

Cystatin C as A Prognostic Biomarker to Monitor Renal Function in Liver Cirrhosis: A Narrative Review

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ABSTRACT

Cystatin C (CysC) is a serum protein that has been accepted as an early and precise biomarker of chronic kidney disease (CKD) that is especially useful in patients for whom creatinine (Cr) is deemed an inadequate marker. Estimates of the glomerular filtration rate using serum CysC are proposed as good predictors of renal function. This narrative review was done to review the use of CysC and its estimated glomerular filtration rate as a prognostic marker for renal function in patients diagnosed with liver cirrhosis. A review of the literature was conducted using databases including PubMed, Google Scholar, Science Direct, and Medline. Twenty-eight studies were included in the review. The discovery of CysC has revolutionized early detection and potential reversal of kidney damage in cirrhotic patients, improving outcomes significantly. Unlike Cr-based equations, CysC offers a promising alternative for detecting decreased glomerular filtration rate (GFR) and shows significant associations with various factors, supporting its reliability as a biomarker. Its role extends beyond renal function, showing potential in cardiovascular disease (CVD), mortality, kidney transplant function, and transplant failure.

Keywords: Cystatin C; glomerular filtration rate; renal failure; biomarker; liver cirrhosis

INTRODUCTION

In patients with liver cirrhosis, renal failure is the most common occurring organ dysfunction. The main cause of renal failure in these patients is portal hypertension caused by cirrhosis which causes impairment in the excretion of sodium and water. Portal hypertension also decreases blood flow to the kidneys due to vasoconstriction [1,2].

Renal function tests are an important indicator for the progression of kidney dysfunction and hence, for the prediction of acute to chronic liver failure [1]. A reliable evaluation of renal function is needed in patients with chronic liver failure in order to delay the progression of renal deterioration and to lower the mortality rate [3]. Early detection of renal failure can be crucial for the patient as, in the early stages of renal failure, the damage is reversible with the appropriate treatment [4]. Evaluation of renal function is usually done by measuring serum Cr in order to assess the GFR [5]. However, in patients with cirrhosis, serum Cr measurements are often inaccurate and often lie within the normal range due to factors such as age, gender, inadequate nutrition, muscle atrophy, bilirubin levels, renal tubular secretion malignancy or liver disease [3,6,7].

Serum Cr is easily available and cost-effective but it cannot be used in patients with liver cirrhosis due to

poor accuracy resulting in poor diagnostic outcomes which are misleading for the patient's course of treatment [6].

A newly discovered biomarker, CysC, is anticipated to be more reliable in measuring renal function in patients with liver cirrhosis [8]. One of the most prevalent complications resulting from hepatic cirrhosis is renal dysfunction. CysC is an inhibitor of cysteine proteinase and is released from all nucleated cells at the same rate making it an optimal biomarker of GFR. The level of CysC varied between 0.6 to 2.2 mg/dl across various studies. CysC is a 122 amino acid, 13 kDa non-glycosylated protein that inhibits protease as it belongs to the family of cysteine proteinase inhibitors [7]. It is formed in the body at a constant rate. Unlike serum Cr, it is not influenced by age, gender, or body/muscle mass [8]. CysC is secreted by the glomerulus and is absorbed in the proximal convoluted tubule; it does not get released into the bloodstream, which means that serum measurements of this biomarker are completely dependent on GFR, making it a more reliable measure of renal function and mortality in cirrhotic patients [8,9]. Along with the detection of renal failure, CysC is also useful in the detection and differentiation of the types of acute kidney injury (prerenal azotemia, hepato-renal syndrome, and acute tubular necrosis) [10].

METHODOLOGY

This study utilizes a narrative review methodology to integrate existing literature. A comprehensive literature search was conducted using diverse databases, including PubMed, Google Scholar, Science Direct, and Medline. The search focused on articles related to three key terms: (1) Cystatin C, (2) Renal Failure, and (3) Liver Cirrhosis. The search for relevant studies and articles was conducted over the period from May to August 2023. All relevant articles were included without placing restrictions based on the publication date, ensuring a comprehensive and unbiased review of the available literature.

DISCUSSION

Introduction to Cystatin C

In 1961, Jorgen Clausen identified CysC as a protein specific to cerebrospinal fluid (CSF), naming it γ -CSF. Over time, CysC has been discovered in various bodily fluids, such as human plasma, ascitic fluid, and pleural fluid. In 1981, Gruff and Lofberg determined the complete amino acid sequence of CysC, naming it γ -trace [11]. According to a study done by Markwardt et al., impairment of kidney function is one of the most common complications associated with hepatic cirrhosis. Early detection, through the use of biomarker CysC, can help reverse functional kidney damage and thus mortality in cirrhotic patients [12]. Mindikoglu et al. reported that CysC and other kidney function markers like beta-trace might offer greater sensitivity in detecting decreased GFR, which can be seen through the use of combined Cr-CysC equations [12]. Accurately assessing GFR using Cr-based equations is unreliable, especially for estimated GFR values above 60 mL/min/1.73m². In this 2014 study, the diagnostic performance of the Cr-CysC equation (2012) showed better results than earlier equations that relied solely on Cr or CysC for estimating GFR [12].

