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Prognostic value of serum cystatin C levels in cirrhotic patients with normal serum creatinine

Research Article

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Abstract: Background/Aims. Accurate assessment of renal function in patients with liver cirrhosis is difficult and of great prognostic importance. The present study aimed to determine the prognostic significance of certain renal markers and to investigate the priority of serum cystatin C (CysC) levels on one-year mortality in cirrhotic patients. Methods. Renal function of 45 liver cirrhotic patientss was evaluated by levels of blood urea nitrogen (BUN), serum creatinine (Cr), CysC , as well as 24-hour creatinine clearance (CCl) and estimated glomerular filtration rate obtained by Cockroft-Gault and MDRD formulas. The endpoint of the follow up was mortality within one year. Spearman's correlation, linear regression analysis and receiver operating characteristic curves were used to investigate prognostic factors. Results. 42 men and 3 women (mean age 53.18 ± 9.71 years) were enrolled in the study. Eleven of the patients (24.4%) died as a result of liver cirrhosis within one year. In predicting mortality, levels of BUN, serum Cr and CysC showed area under the curves (AUC) values of 0.719 (95% CI, 0.539-0.899, p = 0.03), 0.726 (95% CI, 0.541-0.911, p = 0.026) and 0.770 (95% CI, 0.620-0.920, p = 0.008). Sensitivity and specificity of a CysC level of >1.3 mg/l in predicting mortality were 72% and 68%, respectively. Univariate regression analysis showed that elevated levels of CysC above the referent ones, increased the risk of one-year mortality nearly six times (p = 0.02, Exp (B) = 5.81). Conclusions. Serum CysC could be used as a good prognostic marker in patients with cirrhosis and normal Cr levels.

Keywords: *Cirrhosis • Renal dysfunction • Cystatin C • Mortality*

1. Introduction

Renal dysfunction is common in patients with liver cirrhosis and is directly linked to the mortality rate of cirrhotic patients. It occurs in about 19% of hospitalized cirrhotic patients [1] due to several reasons, including intravascular volume depletion (as a result of gastrointestinal bleeding, e.g. variceal bleeding), diuretics use, lactulose-induced diarrhea or infection, as well as spontaneous bacterial peritonitis. They are often exposed to nephrotoxic agents (e.g. nonsteroidal anti-inflammatory drugs, intravenous radiocontrast agents and aminoglycosides) and frequently receive paracentesis. Moreover, with the progression of liver cirrhosis and portal hypertension, renal dysfunction usually progresses to hepatorenal syndrome (HRS) which is associated with poor outcome [2,3]. Therefore, a precise assessment of renal function in cirrhotic patients is required in order to estimate the prognosis and determine the correct therapeutic intervention and response.

The most frequently used clinical markers of renal function are serum creatinine (Cr), creatinine clearance (CCl) and glomerular filtration rate (GFR) measured by dynamic methods [4]. Unfortunately, in cirrhotic patients, serum Cr measurement must be interpreted with caution since it is highly influenced by various extrarenal factors including age, sex, muscle mass and protein intake. In cirrhosis, discrepancies between serum Cr level and renal function can be accentuated by malnutrition, reduced muscle mass and increased tubular secretion

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of Cr. In addition, hyperbilirubinemia can interfere with the measurement of Cr using the Jaffe method, and ascites and peripheral oedema can further decrease the Cr level by widening the distribution of Cr in the body [4]. Cr-based methods of estimation of GFR including CCl and predictive equations such as Cockroft-Gault and MDRD (Modification of Diet on Renal Diseases) formulas could also overestimate renal function in patients with cirrhosis, rendering it impossible to detect a slightly or a moderately decreased GFR [4]. Some early markers of renal dysfunction have been recently proposed, such as urine neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 and interleukin-18 [5-8]. However, these markers require further research regarding their efficacy in cirrhosis [8].

