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# Cystatin C as a Predictor for Acute Kidney Injury

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**Abstract:**

**Background:** Acute kidney injury (AKI) is a frequent and serious clinical complication encountered in hospitalized patients, particularly in critically ill individuals and those undergoing major surgical or interventional procedures. It is associated with increased morbidity, mortality, prolonged hospital stay, and a higher risk of progression to chronic kidney disease. Despite its clinical significance, early diagnosis of AKI remains challenging, which limits the opportunity for timely preventive and therapeutic interventions. Serum creatinine, the conventional biomarker used for diagnosing AKI, has well-recognized limitations. Its concentration is affected by several non-renal factors, including age, sex, muscle mass, nutritional status, and fluid balance. Moreover, serum creatinine typically rises only after a substantial decline in glomerular filtration rate, resulting in delayed detection of renal injury. These limitations have driven the search for more sensitive and earlier biomarkers of kidney dysfunction. Importantly, serum cystatin C levels are less influenced by muscle mass and other demographic factors compared to serum creatinine. Emerging evidence suggests that cystatin C may rise earlier than serum creatinine in the setting of acute kidney injury, allowing for earlier identification of patients at risk. Therefore, evaluating the predictive value of cystatin C for AKI may improve early diagnosis, risk stratification, and clinical outcomes.

**Conclusion:** Cystatin C appears to be a reliable and sensitive biomarker for the early prediction of acute kidney injury. Its early rise compared to serum creatinine may allow for timely identification of patients at risk of AKI and facilitate earlier preventive and therapeutic interventions.

**Keywords**: Cystatin C; Acute kidney injury; Early biomarkers; Renal function; Serum creatinine

## Introduction:

Cystatin C is a cytoplasmic protein with a modest molecular weight (13.4 kDa) that inhibits several cystein proteases in the blood. Its production rate is steady, and glomerular filtration eliminates it from the bloodstream. Cystatin C is entirely reabsorbed and broken down in the tubules of healthy people. Normal serum levels of cystatin C range from 0.8 to 1.2 mg/L, depending on the analytical technique used. In patients with renal tubular diseases, these levels

can rise to 2 to 5 times normal. In contrast to creatinine, which has different normal values for men, women, and children, normal serum levels of cystatin C are the same for all three categories **[1].**

A sensitive indicator of renal function is Cystatin C (CysC). Nearly all nucleated human cells generate CysC, a cysteine protease inhibitor, at a relatively steady rate (housekeeping gene), which is then transported through the circulation. Age, sex, and ethnicity have less of an impact on CysC levels than creatinine does. Despite being digested by the proximal tubular cells, it is freely filtered due to its low molecular weight (13 kDa) and is neither released from nor reabsorbed into the circulation. Because of all these characteristics, CysC may be a more accurate estimate of GFR than estimations based on sCr. CysC has been included in the updated formulae for GFR estimates in the population with chronic renal disease. CysC has also been demonstrated to be a more accurate predictor of mortality and cardiovascular events than sCr-based predictions in the different populations studied (coronary heart disease, acute and chronic heart failure). **[2].**

Early alterations in glomerular filtration rate take place in the setting of acute renal damage prior to obvious clinical signs or notable increases in blood creatinine. Numerous investigations have shown that in patients who later develop AKI, cystatin C levels rise before serum creatinine, indicating modest declines in GFR that are not immediately apparent using traditional indicators. Cystatin C is very useful for the prompt identification of individuals at high risk for AKI because of this early elevation, particularly in critically sick patients, postoperative settings, and those exposed to nephrotoxic drugs or contrast media. Therefore, early diagnosis with cystatin C may enable physicians to put preventive measures into place before irreparable kidney damage happens. **[3].**

In addition, cystatin C has demonstrated significant predictive significance in AKI that goes beyond the straightforward identification of renal failure. Increased AKI severity, longer hospital admissions, a greater requirement for renal replacement treatment, and higher short- and long-term mortality have all been linked to elevated cystatin C levels. Numerous clinical contexts, including as intensive care units, heart surgery, sepsis, and contrast-induced nephropathy, have verified its predictive performance. These results demonstrate cystatin C's potential as a supplemental biomarker to serum creatinine in enhancing the diagnostic and prognosis evaluation of acute renal damage and justify its inclusion in clinical risk stratification models. **[4].**

**Historical background:**

In 1961, cystatin C was initially identified as "gamma-trace" as a trace protein found in the urine and cerebrospinal fluid of patients suffering from renal failure, along with other proteins like beta-trace. Patients with advanced renal failure had higher levels of it. The GFR was shown to be accurately reflected by the use of serum creatinine and cystatin C. **[5]**.

**Molecular biology:**

Proteins with many cystatin-like sequences are included in the cystatin superfamily. While some members have lost or may never have gained this inhibitory ability, others are active inhibitors of cysteine protease. The superfamily is composed of three inhibitory families: kininogens, type 2 cystatins, and type 1 cystatins (stefins). Type 2 cystatin proteins, a class of cysteine proteinase inhibitors that appear to have protective qualities, are found in many human fluids and secretions. The cystatin locus on the short arm of chromosome 20 contains the majority of type 2 cystatin genes and pseudogenes. **[6]**.