Other studies have also highlighted the possible use of CysC as a prognostic marker for renal dysfunction in patients with diabetes. In 2005, Buturovic and Cavaljuga emphasized the need for early markers of diabetic nephropathy, as such, a CysC screening test was recommended for patients with type 2 diabetes mellitus. The study included 49 patients who were divided into 2 groups based on albumin urine excretion rate (normal and abnormal). Both groups had serum Cr levels within the reference range, which meant that serum Cr could not be used as a relevant early indicator of diabetic nephropathy. However, serum CysC was found to be higher in the group with abnormal albumin urine, indicating that serum CysC could be used as a potential early indicator of diabetic nephropathy [14].

However, despite its potential for many uses, CysC has not been implemented into current clinical practice for a number of reasons. A study by Chew et al. reported that CysC remains a research tool possibly because clinicians are reluctant to substitute familiar markers with new tests unless their substantial influence on clinical decision-making is extensively proven.

Additionally, various reference ranges have been proposed for different age groups, and the clinical decision points for CysC are not clearly defined. Conflicting results in the existing literature persist, although a majority of studies suggest the superiority or, at the very least, comparable performance of CysC compared to serum Cr in detecting renal impairment [11].

CysC remains unaffected by factors such as age, gender, or body/muscle mass. Produced by the glomerulus and absorbed at the proximal convoluted tubule, CysC does not enter the bloodstream. Consequently, serum assessments of this biomarker rely solely on GFR, enhancing its reliability as a measure of renal function and mortality in individuals with cirrhosis [11,12,14].

Factors affecting Cystatin C levels

Understanding the factors that influence CysC levels is crucial for interpreting its diagnostic significance. Studies have explored variables that possibly contribute to the changes in CysC, including gender, Child-Pugh (CP) stages, Model for End-Stage Liver Disease (MELD) score, GFR, thyroid status, and high C-reactive protein (CRP) [1,4,14,17].

In 2013, Mindikoglu et al. discovered that female participants did not exhibit a significant difference in CysC compared to their male counterparts ($P=0.526$). Conversely, serum Cr demonstrated a significant association with female sex ($P=0.007$). This discrepancy can be attributed not to variations in renal function, but rather to differences in the production of Cr between males and females [17].

Mindikoglu et al. provided further insights into the prediction of CysC levels by measured (m)GFR ($P<0.0001$), even after adjusting for age and comorbidities [17]. However, a study conducted by Nasser-Moghaddam et al. presented an alternative perspective, revealing no significant correlation between CysC and GFR. This contrast may be attributed to the study's relatively small sample size of 48 participants, as well as the variability in CysC levels influenced by factors such as inflammation, medication, immune function, and biological variation [19]. These conflicting findings emphasize the complexity of CysC dynamics and the necessity for comprehensive consideration of influencing factors in its interpretation.

In 2014, Čulafić et al. observed that CysC exhibits variations corresponding to CP stages, which categorize the severity of liver cirrhosis based on clinical and laboratory parameters such as bilirubin levels, albumin, prothrombin time, ascites, and hepatic encephalopathy. The study revealed statistically significant differences in CysC values between stages A and B ($P=0.014$) and between stages A and C ($P=0.007$). This implies that CysC has predictive potential for determining the stage of liver dysfunction, a hypothesis that is further supported by the fact that CysC was also significantly correlated with the MELD score ($P<0.001$) [4].

The MELD score is a numerical scale that predicts the three-month survival probability in individuals with advanced liver disease. This finding was reinforced in a 2010 study by Chung et al., through the establishment of a positive correlation between CysC and both MELD ($P=0.011$) and MELD-Na scores ($P=0.001$) [1].

Yang et al. demonstrated a significant association between CysC and serum Cr ($P<0.001$) [6]. This finding aligns with the observations of Nasser-Moghaddam et al., who also noted a weak correlation between CysC and serum Cr ($P=0.05$) [19]. These studies collectively stress the relationship between CysC and serum Cr levels, emphasizing the potential use of CysC as a valuable biomarker in renal function assessment.