Recent studies suggest that serum cystatin C (CysC) is a more sensitive marker of GFR than serum Cr [9]. CysC is a nonglycosylated 13 kDa protein, a member of the cystatin superfamily of cysteine protease inhibitors [10]. It is produced at a constant rate in all nucleated cells, freely crosses the glomerular membrane to be reabsorbed and metabolized in the renal proximal tubular cells, and has no extrarenal elimination. Unlike serum Cr, CysC levels are independent of age, sex, muscle mass, inflammatory conditions or malignancy [4,9,10]. Several reports have suggested that increased CysC levels are more sensitive in detecting renal dysfunction in patients with cirrhosis than increased Cr levels, and that measurement of serum CysC could offer a good alternative to serum Cr for the assessment of renal function in these patients [11-13]. Gerbes et al. found that serum CysC is more effective in detecting kidney injury in advanced cirrhotic patients than serum Cr [12]. Kim et al. published similar results, reporting CysC as a useful marker for detecting significant renal dysfunction in cirrhotic patients with ascites and normal serum Cr levels [14]. CysC is supported by additional studies to be a good early predictor of acute kidney injury [15]. It has already been reported that CysC is linked to the mortality rate of patients with heart failure, regardless of objective renal function [16], and that it yields a higher rate of accuracy than serum Cr in predicting the mortality rate of diabetic patients [17].

The aim of this study was to determine the prognostic value of specific renal markers in predicting one-year mortality in cirrhotic patients with normal serum Cr and to investigate the priority of serum CysC in these patients.

2. Patients and methods

2.1. Patients

Forty five consecutive patients with cirrhosis and normal serum Cr levels, hospitalized in Gastroenterology Department at the University Hospital “St. George” in Plovdiv between March 2010 and November 2011 were enrolled in this study. The diagnosis of liver cirrhosis was defined in each participant through a combination of a physical examination, laboratory tests, an endoscopy showing existence of varices, and an abdominal ultrasonography or computed tomography indicating cirrhosis of the liver. At the time of admission patients with intrinsic renal disease, acute renal failure, as well as those undergoing hemodialysis due to chronic kidney disease, hepatocellular carcinoma, congestive heart failure, chronic obstructive pulmonary disease, spontaneous bacterial peritonitis, severe malnutrition, sepsis or gastrointestinal bleeding during the month before enrollment were excluded from the study. Patient follow-up occurred every three months with the endpoint occurring at the time of mortality within one year.. Informed consent was obtained from each patient and the study protocol was approved by the hospital ethics committee.

2.2. Methods

2.2.1. Laboratory analyses

To evaluate liver function of cirrhotic patients, a range of tests consisting of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, bilirubin, prothrombin index, international normalized ratio (INR) and electrolytes were implemented on analyzer “Konelab 60i” (Thermo Fisher, USA). The Child-Pugh score was determined applying Pugh’s commonly used modification, which is based on the levels of serum bilirubin and albumin, the presence and severity of ascites and hepatic encephalopathy, and prolongation of the prothrombin time [18]. The Child-Pugh score was assigned as a number between 5 and 15 and then divided into three grades: Child-Pugh grade A (5-6), B (7-9), and C (10-15) [18]. The MELD score (Model for End-stage Liver Diseases) was calculated according to the following equation: MELD = 9.57 × loge (creatinine, mg/dl) + 3.78 × loge (bilirubin, mg/dl) + 11.20 × loge (INR) + 6.43,

where 6.43 is the constant for liver disease etiology [19]. The minimum value was set at 1.0 for calculation purposes. The MELD-Na score was obtained by the formula: MELD-Na = [0.025 × MELD × (140 − Na)] + 140. Renal function of cirrhotic patients was evaluated through measurement of blood urea nitrogen (BUN), serum Cr and CysC on admission. Serum Cr levels were determined using the kinetic Jaffe method (coefficient of variation (CV) was up to 5%). The serum CysC assay was implemented using latex-particle-enhanced turbidimetric immunoassay-PET (Thermo Fisher Scientific Oy) (CV was up to 3.2%). Normal levels of CysC are 0.55-1.15 mg/l for age < 50 years old and 0.63-1.44 mg/l for > 50 years old. We also determined 24-hour creatinine clearance (CCl) for each patient using the formula: CCl = (Cr /urine/ x urine volume) ÷ (Cr /serum/x 1440). The CCl was then corrected according to the body surface area (BSA) using nomograms as follows: CCl (ml/min/1.73 m^2) = CCl x 1.73 ÷ BSA. We used measured CCl as a referent method for determining GFR in our study and values above ≥ 80 ml/min/ 1.73 m^2 were considered normal. The Cockroft-Gault formula (e-GFRC.G.) [20] and 6-variable Modification of Diet in Renal Disease equation (e-GFRMDRD) [21] were used to calculate the estimated GFR (e-GFR):

