

CYSTATIN-C AS AN EARLY INDICATOR FOR INCIPIENT RENAL DISEASE IN RHEUMATOID ARTHRITIS-A HOSPITAL BASED CROSS SECTIONAL STUDY

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Abstract

Background: The aim of the present study was to examine the diagnostic capacity of this new parameter towards early signs of renal disease in patients suffering from prolonged RA requiring potential nephrotoxic therapy.

Methods: The present study was a cross sectional observational type of study conducted in the department of medicine Mathura Das Mathur Hospital, Dr. S.N. Medical College, Jodhpur. A total of 50 subjects that fulfilled the inclusion and exclusion criteria were enrolled in the study after informed and written consent. As per methodology complete blood count, ESR, liver function test, kidney function test, cystatin-c, urine complete, 24 hours urine creatinine, USG abdomen for kidney size were performed.

Results: cystatin-C level below 0.95 mg/dl was considered normal. 19 patients have normal and 31 patients have abnormal more than 0.95 mg/dl.

Conclusion: In conclusion, as compared to serum creatinine, the determination of serum cystatin C is comparably simple, but by far more sensitive for the diagnosis of incipient renal damage in RA, and therefore valuable for clinical screening particularly in cases with prolonged antirheumatic treatment.

Keywords: Cystatin C, RA, KFT

Introduction

Rheumatoid arthritis (RA) is a chronic disease requiring long-term therapy with nonsteroidal anti-inflammatory drugs (NSAID) and disease modifying antirheumatic drugs (DMARD). The fact that it is a longstanding disease and prolonged antirheumatic treatment particularly (NSAID and/or RA itself can cause renal damage.¹ This renal disorder can be diagnosed in early stage may helpful in management of the patients. Recent studies have shown that plasma Cystatin-C reflects glomerular filtration rate (GFR) better than serum creatinine, blood urea nitrogen since the later is affected by many nonrenal factors, such as muscle mass, hydration, physical activity, body surface area, sex, and age². Cystatin-C, a member of the cystatin super family of cysteine protease inhibitors, is a non-glycosylated, low-molecular weight (13 kDa) basic protein of 120 amino acid³, which is produced by all nucleated cells with a stable production rate unaffected by change in muscle mass, sex and chronic inflammatory conditions. The low molecular weight and a high isoelectric point allow plasma Cystatin-C to be freely filtered through the glomerular basement membrane.⁴These biochemical and biological features suggest Cystatin-C as a sensitive and specific clinical marker of GFR. The aim of the present study was to examine the diagnostic capacity of this new parameter

towards early signs of renal disease in patients suffering from prolonged RA requiring potential nephrotoxic therapy.

Material and Methods

Study Settings: The study was conducted in Department of Medicine, Mathura Das Mathur Hospital, Dr. S.N. Medical College, Jodhpur. It is one of the largest hospital of Western Rajasthan and caters all sections of the society.

Study Type: Hospital based observational study.

Study Design: Cross sectional study.

Study Period: A minimum of 50 Study subjects were recruited for a period of 6 months.

Study subjects: The study was conducted in selected patients attending the medical outdoor and indoor of Department of Medicine M.D.M. Hospital, Jodhpur. Consecutive sampling method was adopted and all the patients fulfilling the following criteria were included in the study:

Inclusion Criteria

Both Male and Female patients aged more than 15 years, with an established diagnosis of Rheumatoid Arthritis, as

defined by the ACR/EULAR criteria for Rheumatoid arthritis of 1-year duration.

Exclusion Criteria

- 1) Patients with evidence of cardiac disease, hypertension, diabetes mellitus.
- 2) Patient with chronic kidney disease (CKD).
- 3) Patient with acute kidney injury (AKI).
- 4) Patient with JRA.

Data Collection

A questionnaire was prepared noting the duration of RA, early morning joint stiffness, the use of current and previous disease-modifying drugs, corticosteroid use and

extra articular complications. Questions were asked relating to previous renal dysfunction like urine problem, swelling over legs and puffiness over face.

