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Serum Cystatin C Compared to Serum Creatinine as an Early Marker of Renal Failure

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A B S T R A C T

The main aim of this study whether serum cystatin C can detect early changes in development of acute kidney injury compared to serum creatinine in critically ill patients and to study the confounding factors that normally can interfere in the analysis of serum creatinine. Serum cystatin C showed a faster increase in critically ill patients who were in the early stages of acute kidney injury compared to serum creatinine. Serum cystatin C showed superior sensitivity in adolescents, adults and in aged peoples compared to serum creatinine in detecting acute kidney injury. Cystatin showed better sensitivity in classifying patients having acute kidney injury into Risk, Injury and Failure categories compared to creatinine. Cystatin C showed excellent diagnostic accuracy in detecting patients having renal injury than creatinine. Using cystatin C measurements, we can diagnose acute kidney injury early and start prompt intervention to prevent adverse outcomes, because such intervention drastically improves the outcomes of acute kidney injury. Cystatin C may be considered as an alternative and more accurate serum marker than serum creatinine in early detection of impairment of GFR. Future studies should focus on GFR staging by standardizing the definition of control groups and the cut-off values for Cystatin C and Creatinine, in order to provide the diagnostic basis for the clinical application of Cystatin C and Serum Creatinine for estimating GFR.

Introduction

Acute kidney injury is the sudden impairment of renal function resulting in retention of nitrogenous and other waste products that are normally excreted by the kidneys. It is a serious complication in critically ill patients admitted to the Intensive Care Unit. Acute kidney injury occurs in 5-7% of hospital admissions and in up to 30-67% of admissions in ICU. It is a major medical complication in the setting of diarrhea, malaria, leptospirosis and natural disasters especially in developing countries. Development of acute kidney injury increases patient's morbidity, predicts higher mortality and consumes considerable health resources. Acute kidney injury in critically ill patients has got a poor survival rate compared to those without it. Many of the survivors of acute

kidney injury are developing evidences of chronic kidney diseases (CKD) and some shows the features of end stage renal diseases(ESRD) requiring renal replacement therapy.

Early detection of renal injury can allow for better care of the patients and to intervene by employing certain therapeutic measures thereby preventing progression to overt AKI. The best global index of renal function is glomerular filtration rate (GFR). Inulin and Cr-EDTA plasma clearance are considered the gold standard methods for estimating GFR. But these methods use exogenous substances and require specialized technical personnel over a period of several hours and high cost. In clinical practice, serum creatinine is the most widely used index of noninvasive assessment of GFR. But serum creatinine has an inadequate sensitivity particularly in early stages of renal impairment. Serum creatinine level is affected by age, muscle mass, physical activity, diet etc. Serum creatinine cannot measure renal function in extremes of ages. It will not detect patients with stage 2 CKD (GFR60-89ml/min/1.73m) and will fail to detect many patients with stage 3(GF30-59). In the clinical laboratory, serum creatinine is usually measured by Jaffe's method. It is not specific for serum creatinine. Many non creatinine chromogens like protein, glucose, ascorbic acid, ketone bodies, hemoglobin F etc can also produce Jaffe's reaction. In patients with CKD, extra renal clearance of creatinine occurs due to bacterial overgrowth in small intestine. Certain drugs can also affect creatinine levels in plasma. So measurement of GFR using serum creatinine is always crude.

Cystatin C is a low molecular weight (12.8kDa) protein synthesized by all nucleated cells at a constant rate. It is a cysteine protease inhibitor. It is freely filtered at the glomerulus and reabsorbed completely and metabolized by proximal convoluted tubule. Its plasma concentration is not affected by age, muscle mass, diet, non creatinine chromogens etc. It is produced by all nucleated cells, and its production rate is relatively constant from age 4 months to 70 years. No extra renal route of excretion is known and clearance from plasma occurs only through glomerular filtration. Its concentration is increased in plasma as the GFR falls below 80ml/ min /1.73m compared to creatinine which is below 40ml/min/1.73m. So it is very useful when we are trying to detect mild to moderate impairment in kidney function. If the serum cystatin C level can detect impairment in renal function in an early stage than creatinine, we can start the essential measures in an early stage to prevent the further progression of renal impairment. However it is less certain whether the measurement of cystatin C has an improvement over creatinine based equations for estimating the GFR.