e-GFRC.G. (ml/min) = [140 − age (years)] × [weight (kg)] / [72×serum Cr (mg/dl)] × 0.85 (if female) / × 1.22 (if male).

$e\text{-}GFR_{MDRD}$ (ml/min) = 170 × [serum Cr (mg/dl)]$^{-0.999}$ × [age (years)]$^{-0.176}$ × [serum BUN (mg/dl)]$^{-0.170}$× [serum albumin (g/dl)]$^{0.318}$ ×–0.762 (if female)/ × 1.180 (if black).

2.2.2. Statistical analysis

Statistical analysis was performed using SPSS version 19.0 k (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation (SD) or as a percent of patients (as a percentage of the entire cohort). Nonparametric methods were used for group comparison and correlation analyses; Fisher's exact and χ^2 test, Mann-Whitney U-test and Spearman's correlation analysis. A logistic regression test was performed to identify factors impacting the patients´ one-year mortality. The efficacy of serum renal markers-BUN, Cr and CysC for predicting mortality was evaluated by receiver operating characteristic curves (ROCs), with the area under the curve (AUCs) and 95% confident intervals (CIs) used as indices of accuracy. The optimal cut-off value for predicting mortality was determined based on the maximum total sensitivity and specificity. A result was deemed statistically significant when $p < 0.05$.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the forty five patients (42; 93.3% males and 3; 6.7% female) with cirrhosis are presented in Table 1. Cirrhosis etiologies comprised of alcohol (n = 34; 75.6%), chronic hepatitis B (n = 6; 13.3%), chronic hepatitis C (n = 3; 6.7%), one patient had co-infection with hepatitis B and hepatitis C (n = 1; 2.2%) and another one had Budd-Chiari syndrome (n = 1; 2.2%). Ascites was found in 35 patients (77.8%) and esophageal varices in 39 patients (86.7%). The average Child-Pugh score was 8.53±2.09, with Child-Pugh A consisting of 7 patients (15.6%), Child-Pugh B of 17 patients (37.8%), and Child-Pugh C of 21 patients (46.7%). The MELD score was 13.84±5.29 and the MELD-Na score was 15.18 ± 5.94.

During the study period a total of 11 cirrhotic patients (24.4%) died as a result of liver related disease (all of them were men). In comparison with the survivors, the non-survivors exhibited higher average serum cystatin C (1.61 ± 0.56 vs. 1.18 ± 0. 42, p = 0.008), serum Cr (84.27 ± 21.70 vs. 67.88 ± 17.52, p = 0.02), BUN (6.20 ± 2.98 vs. 4.28 ± 1.56, p = 0.03) concentrations and lower e-GFRC.G. (98.55 ± 39.26 vs. 148.35 ± 112.64, p = 0.009) and e-GFRMDRD (93.71 ± 26.84 vs. 140.25 ± 156.81, p = 0.041) (Table 2). There was no significant difference

Table 1. Baseline characteristics of the enrolled patients with liver cirrhosis and normal serum creatinine levels (mean ± SD).