All the patients who met the inclusion and exclusion criteria were recruited in the study and details were documented in the proforma which included name, age, sex, registration number, contact details, past history and family history of diabetes mellitus, hypertension, CAD along with documentation of symptoms at presentation. Furthermore, the study subjects were tested for Cystatin-C levels along with complete blood counts, renal functions and liver functions.

Results

Table 1: SOCIO-DEMOGRAPHIC WISE DISTRIBUTION OF CASES

Mean age (in years)	41.28±12.60
Male : Female	8:42
Mean age (in years)	6.74±4.30

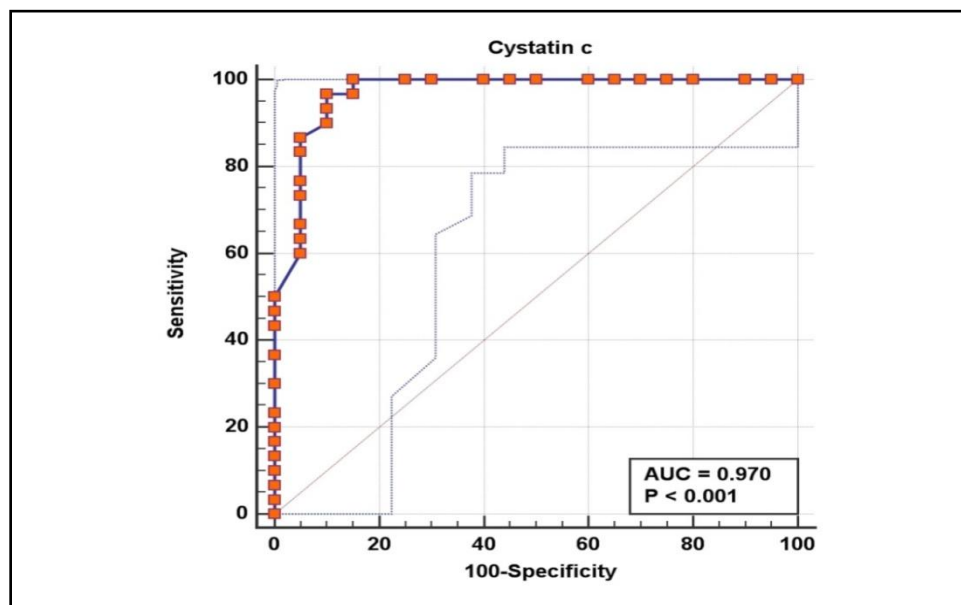


Figure 1:

Receiver operating characteristic (ROC) plot was prepared to assess the diagnostic efficacy of Cystatin-C for early detection of renal dysfunction with normal and abnormal GFR.

Sample size = 50

GFR abnormal = 30

GFR Normal = 20

Disease prevalence = 60%

AUC – Area under curve = 0.970

95% Confidence interval [0.87-0.99]

z statistic = 19.62; P < 0.0001

Associated criterion = >0.96 [Cutoff value] 95% Confidence interval [>0.93 to >0.99]

Sensitivity = 96.67%, Specificity = 90.00%, PPV = 93.50, NPV = 94.70

LR + = 9.67, LR - = 0.037, Diagnostic accuracy = 94.00

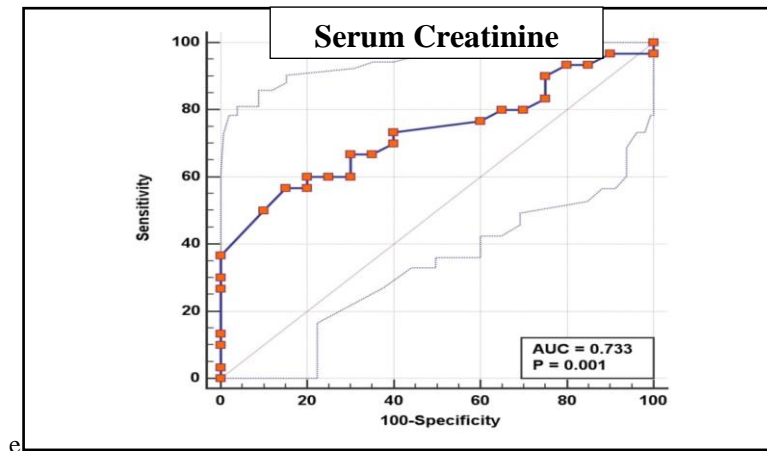


Figure 2:

Receiver operating characteristic (ROC) plot was prepared to assess the diagnostic efficacy of serum creatinine for early detection of renal dysfunction with normal and abnormal GFR.

Sample size = 50

GFR abnormal = 30

GFR Normal = 20

Disease prevalence = 60%

AUC – Area under curve = 0.733

95% Confidence interval [0.58-0.84]

z statistic = 3.30; P = 0.0009

Associated criterion = >0.98 [Cutoff value] 95% Confidence interval [>0.88 to >1.00]

Sensitivity = 56.67%, Specificity = 85.00%, PPV = 85.00, NPV = 56.70

LR + = 3.78, LR - = 0.51 Diagnostic accuracy = 68.00

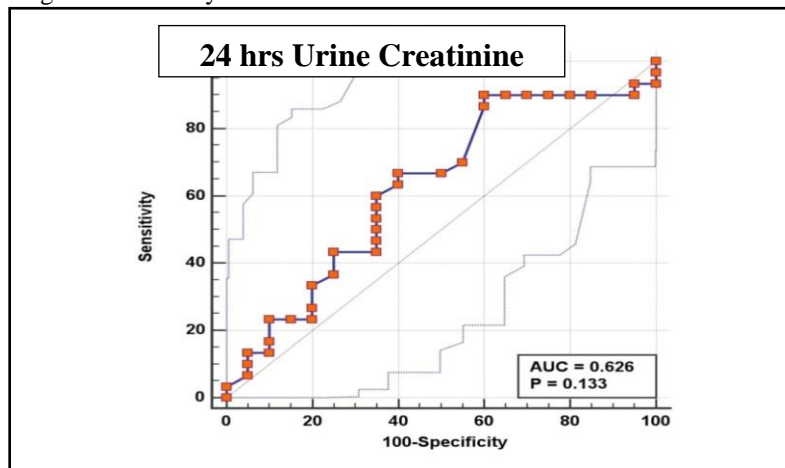


Figure 3:

Receiver operating characteristic (ROC) plot was prepared to assess the diagnostic efficacy of 24 hours urine creatinine for early detection of renal dysfunction with normal and abnormal GFR.

Sample size = 50

GFR abnormal = 30

GFR Normal = 20

Disease prevalence = 60%

AUC – Area under curve = 0.626

95% Confidence interval [0.47-0.75]

z statistic = 1.50; P = 0.132

Associated criterion = ≤ 0.91 [Cutoff value] 95% Confidence interval [≤ 0.91 to ≤ 1.20]

Sensitivity = 90.00%, Specificity = 40.00%, PPV = 69.20, NPV = 72.70

LR + = 1.50, LR - = 0.25 Diagnostic accuracy = 70.00%

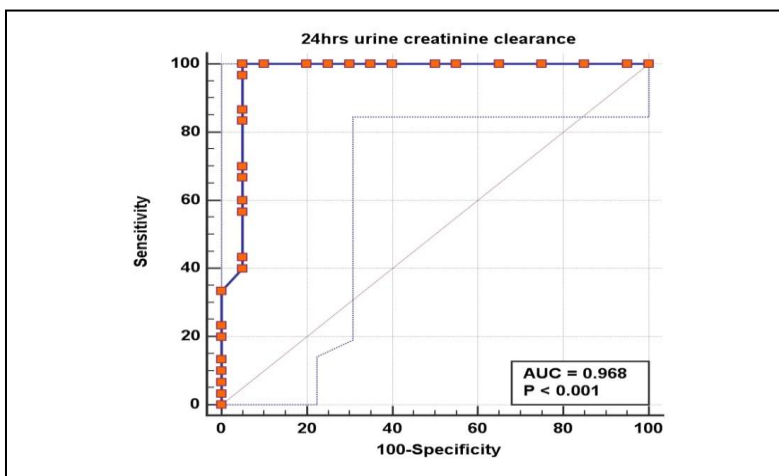


Figure 4:

Receiver operating characteristic (ROC) plot was prepared to assess the diagnostic efficacy of 24 hours urine creatinine clearance for early detection of renal dysfunction with normal and abnormal GFR.

Sample size = 50

GFR abnormal = 30

GFR Normal = 20

Disease prevalence = 60%

AUC – Area under curve = 0.968

95% Confidence interval [0.87-0.99]

z statistic = 14.65; P <0.0001

Associated criterion = ≤91 [Cutoff value] 95% Confidence interval [≤87 to ≤91]

Sensitivity = 100.0%, Specificity = 95.00%, PPV = 96.80%, NPV =100%

LR + = 20.0, LR - = 0.00 Diagnostic accuracy = 98%

Comparison of ROC curves

Variable 1	Cystatin-C
Variable 2	Creatinine
Variable 3	24hrs urine creatinine clearance
Classification variable	eGFR

Sample size	50	
Positive group	eGFR<80ml/min	30(60.00%)
Negative group	eGFR>80ml/min	20(40.00%)

Variable	AUC	SE	95% CI
Cystatin c	0.970	0.0241	0.878 to 0.998
Creatinine	0.733	0.0699	0.588 to 0.848
24hrs urine creatinine clearance	0.968	0.0315	0.875 to 0.997

Table 1: PAIRWISE COMPARISON OF ROC CURVES

Cystatin c ~ creatinine	
Difference between areas	0.238
Standard Error	0.0712
95% Confidence Interval	0.0980 to 0.377
z statistic	3.337
Significance level	P = 0.0008
Cystatin c ~ 24hrs urine creatinine clearance	
Difference between areas	0.00167
Standard Error	0.0301
95% Confidence Interval	-0.0572 to 0.0606

z statistic	0.0555
Significance level	P = 0.9558
Creatinine ~ 24hrs urine creatinine clearance	
Difference between areas	0.236
Standard Error	0.0660
95% Confidence Interval	0.106 to 0.365
z statistic	3.572
Significance level	P = 0.0004

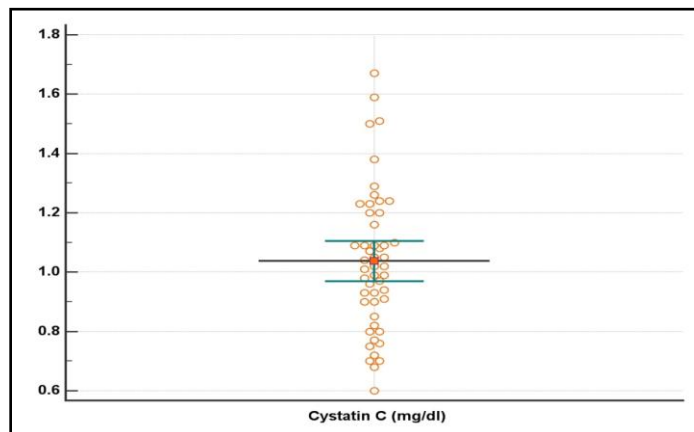


Figure 5:

In figure 5 cystatin-C level below 0.95 mg/dl was considered normal. 19 patients have normal and 31 patients have abnormal more than 0.95 mg/dl.

Discussion

Cystatin-C, a non-glycosylated protein with cysteine protease inhibitor activity, has been considered as a marker of renal function. Because of constant rate of production by all nucleated cells, the Cystatin-C serum level only determined by GFR, which is independent of sex, age and body weight⁵.