The main aim of this study whether serum cystatin C can detect early changes in development of acute kidney injury compared to serum creatinine in critically ill patients. To study the confounding factors that normally can interfere in the analysis of serum creatinine. Also to study the effect of the confounding factors on serum cystatin.

Materials and Methods

Study design: Diagnostic test evaluation.

Study setting: Study will be conducted in the Departments of Biochemistry and General Medicine, Medical College Thiruvananthapuram, India.

Study period: One year. (From 2012 Jan-2013 Jan).

Study population: Patients admitted in MICU, Medical College, Thiruvananthapuram with critical illnesses who are at high risk to develop acute renal failure

Results and Discussion

The present study attempted to determine whether the serum cystatin C can help in early detection the development of acute kidney injury in critically ill patients compared to serum creatinine. 95 patients admitted in our MICU satisfying the inclusion criteria were included in the study. Acute kidney injury is detected by serum creatinine using RIFLE criteria i.e. increase in serum creatinine > x50% (Risk), > x 100% (Injury), and > x 200% (Failure). In analogy, acute kidney injury was detected when cystatin C increased by >50%, by >100%, or by >200%.

69.5% of patients were in the age group 18-59years, 23% were above 60 years and 7.4% were below 18 years. Blood urea levels of these patients did not show any statistically significant variation during the 5 day stay in MICU.

At the time of initial evaluation, the mean creatinine value for the whole patients was 0.92mg/dl, i.e. a high normal value (normal0.5-0.9mg/dl) and it showed 32 % increase (1.21mg/dl) during the 5 day stay in MICU. While the mean initial cystatin C value at the first analysis itself was 1.4mg/dl (normal0.5-lmg/dl) and it showed a 13% increase during the 5day hospital stay. It shows that cystatin increased a few days early in these patients. These observations are important when compared to a study done by Dharnidharka VR *et al.*,[102] which showed that serum cystatin C is a superior marker of renal function compared to serum creatinine.

We classified the patients into 3 groups based on the age and the adolescent age group (<18 years) showed the least mean creatinine values during both analysis and there was a 27% increase in 5 days stay. The age group (18-59years) showed the highest mean creatinine values on both analysis and there was an increase of 37% in the mean creatinine value during 5 days stay in hospital. The third group (>60 years) showed 20% increase of mean creatinine values in 5 days hospital stay.

Cystatin C showed an 22% increase of mean value in the adolescent group, 13% increase in the age group 18-59 and a 4% increase in the age group >60 years. The percentage changein cystatin C is less because it was already elevated in the first analysis itself. Thus cystatin showed an early change in all the 3 age groups during the period of hospital stay. This finding is important when viewed in the light of the study by Newman *et al.*, which showed that serum cystatin C is a more sensitive marker of changes in GFR than serum creatinine.

Acute kidney injury

Of the 95 patients we studied, 54 patients (57%) showed normal renal function throughout the hospital stay and 41 patients (43%) developed renal impairment according to their final laboratory status. Of these 41 patients who developed renal impairment, some patients showed certain degree of renal impairment during the first evaluation itself and some developed during the course of hospital stay. 15 patients were in the Risk category (16%), 13 patients were in the Injury (14%), and 13 patients were in Failure (14%) after the study.

During the first evaluation using creatinine, we could identify 81 patients as normal and 14 having renal impairment with sensitivity of 34 %(95% C.I -21.7- 419.4). During second evaluation, 13 more patients developed renal impairment and 68 were normal with sensitivity 66 % (95% C.I 50.5-78.4). But

based on serum cystatin C levels, we could find 18 more people having renal impairment during the first evaluation itself, i.e. 32 patients showed renal impairment and 63 were normal, sensitivity 78 % (95% C.I 63.3-88). During the second analysis, only 5 more people showed newly developed renal impairment, sensitivity - 90.2%, (95% C.I 77.4-%. 1).

