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Original Article OPEN ACCESS

Efficacy of Serum Cystatin C as a Diagnostic Marker of Early Renal Dysfunction in Hypertensive Individuals

Saima Shakila[*1], MD. Monaim Farhad[2], Farhana Hasan[3], Shaila Sharmin[4], MD. Monzurul Alam Bhuiyan[5], Tuhin Sultana[6], Iltutmish Akanda[7]

Abstract

Introduction: *The aim of the present study was to find out the efficacy of serum Cystatin C as a diagnostic marker of early renal dysfunction in hypertensive individuals.* ***Materials and Methods:*** *This cross-sectional study was conducted from March 2022 to February 2023 in the Departments of Laboratory Medicine & Internal Medicine, BSMMU. All adult individuals (>18 years) attending OPD of Internal Medicine Department were enrolled in this study who fulfilling the inclusion and exclusion criteria. Then, 5 ml of venous blood was collected for the estimation of serum Cystatin C and serum creatinine. Five ml urine was collected for the estimation of spot urinary microalbumin. After data collection and processing, all statistical analysis was done by SPSS software windows version 26.* ***Result:*** *Total of 103 respondents from OPD of Internal Medicine was enrolled in this study. The mean age of the study population was 53.0±11.0 years. The male: female ratio is 2:1. The diagnostic performance of serum Cystatin C based on urinary microalbumin as the gold standard determining the best cut-off of 1.17 mg/L at an optimum sensitivity of 93.8% and specificity of 97.7%, PPV 88.2%, NPV 98.8% and accuracy 97.1%. The diagnostic performance of serum creatinine based on urinary microalbumin as the gold standard determining the best cut-off of 1.20 mg/L at an optimum sensitivity of 81.3%, specificity 98.9%, PPV 92.9%, NPV 96.6% and accuracy 96.1%.* ***Conclusion:*** *Serum Cystatin C level had significantly more correlation with microalbuminuria in hypertensive individuals. The area under the curve had shown that serum Cystatin C had an excellent discriminative ability to detect early renal dysfunction in hypertensive individuals.*

Keywords: *Hypertension, Serum Cystatin C, Serum creatinine, urinary microalbumin.*

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***1. Corresponding Author:**
Dr. Saima Shakila
Assistant Professor
Department of Laboratory Medicine
Chattagram Maa o Shishu Medical College and Hospital
Chattagram, Bangladesh.
Email: saimashakila81@gmail.com
Contact: 01855060613

2. Dr. MD. Monaim Farhad
Resident, Phase B
Department of Orthopedic Surgery
Chittagong Medical College and Hospital
Chattagram, Bangladesh.

3. Dr. Farhana Hasan
Consultant
Laboratory Medicine
Ibn Sina Diagnostic and Consultation Centre
Uttara, Dhaka, Bangladesh.

4. Dr. Shaila Sharmin
Clinical Pathologist
Dhaka Medical College
Dhaka, Bangladesh.

5. Dr. MD. Monzurul Alam Bhuiyan
Assistant Professor
Department of Laboratory Medicine
BSMMU
Dhaka, Bangladesh.

6. Prof. Dr. Tuhin Sultana
Professor
Department of Laboratory Medicine
BSMMU
Dhaka, Bangladesh.

7. Dr. MD. Iltutmish Akanda
Upazila Health and Family Planning Officer
Hakimpur, Dinajpur, Bangladesh.

Introduction:

Hypertension is a multifactorial disorder. It involves an abnormality of renal, neural, endocrine and vascular mechanisms. Blood pressure is the product of cardiac output and peripheral resistance. Hypertension is caused by increased cardiac output and/or increased peripheral resistance[1]. Hypertension is an independent risk factor for renal impairment and end-stage renal disease[2]. The best overall index of renal function is GFR. Isotope clearance procedures can be used to determine precise GFR, however, they are all time-consuming,