In study by Jeon et al. they found Cystatin-C level is increased with increasing CKD stage 1 to 3 and from normo- to microalbuminuria and showed a positive correlation with ACR (Albumin to creatinine ratio). In a comparison of renal function markers in diabetic patients according to serum Cystatin-C level, all markers including ACR, serum creatinine and eGFR showed significant differences between patients with Cystatin-C level <1.06mg/l and those with >1.06mg/l. Serum Cystatin-C is a useful marker of renal impairment in DM because it reflects both, a decreased in GFR and elevated ACR.⁶ We also found that all marker including serum creatinine and eGFR showed significant difference between patients with Cystatin-C level <0.95 mg/dl and those with >0.95mg/dl.

A study done by M S N Murty on 200 healthy subjects and 130 AKI patients over a period of 2 years. He found that 56.2% of patients have normal level of serum creatinine, while all the patients have elevated serum Cystatin-C.² In our study we found increase Cystatin-C level in 62% patients and only 2% patients with increase serum creatinine.

A study on 1908 RA patients was done in Japan by Shunsuke Mori, prevalence of renal dysfunction was defined as BSA (Body surface area)- indexed eGFR <60 ml/min/1.73m², it was 18.6%. In this study the prevalence of renal dysfunction was 33.8%, defined as absolute eGFR <60 ml/min. Only 2.1% patients have end stage kidney disease defined as absolute eGFR <30ml/min⁷. The prevalence of albuminuria was 8.1% and hematuria was 7.5%. In our study the 60% patients have decreased eGFR <80 ml/min, albuminuria was in 10% patients and no hematuria was found. No patient found with end stage kidney disease. In our study albuminuria was synchronized with above study.

A study done by Herald Mangge, the lower co-relation between Cystatin-C and plasma creatinine was explained by the fact that 60% of the RA patients showed elevated plasma Cystatin-C level, whereas creatinine was increased in 5% patients only. A decreased creatinine clearance in 57% of RA patients strengthens the notion of renal dysfunction despite largely normal plasma creatinine⁸.

In our study 1 patient (2%) has elevated serum creatinine level (Normal <1.2 mg/dl) and 49 patients (98%) have normal creatinine level. Serum creatinine level. The ROC curve of serum creatinine shows diagnostic accuracy 68%. In the study by Herald Mangge et al. 3 patients (5%) have elevated serum creatinine level and 53 patients (95%) have normal serum creatinine level⁸.

In our study 30 (60%) out of 50 RA patients have decrease creatinine clearance. The ROC plot of creatinine clearance shows diagnostic accuracy 98%. In the study by Herald Mangge et al; 32 (57%) out of 56 RA patient have decrease creatinine clearance. Our result of creatinine clearance was found similar with above study⁸

In our study, 19 patient (38%) patient have normal Cystatin-C level (Normal<0.95 mg/dl) and 31 (62%) patients have high cystatin-C level. Shows cystatin c level. The ROC curve of Cystatin-C diagnostic accuracy 94%. In the study by Herald Mangge et al 60% patient have elevated Cystatin-C level & 40% patient have normal Cystatin-C level⁸. The result of the Cystatin-C level was found similar with the above study.

It turned out that 60% of the investigated patients who showed a pathologically decreased creatinine clearance in spite of normal creatinine serum levels indicating an early renal impairment, which cannot be detected by serum creatinine measurement. Creatinine clearance values were by far better correlated with serum Cystatin-C than with serum creatinine. This diagnostic inaccuracy of serum creatinine especially in RA patients may be due to the fact that it is influenced by physical activity and muscle mass, which both are usually low in RA patients because of chronic joint pain.

Conclusion

In conclusion, as compared to serum creatinine, the determination of serum cystatin C is comparably simple, but by far more sensitive for the diagnosis of incipient renal

damage in RA, and therefore valuable for clinical screening particularly in cases with prolonged antirheumatic treatment.

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