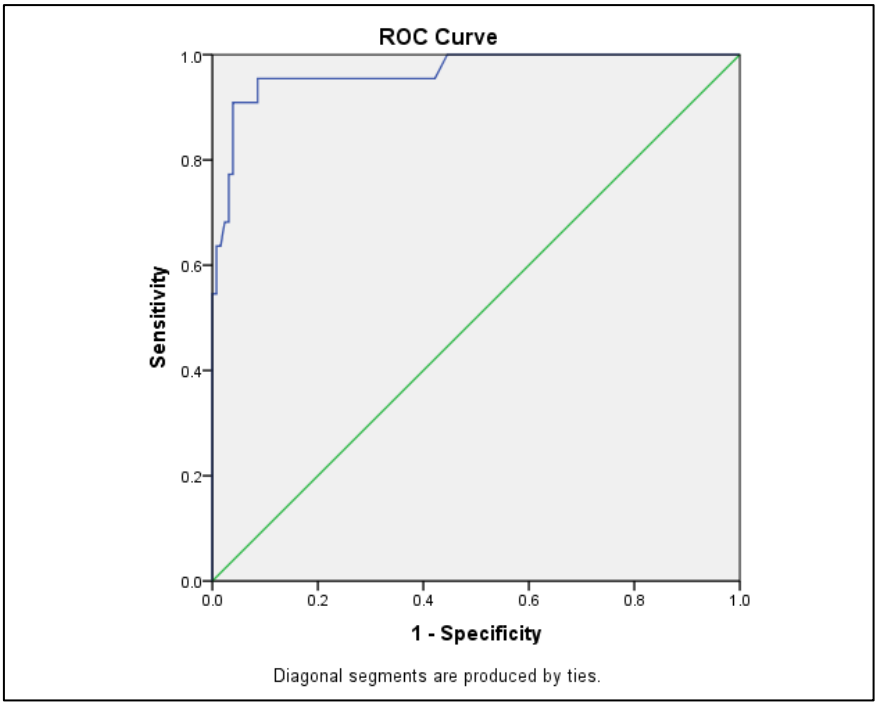

Figure 2: ROC for serum creatinine (24 hours)

Table 3: Receiver operating characteristics curve analysis of Cystatin C for CIN diagnosis

	VALUE	CI (95%)
Optimum cut off for cystatin c	**(≥10%)**	
Sensitivity	86.2%	94.8%-97.6%
Specificity	81.0%	892%-96.0%
Area under the curve	0.967	0.682-0.833 (P=0.00)

Table 4: Receiver operating characteristics curve analysis of creatinine for CIN diagnosis

	VALUE	CI (95%)
Sensitivity	66.2%	94.8%-97.6%
Specificity	57.%	892%-96.0%
Area under the curve	0.967	0.682-0.833

6. DISCUSSION

The mechanism of CIN is complex and poorly understood. Some of the reported mechanisms include

- Renal ischemic injury, tubular epithelial cell toxicity or immunological reaction.
- Osmolality and viscosity of CM increase hypoxia of renal medulla and free radicles production through post ischemic oxidative stress.
- Direct effect of CM on kidney and toxic effect on tubular cell.
- Contrast often induces natriuresis and diuretics which activate tubuloglomerular feedback response – a process involved in GFR regulation, ultimately causing glomerular afferent arterioles vasoconstriction and decline in GFR.

This study showed that, using cross tabulation analysis, cystatin C at 24 hours is 86.2% sensitive and 81.2% specific when compared to serum creatinine in the diagnosis of CIN. This is similar to a study conducted by Koji Kato *et al.,*[12] in 2008, they reported that Cystatin C has highest discrimination power by receiver characteristic curve (ROC) to diagnose CIN at cut-off value of 1.2 mg/L with sensitivity of 94.7% and 84.8% specificity. Qian xu [13] in his study found out that cystatin c is not superior to creatinine in early diagnosis of CIN. Carlo Briguori *et al.,*[14] showed that <10% rise of serum cystatin C at 24 h is reliable marker of CI-AKI whereas a rise of 10% at 24hour is an independent predictor of 1-year major adverse events. Herewith, they reported that a rise of 10% of cystatin C from baseline could be effectively used in clinical settings which is similar to other internationally accepted diagnostic cut-offs.

Acute renal insult is commonly encountered in investigations requiring intravenous iodinated contrast administration. Contrast-induced nephropathy after such procedures is thought to be primarily caused by procedural exposure to contrast agent, which is nephrotoxic at high-doses [15]. The most important risk factor that has been linked to the development of CIN

after these procedures is the presence of pre-existing CKD [16]. Other clinical factors like hemodynamic instability and diabetes mellitus, which are commonly prevalent in this population, may also contribute to its clinical course. In a small proportion of such patients, CIN may be due to renal atheroembolism from diffuse aortic atherosclerosis. Using a definition of contrast-induced nephropathy (a rise in sCr levels of 0.5 mg/dL or 25% increase from baseline), the reported incidence ranges from 8% to 15% in the general population and upto 28% in those with acute coronary syndromes (ACSs) [17]. A rise in sCr concentration is widely accepted method for detecting changes of renal function receiving CM. However, sCr possesses two important drawbacks: 1) The level of sCr is a result of both glomerular filtration rate and of renal tubular secretion and hence the changes in sCr will underestimate the actual alteration in GFR. 2) During acute deterioration of renal functions when GFR reduces drastically, less creatinine is excreted and the remaining creatinine gets distributed in total body water. Thus, the serum level can be expected to rise slowly and will continue to rise until new steady state has occurred. Therefore, although the injury induced by CM impairs GFR almost immediately, it requires 24 to 48 h for the fall in GFR to be reflected in an elevated level of sCr [18-21].

7. CONCLUSION

Contrast induced nephropathy substantially increases morbidity and mortality, a rise of 10% in sCyC levels at 24 h after CM exposure allows an early diagnosis of CIN as compared to sCr. The use of newer biomarkers such as cystatin c in the diagnosis of CIN will help in the early detection and improved outcome of CIN.

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