Characteristics	All patients (N = 45)
Age (years)	53.18 ± 9.71
BMI *(kg/m^2)	26.36 ± 3.94
AST (IU/L)	89.93 ± 81.45
ALT (IU/L)	47.47 ± 42.58
Bilirubin (μmol/l)	66.68 ± 81.82
Albumin (g/d)	30.44 ± 5.91
INR	1.44 ± 0.38
Prothrombin index (%)	61.12 ± 17.61
Sodium (mmol/l)	139.24 ± 5.01
BUN (mmol/l)	4.75 ± 2.13
Creatinine (μmol/l)	71.88 ± 19.70
Cystatin C (mg/l)	1.28 ± 0.49
CCl (ml/min/1.73 m^2)	80.16 ± 37.00
e-GFRC.G. (ml/min)	136.18 ± 101.66
e-GFRMDRD (ml/min)	128.87 ± 137.89
Child-Pugh score	8.53 ± 2.09
MELD score	13.84 ± 5.29
MELD-Na score	15.18 ± 5.94

Table 2. GFR markers and liver function scores according to overall mortality (mean±SD; Mann-Whitney U test).

Variables	Survivors (n = 34)	Nonsurvivors (n = 11)	U	p-value
Age (years)	52.35 ± 9.29	55.73 ± 11.00	1.15	0.25
BMI (kg/m^2)	26.77 ± 4.03	25.11 ± 3.54	1.04	0.29
AST (IU/L)	92.41 ± 73.109	82.27 ± 107.08	1.25	0.21
ALT (IU/L)	49.00 ± 40.60	42.73 ± 50.05	1.14	0.25
Bilirubin (μmol/l)	69.63 ± 84.00	57.54 ± 77.79	0.79	1.93
Albumin (g/d)	31.03 ± 6.09	28.64 ± 5.18	1.28	1.19
INR	1.40 ± 0.35	1.57 ± 0 .45	0.96	0.33
Prothrombin index (%)	62.87 ± 16.83	55.71 ± 19.68	0.99	0.32
Sodium (mmol/l)	139.55 ± 4.84	138.27 ± 5.65	0.53	0.59
BUN (mmol/l)	4.28 ± 1.56	6.20 ± 2.98	2.16	0.03
Creatinine (μmol/l)	67.88 ± 17.52	84.27 ± 21.70	2.23	0.02
Cystatin C (mg/l)	1.18 ± 0.42	1.61 ± 0 .56	2.66	0.008
CCl (ml/min/1.73 m^2)	85.57 ± 36.76	63.45 ± 34.03	1.71	0.08
e-GFRC.G. (ml/min)	148.35 ± 112.64	98.55 ± 39.26	2.60	0.009
e-GFRMDRD (ml/min)	140.25 ± 156.81	93.71 ± 26.84	2.04	0.04
Child-Pugh score	8.41 ± 2.14	8.91 ± 1.97	0.59	0.55
MELD score	13.56 ± 4.949	14.73 ± 6.42	0.49	0.62
MELD-Na score	14.74 ± 5.66	16.55 ± 6.81	0.83	0.40

between the two groups of patients according to Child-Pugh grade (χ^2 = 3.35, p = 0.18), the presence of ascites (Fisher's = 0.40) or varices (Fisher's = 0.31). Ten of the patients presented reduced GFR (CCl<80 ml/min/1.73 m^2) and increased CysC levels, while Cr concentrations remained within normal limits.

3.2. Correlations of serum CysC with the other renal parameters

Serum CysC correlated better with CCl (Spearman´s coefficients r = -0.46; p = 0.01) than did BUN (r = -0.33, p = 0.02) and serum Cr (r = -0.39, p = 0.007). MDRD formula showed a stronger correlation of WHICH MARKER with CCl than Cockroft–Gault formula – r = 0.33 (p = 0.02) and r = 0.03 (p = 0.02), respectively. Serum sodium showed a negative correlation with Child-Pugh and MELD scores(r = -0.365; p = 0.01 and r = -0.447; p = 0.002, respectively). In comparison to the rest of the serum renal parameters, only CysC correlated significantly with serum sodium levels (r = -0.30. p = 0.04). We observed a strong positive correlation between Child-Pugh and MELD scores (r = 0.82, p<0.001).