As determined by Mindikoglu et al., CysC levels remained non-significantly different in patients with comorbidities such as diabetes ($P=0.761$), hepatitis C ($P=0.370$), hypothyroidism ($P=0.484$), or CRP levels above 1 mg/dL ($P=0.286$) [17]. This suggests that the presence of these medical conditions did not have a statistically significant impact on CysC concentrations, as determined by their comprehensive analysis. However, the 2005 study done by Buturovic and Cavaljuga suggested that serum CysC should be used as a prognostic marker for diabetic nephropathy based on the higher serum CysC levels in the abnormal albumin urine group [14]. Fluctuations in CysC levels have also been observed in response to changes in thyroid status and the use of steroids. Factors such as high CRP levels and smoking have been identified to affect CysC metabolism as well [5,9,13]. Supporting this, a study by Barr et al. further corroborated that chronic inflammation may contribute to the suboptimal performance of CysC GFR equations [20].

These observations emphasize the need for careful consideration of various influencing factors when interpreting serum CysC levels in clinical settings. Its resilience to significant changes in various comorbidities, emphasizes its reliability. In essence, CysC holds promise as a biomarker for evaluating renal and liver function in diverse clinical contexts [1,4,6,17].

Cystatin C-based GFR equation

Several equations, including the widely used MELD score, the Modification of Diet in Renal Disease, Cockcroft-Gault, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation, utilize serum Cr levels to estimate GFR in cirrhotic patients. Despite their widespread use, these equations, which consider serum Cr, have been noted to exhibit reduced reliability in cirrhotic individuals [5,12,17].

Multiple studies have undertaken a comparative analysis of Cr-based GFR versus CysC-based GFR equations, yielding diverse outcomes. Studies by Wang et al., and Kronen et al. have shown that cirrhotic patients have altered synthesis and excretion of serum Cr which limits the reliability of

serum Cr in estimating GFR [3,5]. Wang et al., concluded that CysC-based equations exhibit greater efficacy in accurately estimating GFR [3]. The use of CysC as a biomarker for GFR calculation also impacts the staging of CKD [21,22]. Wang et al. highlighted that diagnostic sensitivity and consistency were consistently higher with CysC estimates compared to Cr estimates ($P<0.05$) [3]. The study conducted by Kronen et al., evaluated renal function in cirrhotic patients and observed that GFR tended to be overestimated in Cr-based equations. Conversely, equations based on CysC measurements tended to underestimate GFR, particularly in individuals with a CP score of C. As a result, the study emphasized the importance of using an equation that combines measurements of serum Cr and CysC. This combined approach demonstrated the best performance, accurately reflecting the estimated GFR in patients with cirrhosis [5].

Furthermore, Orlando et al. argued that CysC serves as a more reliable GFR marker than Cr, maintaining accuracy in both cirrhotic and healthy individuals [15]. CysC's advantage over Cr clearance lies in its avoidance of the need for urine collection, a process prone to inaccuracies [15]. Moreover, the practical value of Cr-based values has been questioned, given variations in Cr reference ranges with the severity of liver disease [23]. Correlations between Cr values and CP scores ($P<0.02$) have further complicated the determination of accurate Cr reference values [15]. Hojs et al. also noted that a CysC-based formula was more effective ($P<0.003$), though both formulas ultimately lacked precision [24]. These collective findings emphasize the growing consensus on the superiority of CysC-based equations in the assessment of GFR, offering advantages over traditional Cr-based approaches. The diminished reliability of serum Cr in estimating GFR in cirrhotic patients is attributed to factors like increased excretion through the tubules, low protein intake, and malnutrition. Unlike serum Cr, CysC remains unaffected by these factors, making it a more accurate choice for GFR equations in cirrhotic patients [3,5,15,24].

Similarly, Ćulafić et al. evaluated the efficacy of CysC in assessing renal function through the CKD-EPI equation: $eGFR = 127.7 \times CysC^{-1.17} \times age^{-0.13} \times 0.91$ (if female) $\times 1.06$ (if African American). The study revealed that using CysC-based equations identified a significantly greater number of patients with reduced GFR compared to the utilization of serum Cr levels ($P<0.001$) [4].

In contrast, Nasser-Moghaddam et al. reported findings suggesting that CysC-based GFR estimates were surpassed by Cr-based GFR estimates [19]. CysC was unable to accurately predict GFR after stratification for CP score, gender, or BMI, whereas serum Cr demonstrated accurate predictions for specific GFR thresholds in females ($P=0.045$), individuals with a BMI > 20 ($P=0.034$), and cirrhotic patients with CP class A & B ($P=0.01$). The reasons for the underperformance of CysC in predicting kidney function in this study remain unclear.

Possible factors, such as the use of multi-drug regimens, other comorbidities, and impaired immune function among these patients, were cited as potential contributors [19].