The CST3 gene spans 4.3 kilobase pairs and consists of three exons (coding portions of a gene as opposed to non-coding areas called introns). The cystatin locus contains it. It encodes the most common extracellular inhibitor of cysteine proteases. It is expressed in almost every organ of the body and is present in biological fluids in high concentrations (CST3 is a housekeeping gene). Semen has the highest levels, followed by breast milk, tears, and saliva. The protein is generally secreted, as indicated by the hydrophobic leader sequence. Two frequent variations are produced by three SNPs in the gene's promoter region. Changes in cystatin C levels have been linked to a number of single nucleotide polymorphisms. **[6]**.

The basic, non-glycosylated protein cystatin C has an isoelectric point of 9.3 pH. The crystal structure of cystatin C is defined by a long alpha helix and a short alpha helix that span a large antiparallel, five-stranded beta sheet. It contains two disulfide linkages, just like other type 2 cystatins. A hydroxylated proline is present in about half of the molecules. Cystatin C exchanges subdomains to form dimers, or molecule pairs; Each half in the paired state is made up of four beta strands from one partner and one beta strand and the long alpha helix of the other partner. **[6]**.

**Clinical applications:**

**Kidney function:**

Unlike creatinine, which is influenced by age, sex, race, lean muscle mass, or inflammatory processes, cystatin C is becoming recognized in clinical practice as the biomarker of choice for identifying renal failure. Some of these characteristics need to be taken into account since creatinine-based estimates of glomerular filtration rates (eGFR) are sensitive to them. Even a 50% decrease in GFR is not invariably linked to an abnormal creatinine concentration, since a sizable portion of people with reduced GFR have normal serum creatinine levels. **[7]**.

**Death and Cardiovascular disease:**

The risk of death and other forms of cardiovascular illness, such as myocardial infarction, stroke, and heart failure, are linked to elevated levels of cystatin C. **[8]**.

**Neurologic disorders:**

The Icelandic form of hereditary cerebral amyloid angiopathy, which increases the risk of intracerebral hemorrhage, stroke, and dementia, is brought on by cystatin C gene abnormalities. The disease has a dominant inheritance pattern. Because it binds to amyloid β and reduces its aggregation and deposition, cystatin C may be a target in Alzheimer's disease. Though not all studies have confirmed this, most research points to CST3 as a susceptibility gene for Alzheimer's disease. It has been noted that individuals with Alzheimer's disease have greater levels of cystatin C. There is ongoing debate regarding cystatin C's involvement in multiple sclerosis and other demyelinating disorders, which are typified by the loss of the myelin nerve sheath. **[9]**.

**Other roles:**

Unfortunately, cancer treatments have the potential to seriously harm the kidneys; therefore, The oncologist could change the medicine dosage before irreparable kidney damage occurred if renal failure was discovered early. Additionally, for individuals with cancer, liver illness, and renal transplants, cystatin C is a more reliable indicator of GFR than creatinine. as well as for simpler GFR change monitoring in the pediatric population. **[10]**.

**Detection method:**

For the precise measurement of cystatin C in blood, Denka Seiken Co., Ltd. has created a simple latex-based Turbidimetric Immuno-Assay (TIA) test that can be utilized with a variety of automated clinical chemistry analyzers. The anti-human cystatin C-coated latex particles used in this test combine with the cystatin C in a blood sample (serum or plasma) to produce a complex. Turbidity changes as a result of this complex formation, and automated clinical chemistry analyzers can measure this shift. The cystatin C value in the tested samples can be accurately determined by direct comparison with known concentrations of standardized materials. **[11]**.

Normal and abnormal levels can be assessed without the need for further dilutions because the accurate measurement range is between 0.1 and 10 mg/L. Prozone tolerance was at least 30 mg/L when tested on a Hitachi 917, and recovery rates were 99% when cystatin C levels exceeded 0.5 mg/L. Blood samples with high levels of hemoglobin, conjugated and free bilirubin, or lipids showed little to no interference. With respective mean values of 0.545 and 1.162 mg/L, the intra-run precision was 1.82% and 1.09%. **[11]**.

**Cystatin C as a predictor for acute kidney injury:**

Although CyC is not frequently found in urine, it has been found in the urine of individuals with tubular disease, suggesting that it could be a sign of renal tubular damage.Healthy people's serum nephelometric CysC readings range from 0.53 to 0.95 mg/L, with higher reference values of 0.28 mg/L in urine. **[12].**

It has been suggested that CysC serves as an additional or potential indicator of baseline renal function. Despite being more costly than SCr, sCysC testing is used to follow kidney transplant recipients and measure juvenile patients' renal function on a regular basis. **[7].**

Additionally, there is evidence that a slight fall in GFR occurs 1 to 2 days before symptoms, an increase in SCr, and/or a decline in renal function, and that this is preceded by an elevation of sCysC. Early increases in uCysC levels were significant predictors of AKI after elective heart surgery and are linked to the need for renal replacement therapy in people with acute tubular necrosis. Other research, however, was unable to support these conclusions and indicates that sCysC is not dependable when postrenal blockage is present. However, in critically ill AKI patients, uCysC was found to be independently linked to mortality. **[13]**.