3.3. Patients one-year mortality assessed by renal parameters

During the study period, the non-survivor group showed significantly lower serum renal markers with higher e-GFR$_{C.G.}$ and e-GFR$_{MDRD}$, compared with survival group. All renal markers correlated significantly with mortality (Table 3). Parameters of liver function: serum albumin, bilirubin, AST, ALT, INR and prothrombin index did not show significant correlation with mortality (r = -0.19; p = 0.2, r = -0.01; p = 0.93, r = -0.18; p = 0.21, r = 0.01; p = 0.91, r = 0.14; p = 0.34 and r = -0.14; p = 0.32 respectively. Serum sodium, Child-Pugh score, MELD and MELD-Na scores also did not correlate significantly with mortality: r = -0.08; p = 0.60, r = -0.25; p = 0.08, r = 0.08; p = 0.56, r = 0.07; p = 0.63 and r = 0.12; p = 0.41, respectively).

Using binary logistic regression analysis, we found that only BUN, serum Cr and CysC were significant predictors for one-year mortality in these patients (Table 3). However, multivariate regression analysis did not prove any of them to be an independent prognostic factor (p>0.05). To investigate the efficacy of BUN, serum Cr and CysC in predicting one-year mortality, the area under ROC curves was calculated (Figure 1). The AUC values were 0.719 (95% CI, 0.539-0.899, p = 0.03) for BUN, 0.726 (95% CI, 0.541-0.911, p = 0.02) for serum Cr and 0.770 (95% CI, 0.620-0.920, p = 0.008) for CysC. Using the ROC curves, the appropriate cut-off values of BUN, serum Cr and CysC for predicting mortality were 4.95 mmol/l (sensitivity 0.636, 1-specificity 0.235), 76.5 µmol/l (sensitivity 0.727, 1-specificity 0.294) and 1.3 mg/l (sensitivity 0.727, 1-specificity 0.324), respectively.

Table 3. Spearman's correlation and univariate regression analysis of the variables for one-year mortality

Variable	Coefficient*	p**	Exp (B)	β (95% CI)
BUN	0.327 (p = 0.02)	0.033	1.57	1.03-2.38
Cr	0.337 (p = 0.02)	0.029	1.05	1.00-1.10
CysC	0.402 (p = 0.006)	0.020	5.819	1.32-25.58
CCl	-0.259 (p = 0.086)	0.088	0.982	0.961-1.003
e-GFRC.G.	-0.392 (p = 0.008)	0.055	0.978	0.95-1.00
e-GFRMDRD	-0.309 (p = 0.03)	0.10	0.975	0.94-1.00

** Spearman's correlation coefficient; ** univariate regression analysis; CI, confidence interval.*

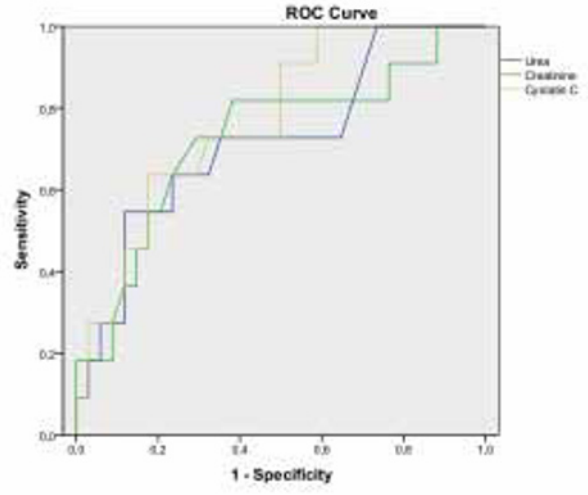

Figure1. Receiver operator characteristic (ROC) curves of BUN (AUC-0.719;95% CI, 0.539-0.899), serum Cr (AUC-0.726,95% CI, 0.541-0.911) and CysC (AUC-0.770;95% CI, 0.620-0.920, p=0.008) for CysC for predicting one-year mortality.

4. Discussion

The results of this study show that serum renal markers BUN, serum Cr and CysC have good prognostic efficacy for one-year mortality in patients with liver cirrhosis. Of those, serum cystatin C offers a higher level of accuracy in predicting mortality.