That means cystatin C detected around 78% of the affected patients in the first analysis itself. This result is comparable to the study done by Stefan Hegret-Roser *et al.*, in which they showed that increase in cystatin C in critically ill patients significantly preceded compared to serum creatinine.

The risk category

In the first analysis, based on serum creatinine levels, we detected 2 positive cases of the 15 patients, who were in the Risk category in the final analysis and classified other 13 as normal, i.e. it identified only 13.3% patients who developed Risk during first analysis (sensitivity 13.3%)(95% C.I 3.7-37.8). During the second analysis, we detected 3 more patients having Risk based on serum creatinine values, sensitivity - 33.3%, (95% C.I 15.18-58.3). Using cystatin C, we detected 6 patients having Risk in the first analysis with sensitivity - 40%, (95% C.I 19.8-64.3) and in the second analysis, we detected 12 patients having Risk, sensitivity - 80%, (95% C.I 54.8-92.9). Thus cystatin showed more increase and sensitivity in the Risk category.

The injury category

There were 13 patients who developed Injury and we classified 3 of them in Risk and 10 as normal in first analysis based on creatinine values, but cystatin detected 7 patients as having Injury and classified other 6 in Risk category, Sensitivity - 100%, (95% C.I 64.5-100). During second analysis, creatinine detected 5 patients having Injury, 4 of the others are classified in Risk and 4 in normal, Sensitivity -55.6%, (95% C.I 26.67-81.12). Cystatin detected 11 of the 13 patients having Injury and 1 patient classified as having Risk and 1 normal, Sensitivity - 91.6%, (95% C.I 69.6-98.5).So in this category also cystatin C increased rapidly than creatinine and showed superior sensitivity.

The failure category

The failure category also included 13 patients. Out of this, we classified 4 cases as normal, 5 cases as risk and 4 cases as injury based on creatinine values in the first analysis. While based on cystatin, we detected 7 patients as having Failure, 6 of them classified in Injury, sensitivity - 100%, (95% C.I 64.5-100). In the second analysis, it we classified 5 cases in Failure, 7 cases in Injury and 1 in Risk based on creatinine. Based on cystatin we classified 12 of the 13 patients in Failure and 1 in Injury during second analysis, sensitivity - 100%, (95% C.I 75.7-100). Thus, in all these three categories, serum cystatin C showed a marked and more rapid rise compared to serum creatinine. These results are also comparable to the findings of Newman *et al.*, and Stefan Hegret-Rosenthal *et al.*

About the final status of renal impairment

Based on the serum creatinine values, there were total 81 cases found to be normal and 14 cases showed acute kidney injury in the first analysis. Among these 81 normal cases in the first analysis, 66 remained as normal itself in the second analysis also, 9 progressed to the Risk category and 6 to Injury category. There were 10 Risk cases found in first analysis, of which 2 cases became normal, 1 remained in the Risk category itself, 5 progressed to Injury category and 2 to Failure in the second analysis. There were 4 patients present in the Injury category initially of which 1 remained

in Injury and 3 progressed to Failure in second analysis.

Regarding serum cystatin C levels, total 63 patients found as normal, and 32 showed acute kidney injury in the first analysis. Of the 63 normal cases in the first analysis, 55 remained as normal itself and 8 progressed to Risk category. There were 12 patients in the Risk category initially, of which 5 remained in Risk, 5 progressed to Injury and 2 became normal. 13 patients were included in the Injury category initially, of which 6 remained in Injury itself, 6 progressed to Failure and 1 became normal in second analysis. There were 7 patients present in the category Failure initially, 6 remained in Failure itself and other progressed to Injury in second analysis.

From these data, we can see that serum creatinine classified 15 patients having acute kidney injury as normal during early days of development of renal impairment. But cystatin C classified only 8 patients having acute kidney injury as normal during the early days of development of renal impairment and it detected more positive cases in few days early compared to serum creatinine.

About the ROC curve

The ROC was plotted using the sensitivity and 1- specificity of serum creatinine and cystatin C during the first and second analysis. The curve for initial creatinine showed an area under the curve of 0.865. Curve for the second creatinine showed some decrease in the area under the curve of 0.834. Cystatin C initially showed an area under the curve of 0.974 and 0.969 in the second analysis.