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expensive and involve radiation exposure[3]. In routine clinical practice, GFR is estimated from a several equations like C & G formula, MDRD formula, and CKD-EPI formula which is expressed by eGFR[4]. Worldwide accepted and used endogenous filtration markers for GFR estimation are serum creatinine, alone or combined with creatinine clearance[3]. Serum creatinine levels are affected by age, gender, muscle mass, and body size and may remain within the normal limit for a long time until >50% loss of nephron has occurred[5]. The creatinine clearance determination may provide greater accuracy but it is difficult to perform for patients to collect 24-hour urine[3]. Microalbuminuria (MAU) is considered to be a marker of early renal damage from hypertension[6]. Hypertension may cause microalbuminuria and subsequent renal damage[7]. Microalbuminuria may be defined as increased excretion of albumin (30-300mg/day) through urine. Microalbuminuria can be measured by albumin creatinine ratio which is a spot test. The excreted urinary albumin can be adjusted to creatininuria due to variations in urine flow rate and concentration[8]. Cystatin C (Cys C) is a 120-amino acid, non-glycosylated LMW protein (Mr=13359) that is thought to be a better marker than serum creatinine because it is produced by all nucleated cells at a constant rate. It is freely filtered by the glomerulus and not secreted but completely reabsorbed and catabolized by proximal convoluted tubular epithelial cells[9]. Cystatin C is a better marker than serum creatinine because it does not depend on muscle mass, age, sex and body size and nutritional status[5]. The aim of the study was to find out the efficacy of serum Cystatin C as a marker in the diagnosis of early renal dysfunction in hypertensive individuals.

Materials & Methods:

A Cross sectional study was conducted from from March 2022 to February 2023 among 103 patients attending at department of Laboratory Medicine and Internal Medicine, BSMMU, Dhaka after obtaining requisite consent from the hypertensive patients. Data were collected through interviewing of the patients. Then, 5 ml of venous blood was collected for the estimation of serum Cystatin C and serum creatinine. Five ml urine was collected for the estimation of spot urinary microalbumin. The collected data were entered into the computer and analyzed by using SPSS (version 26) to assess the efficacy of serum Cystatin C as a marker in the diagnosis of early renal dysfunction in hypertensive individuals. The study was approved by the institutional ethical committee. The interviews were held directly in the corridor just outside the Outpatient Department.

Results:

Table I reveals that maximum number of the patients (65%) was found below 60 years. The mean age of the study population was 53.0±11.0 years. Majority of the patients (67.0%) were male and 33% patients were female. The male: female ratio is 2:1

Table I: Socio-Demographic Charateristics of the study subjects (n=103)

Parameter	Number	Percentage%
Age (Range 20-75 years)		
< 60	67	65.0
≥ 60	36	35.0
Mean±SD	53.0±11.0	
Sex		
Male	69	67.0
Female	34	33.0
Male: female ratio	2 : 1	

ROC curve analysis of serum Cystatin C based on urine microalbumin as gold standard revealed an area under the curve (AUC) of 0.981, determining a best cut-off of 1.17 mg/L at an optimum sensitivity of 93.8% and specificity of 97.7% at 95%. Confidence interval (0.956-1.000) and p-value= <0.001. ROC curve analysis of serum creatinine based on urine microalbumin as gold standard revealed an area under the curve (AUC) of 0.895, determining a best cut-off of 1.2 mg/dl at an optimum sensitivity of 81.3% and specificity of 98.9% at 95%. Confidence interval (0.775-1.000) and p-value =<0.001 (Figure 1).

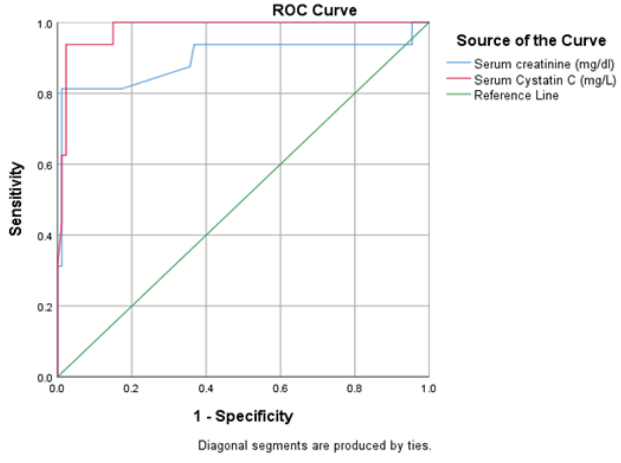

Figure 1: Receiver operating characteristic (ROC) curve of serum Cystatin C, serum creatinine and cut-off value for prediction of early renal dysfunction of hypertensive individual.