The development of renal dysfunction significantly affects the prognosis of patients with cirrhosis and it progresses in parallel with liver insufficiency and portal hypertension [2,3]. The extreme expression of the hyperdynamic circulation state in cirrhosis is HRS, which is characterized by splachnic arterial vasodilatation, extreme activation of vasoconstrictive systems, arterial hypotension and renal arterial vasoconstriction [2]. Once it is developed, the prognosis for these patients is poor [2,3]. Since serum creatinine levels in cirrhotic patients with acute kidney injury usually remain within normal range and increase only after the injury has progressed to a certain degree, other prognostic factors have been studied as potential early markers. Active effort should be devoted to identify and correct the causative factors for renal dysfunction in such patients.

The results of this study further show that CysC correlated better with CCl (r = -0.46; p = 0.01) than did the other two serum renal markers. In fact, 16 patients (35.6%) had serum CysC levels above the referent ones, while serum Cr levels remained within normal values. Ten of these patients (62.5%) had reduced GFR (CCl<80 ml/min/1.73 m^2). These results were consistent with previous studies that proved serum CysC to be a better marker of GFR than serum Cr in cirrhotics [12,13]. We used measured CCl as a referent method for determining GFR because it is a reliable and not an expensive method. However, several studies proved that CCl from timed urine collections overestimates true GFR about 13 ml/min/1.73 m^2 compared to inulin clearance in patients with cirrhosis [13,22]. The reasons for this are the increased proportion of Cr secreted by the tubule compared to Cr filtered by the glomerulus in these patients and nonspecific factors, including incomplete urine collection due to hepatic encephalopathy and errors in the timing of collection [3]. Therefore, one of the drawbacks of the study was that we did not measured GFR by a more accurate method, such as dynamic methods or inulin clearance (still considered as gold standard for determination of GFR in cirrhosis) [3], and we are not able to confirm whether CysC levels objectively represent renal function status. Other limitations of this study are the lack of a control group and the small number of participants.

We expected that the serum CysC level would be a good prognostic factor for one-year mortality in cirrhosis since it better reflects renal dysfunction. Seo et al. reported that serum CysC was a good prognostic marker for cirrhotic patients with ascites [23]. Another research group showed similar outcomes in all 53 cirrhotic patients enrolled in their study, not only for those with ascites [15]. CysC was an independent predictor of kidney injury and mortality [15].

Our results show that serum renal markers (BUN, Cr, CysC), CCl, e-$GFR_{C.G.}$ and e-GFR_{MDRD} were significantly different between the survival and non-survival group. BUN, Cr and CysC levels proved to be significant prognostic factors. CysC appeared to provide a higher

accuracy for predicting one-year mortality; AUC was 0.770 (95% CI, 0.620-0.920, p = 0.008), though the differences between its AUC and AUCs of the other two serum renal markers were not significant. The sensitivity and specificity of a serum CysC level >1.3 mg/l to mortality were 72% and 68%. Using univariate regression analysis, we found that elevated levels of CysC above the referent ones, increased the risk of one-year mortality nearly six times (p = 0.02, Exp(B) = 5.81). In multivariate regression analysis, none of the markers proved to be an independent prognostic factor in contrast with the results of previous research groups [15]. This could be explained by the small number of patients in our study and the probability of a type II error (beta error). Some authors have suggested that renal function parameters are better prognostic factors than liver function markers in cirrhotic patients [24,25]. Our data also revealed that the parameters of liver function did not differ between the two groups of patients and that they were not as strong prognostic factors for one-year mortality as the renal parameters turned out to be.

In conclusion, the results of the present study indicate that serum renal markers have reasonable prognostic value for one-year mortality in non-azotemic patients with liver cirrhosis. Serum CysC appeared to provide better prognostic efficacy than did BUN and serum Cr. However, additional research is necessary to ascertain precisely how CysC affects patient survival rates.

Conflict of interest statement

Authors state no conflict of interest.

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