From this we can say that the initial cystatin C shows the most accurate values as it got the most area under the curve. These observations are important when compared to the outcomes of the study done by Dharnidharka *et al.*, which showed that the ROC plot of systatin C is superior to serum creatinine as a marker of GFR.

Confounding factors

In our study, we also tried to determine whether the 2 confounding factors in the creatinine estimation using Jaffe's method have any effect on cystatin C estimation. They are high sugar values and bilirubin.

High blood glucose

Patients are divided into 2 groups based on blood sugar levels, those having less thanl26mg/dl and those having above 126mg/dl. 73 patients had blood glucose level<126mg/dl. We detected 9 patients (12.3%) as having acute kidney injury in first analysis and 18 (24.7) patients in second analysis based on serum creatinine levels in this group. 22 patients had blood sugar levels above 126mg/dl and we detected 5 (22.7%) acute kidney injury cases in first analysis and 9 (40.9%) in second based on serum creatinine. It shows that there was no statistically significant correlation obtained between blood glucose levels and serum creatinine estimation.

Based on cyststin C levels, we detected 22 acute kidney injury patients in the first analysis (30.1%) and 25 in the second analysis (34.2%) among the first group and 10 patients in the first analysis (45.5%) and 12 patients (54.5%) in second among second group. Even though cystatin performed better, we didn't get a statistically significant correlation between blood sugar values and cystatin estimation.

High bilirubin

We also classified the patients according to serum bilirubin levels into 2 groups, i.e. those having bilirubin levels below 2 mg/dl and

those having above 2 mg/dl. 75 patients showed serum bilirubin below 2mg/dl and 20 patients showed above 2 mg/dl. Based on serum creatinine levels, we detected 12 patients having acute kidney injury in the first analysis (16%) and 21 patients from second (28%) among the first group and 2 patients (10%) in first analysis and 6 patients (30%) in the second analysis among second group.

Based on cystatin levels, we detected 27 patients (36%) in the first analysis and 29 patients (38.7%) in the second analysis from the first group of patients and 5 patients in first analysis (25%) and 8 patients in the second analysis (40%) among the second group, having acute kidney injury. Here also cystatin outperformed creatinine but correlation is statistically insignificant.

Future perspectives

In order to prevent the complications of acute kidney injury, early diagnosis and intervention is essential. For that, cystatin C can replace serum creatinine as the primary diagnostic marker of impairment in GFR. Cystatin C can be used as a screening test for detecting acute kidney injury as early and more accurately in future. Many studies have showed that cystatin C has important association with the development of cardio vascular diseases, cerebral vascular accidents, carcinomas, inflammation etc. So, more research should be done on those subjects to have a better patient care.

Limitations of the study

Sample size was only 95 and that included a heterogeneous group of people. Complete follow up of the patients was not done in our study. Extreme age groups are not included in the study and we could not evaluate the effect of different analytical methods on cystatin C values and also the different clinical conditions.

In conclusion,

1. Serum cystatin C showed a faster increase in critically ill patients who were in the early stages of acute kidney injury compared to serum creatinine.

2. Serum cystatin C showed superior sensitivity in adolescents, adults and in aged peoples compared to serum creatinine in detecting acute kidney injury.

3. Cystatin showed better sensitivity in classifying patients having acute kidney injury into Risk, Injury and Failure categories compared to creatinine.

4. Cystatin C showed excellent diagnostic accuracy in detecting patients having renal injury than creatinine.

5. Using cystatin C measurements, we can diagnose acute kidney injury early and start prompt intervention to prevent adverse outcomes, because such intervention drastically improves the outcomes of acute kidney injury.

6. Cystatin C may be considered as an alternative and more accurate serum marker than serum creatinine in early detection of impairment of GFR.

7. Future studies should focus on GFR staging by standardizing the definition of control groups and the cut-off values for Cystatin C and Creatinine, in order to provide the diagnostic basis for the clinical application of Cystatin C and Serum Creatinine for estimating GFR.

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