Table II reveals that 17 people had serum Cystatin c level was ≥1.17 mg/L of which 15 people had microalbuminuria and 2 people had normoalbuminuria and 86 people had serum cystatin c level was <1.17 mg/L of which 1 person had microalbuminuria and others were normoalbuminic. Cut off value for serum Cystatin C was 1.17 mg/L according to ROC curve (Table II).

Table II: Diagnostic validity test of serum Cystatin C with urinary microalbumin (N=103)

Serum cystatin C (mg/L)	Microalbuminuric subjects (≥30 mg/g) (n=16)	Normoalbuminuric subjects (<30 mg/g) (n=87)	Total
≥1.17	15(93.8%)	2(2.3%)	17(16.5%)
<1.17	1(6.3%)	85(97.7%)	86(83.5%)
Total	16(100.0%)	87(100.0%)	103(100.0%)

Table III reveals that the diagnostic performance of serum Cystatin C based on urinary microalbumin as the gold standard determining the best cut-off of 1.17 mg/L at an optimum sensitivity of 93.8% and specificity of 97.7%, PPV 88.2%, NPV 98.8% and accuracy 97.1%.

Table III: Diagnostic performance of serum Cystatin C

Statistic	Value
Sensitivity	93.8%
Specificity	97.7%
PPV	88.2%
NPV	98.8%
Accuracy	97.1%

Table- IV reveals that 14 people had serum creatinine level was ≥1.20 mg/dl of which 13 people had microalbuminuria and 1 people had normoalbuminuria and 89 people had serum creatinine level was <1.20 of which 3 person had microalbuminuria and others were normoalbuminic. Cut off value for serum creatinine was 1.20 mg/dl according to ROC curve.

Table IV: Diagnostic validity test of serum creatinine with urinary microalbumin (N=103)

Serum creatinine (mg/dl)	Microalbuminuric subjects (≥30 mg/g) (n=16)	Normoalbuminuric subjects (<30 mg/g) (n=87)	Total
≥1.20	13(81.3%)	1(1.1%)	14(13.6%)
<1.20	3(18.8%)	86(98.9%)	89(86.4%)
Total	16(100.0%)	87(100.0%)	103(100.0%)

Table- V shows that the diagnostic performance of serum creatinine based on urinary microalbumin as the gold standard determining the best cut-off of 1.20 mg/L at an optimum sensitivity of 81.3%, specificity 98.9%, PPV 92.9%, NPV 96.6% and accuracy 96.1%.

Table V: Diagnostic performance of serum creatinine

Statistic	Value
Sensitivity	81.3%
Specificity	98.9%
PPV	92.9%
NPV	96.6%
Accuracy	96.1%

Figure-2 Scatter diagram shows that serum Cystatin C had moderately significant correlation with urinary microalbmin in hypertensive individuals (r value = +0.662, p<0.001). The Pearson's correlation was statistically significant (p<0.001)

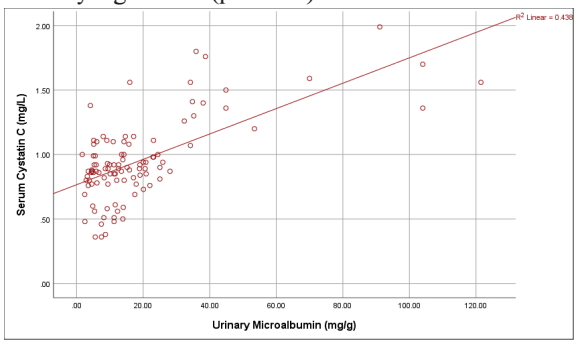

Figure-2: Correlation of serum Cystatin C with urinary microalbumin in hypertensive individuals.