A deterioration in renal function one year after surgery was predicted by elevated levels of both SCr and sCysC on the first postoperative day in patients undergoing partial or radical nephrectomy; however, in the "SCr-blind" area, sCysC showed a stronger correlation with estimations of renal function than SCr. **[14].**

**Nakai et al. [15]** have looked into using cystatin C as a kidney function indicator while modifying drug dosages. Patients with cancer, thyroid dysfunction (even mild), and glucocorticoid medication have been shown to have changed levels of cystatin C.

**Risk stratification STARZ score**

Given the increasing prevalence and significant susceptibility to AKI in neonates, a thorough investigation into the value of novel biomarkers or risk stratification scores for early detection/prediction of AKI is necessary. Numerous risk stratification scores for mortality in critically ill children have been effectively applied by critical care units worldwide. The two often used scoring systems are the Pediatric RISk of Mortality (PRISM) and the Pediatric Index of Mortality (PIM 1, 2, 3) **[16]**.

They are useful in evaluating newborn outcomes, despite being verified in a variety of populations. The risk scoring systems for illness severity and mortality in neonates that have been studied include the Neonatal Therapeutic Intervention Scoring System (NTISS), Score for Neonatal Acute Physiology (SNAP), Transport Risk Index of Physiologic Stability (TRIPS), Clinical Risk Index for Babies (CRIB), simplified age–weight–sex (SAWS) score, and NMR-2000 score. With the exception of SAWS and NMR-2000, none of the aforementioned scores are useful enough to be applied in environments with low resources. **[17]**.

Since AKI independently deteriorates patient outcomes, it makes up a significant portion of pediatric ratings. We urgently need a specific AKI risk stratification score. The Renal Angina Index (RAI), which is based on cardiac angina and performs better than the traditional measures of illness severity (PRISM and PIM), is the only AKI-specific risk stratification score that has

been thoroughly investigated in many pediatric cohorts. AKI is classified using KDIGO staging. **[18]**.

Patients who have a high score upon admission may be more likely to develop severe AKI later on. Using patient demographics and early indicators of injury, RAI, an empirical clinical model of renal angina, was created to identify which critically ill patients would be most at risk of AKI. Despite all the support from the pediatric (non-neonatal) community, RAI is still not accepted as a risk stratification score for neonates **[19]**.

In order to detect AKI early and initiate preventive and therapeutic treatments as soon as possible, it is crucial to identify "at-risk" infants and perform routine tests on them. The Nephrotoxic Injury Negated by Just-in-time Action (NINJA) program was shown to have successfully reduced the rates of AKI in neonates in the NICU in the United States by a recent adjustment. Integrating these tools into the electronic medical record (EMR) could be advantageous for all neonatologists currently in practice. **[20]**.

**Wazir et al. [21]** have made an effort to close this gap in the management of neonatal AKI by developing the STARZ (Sethi, Tibrewal, Agarwal, Raina, and Wazir) newborn score, a novel risk stratification score tailored to AKI. Neonatals' risk of AKI at NICU admission was predicted using this scoring model.

After analyzing risk variables for AKI in neonates admitted to the NICU, the STARZ score was developed. The model of best fit was used to assign a score to each significant variable. STARZ score variables were designed to be easy to extract and use. Age in hours upon admission to the NICU, gestational age, whether positive pressure ventilation was required in the delivery room, sepsis, cardiac disease, urine output within 12 hours of admission < 1.32 ml/kg/h, use of nephrotoxic drugs, use of furosemide or inotropes, and serum creatinine levels within 12 hours of admission ≥ 0.98 mg/dl were among these variables. This model uses a scoring system of 0 to 100, and the likelihood of AKI at 7 days is proportional to a greater overall score. **[21]**.

**Wazir et al. [21]** asserted that the STARZ neonatal score can rapidly and quantitatively evaluate the risk of AKI in newborns admitted to the neonatal intensive care unit. Its sensitivity, specificity, positive predictive value, negative predictive value, and accuracy are 92.8%, 87.4%, 80.5%, 95.6%, and 89.4%, respectively.

**Sethi et al. [19]** stated that the STARZ score has been validated on 744 neonates and that it is a clinical adjunct that will improve the lives of newborns around the world by optimizing the performance of AKI biomarkers in the neonatal population. **Dhooria et al. [22]** claimed that by enabling AKI risk categorization, the STARZ score offers therapeutic treatments that could enhance the prognosis of critically unwell newborns.

**Conclusion:**

Cystatin C appears to be a reliable and sensitive biomarker for the early prediction of acute kidney injury. Its early rise compared to serum creatinine may allow for timely identification of patients at risk of AKI and facilitate earlier preventive and therapeutic interventions.

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