Renal function assessment in cirrhotic patients continues to present a challenge, especially with equations that rely on serum Cr. Studies, such as the one by Ćulafić et al., emphasize the advantages of CysC-based equations over those relying on serum Cr, revealing a greater sensitivity in identifying patients with reduced GFR. This stresses the potential of CysC as a valuable biomarker for precise renal function assessment in cirrhotic patients [4,5,12].

Other roles of Cystatin C

In addition to its role in estimating kidney function, CysC-based eGFR has emerged as a possible indicator and predictor of CVD and mortality. It has been shown to enhance predictive discrimination and is recommended for inclusion in routine CVD risk assessment.

A study done by Fernando and Polkinghorne consistently highlighted CysC as a superior marker for assessing kidney transplant function, predicting CVD risk, and anticipating transplant failure [25]. The study reported that CysC eGFR added predictive discrimination to CVD risk scores that are routinely used, specifically, when combined with albuminuria. Moreover, CysC emerges as a more precise measure of function within specific sub-populations, such as patients with liver cirrhosis and in oncology contexts [25].

These findings highlight the broader clinical utility of CysC beyond its primary role in renal function estimation and emphasize the possible use of CysC as a CVD risk marker.

Contrastingly, a study done by Moreira et al. further investigated how CysC is associated with CVD in patients on peritoneal dialysis [28]. The study focused on 52 stable peritoneal dialysis patients with adequate residual renal function (RRF); minimal RRF was described as $> 2\text{mL}/\text{min}/1.73\text{m}^2$. Findings indicated that the association between CysC and cardiovascular disease was not significant ($P=0.28$). CysC levels were elevated in older patients and patients who had a past or present history of smoking, CVD, or ischemic heart disease. However, these factors proved to have no statistical significance. While acknowledging its limitations of a small cohort of peritoneal dialysis patients, this study concluded that there is no significant link between CysC levels and CVD events [28].

In summary, CysC-based eGFR has expanded beyond its primary role, showing potential as an indicator and predictor of CVD and mortality. Supported by Fernando and Polkinghorne's study, it proves superior in assessing kidney transplant function, predicting CVD risk, and anticipating transplant failure, offering added value to routine CVD risk assessments. However, Moreira et al.'s study on peritoneal dialysis patients with RRF suggests a non-significant association between CysC levels and CVD events, highlighting the need for further exploration and clarification of CysC's role in its predictive value in cardiovascular outcomes [25,28].

TABLE 1: Showing the summary of cutoff values of CysC to predict GFR.

Author /Year	Sample size /Country	Comorbidities	Gender M/F (%)	CysC level cut-off (mg/L)	Mean GFR (mL/min/1.73 m ²)	P- value
Velayudham et al. 2020 [27]	41/India	Liver cirrhosis	Predominantly male	2.2	55.2± 6.4	<0.05
Krones et al. 2015 [5]	50/Austria	Liver cirrhosis	60/40	1.1 ± 0.5	89.6±27.5	<0.05
Belcher et al. 2014 [16]	106/USA	Liver cirrhosis, Acute kidney injury	66/34	-	-	<0.0001
Ćulafić et al. 2014 [4]	63/Serbia	Liver cirrhosis	75/25	1.09 ± 0.42	113.5	0.01
Xirouchakis et al. 2011 [26]	65/UK	Liver cirrhosis	60/40	1.14	70	<0.001
Chung et al. 2010 [1]	53/South Korea	Liver cirrhosis	71.7/28.3	1.23	84.1±27.50	<0.001

LIMITATIONS

A few limitations should be acknowledged when interpreting the findings of this study. Firstly, the total pool of patients and studies available for analysis was relatively limited, impacting the generalizability of the results.

Additionally, CysC is not a regularly ordered investigation in clinical settings, thereby potentially affecting the comprehensiveness of the data. Lastly, the shortage of studies and data emphasizes the need for more extensive research and a broader inclusion of patient populations to enhance future analyses.

CONCLUSION

The discovery of CysC has provided the opportunity for early detection and potential reversal of kidney damage in cirrhotic patients - thus emphasizing its significance in improving patient outcomes. While the Cr-based equations for estimating GFR draw challenges in accuracy, CysC (along with other markers) presents a more promising alternative for detecting decreased GFR.

Future research should focus on standardized protocols for CysC measurement. Factors that may influence its level and concentration should thus be considered in order to enhance the consistency and applicability of results in clinical practice.

CONTRIBUTION

All authors of this paper made significant contributions to the idea and design, collection and analysis of data, and interpretation of data findings. Each author participated in either writing the article or giving it a close, thoughtful review to ensure important intellectual content. Furthermore, all authors provided final approval for the version to be published and agreed to be committed to taking responsibility for every part of the work, making sure to carefully look into and solve any questions about accuracy or integrity.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest in this paper.

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