Figure-3 shows that serum creatinine had moderately significant correlation with urinary microalbmin in hypertensive individuals (r value = +0.530, p<0.001). The Pearson's correlation was statistically significant (p<0.001).

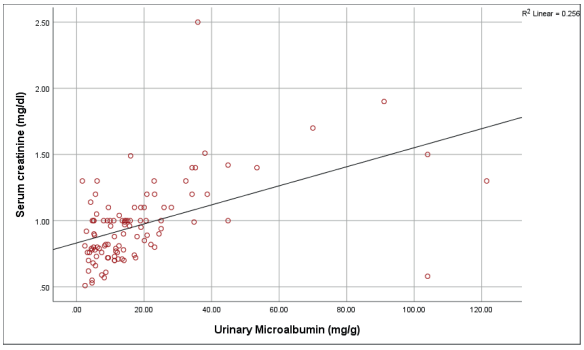

Figure-3: correlation of serum creatinine with urinary microalbumin in hypertensive individuals.

Discussion:

In this present study, it was observed that in hypertensive individuals the mean±SD age was found 53.0±11.0 years. The maximum of the patients (65%) was found below 60 years age group. Salgado et al., 2013 found the mean±SD age was 60.6 ± 11.8 years[10]. In this study, it was observed that 67 % (69) were male and 33% (34) were female and the male-female ratio was 2:1. Rahman et al. (2018) found that there was no significant difference in sex among Bangladeshi hypertensive patients[11]. In the present study, the diagnostic accuracy of serum Cystatin C and serum creatinine was also found by the ROC curve. Urinary microalbumin (30-300mg/g) was used as a gold standard. The area under the ROC curve (AUC) value for Cystatin C was found to be superior (AUC: 0.981) to serum creatinine (AUC: 0.895). It was determined the best cut-off of 1.17 mg/L at an optimum sensitivity of 93.8% and specificity of 97.7% at a 95% confidence interval and p-value= <0.001 for serum Cystatin C. The PPV, NPV and diagnostic accuracy were 88.2%, 98.8% and 97.1% respectively according to the present study. This study also determined the best cut-off of 1.2 mg/dl at an optimum sensitivity of 81.3% and specificity of 98.9% at a

95% confidence interval and p-value= <0.001 for serum creatinine. According to this study, the PPV, NPV and diagnostic accuracy were 92.9%, 96.6% and 96.1% respectively. Ozer et al., 2005 showed a ROC curve in which eGFR was used as the gold standard. They found an area under the ROC curve (AUC) for serum Cystatin C was 0.900 and for serum creatinine was 0.847. The sensitivity and specificity of serum Cystatin C were 91.7% and 89.7% respectively, according to their study. They also found the PPV and NPV were 73.25 and 97.24 respectively. They found the sensitivity and specificity of serum creatinine were 100% and 59% respectively. The PPV and NPV were 42.83 and 100 respectively according to them (Ozer et al., 2005)[12]. It was observed that serum Cystatin C level had a greater association with microalbuminuria than serum creatinine in hypertensive individuals. AUC suggested that serum Cystatin C level had an excellent discriminative ability than serum creatinine to detect early renal dysfunction in hypertensive individuals. So, serum Cystatin C may be used as a biomarker for the diagnosis of early renal dysfunction in hypertensive individuals. In the current study, the correlation of microalbuminuria with serum Cystatin C and serum creatinines in hypertensive group were done by Pearson's correlation coefficient test. Microalbuminuria had a greater correlation with serum Cystatin C level (r-value = +.662, p<0.001) than serum creatinine level (r-value = +.530, p<0.001). Microalbuminuria has a positive correlation with serum Cystatin C level (r-value = 0.38 and p =<0.001) and serum creatinine (r-value = 0.31, p = <0.001) which was observed by Salgado et al., 2013. This was consistent with our study[10].

Conclusion:

It was observed that serum Cystatin C level was found significantly correlated with microalbuminuria in hypertensive individuals. The area under the curve had shown that serum Cystatin C had an excellent discriminative ability to detect early renal dysfunction in hypertensive individuals. Therefore, it may be used as a diagnostic marker for early renal dysfunction in hypertensive individuals.

Conflict of Interest: None.

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