*Jerzy Jaroszewicz, Magdalena Rogalska-Taranta, Magdalena Płońska-Rogalska, Tomasz Szulżyk, Paweł Kozłowski, Tadeusz W. Łapiński, Robert Flisiak

Serum cystatin C in chronic liver disorders – not a simple marker of renal function impairment

Cystatyna C w przewlekłych chorobach wątroby – nie tylko wskaźnik upośledzenia funkcji nerek

Department of Infectious Diseases and Hepatology, Medical University of Białystok
Head of Department: prof. Robert Flisiak, MD, PhD

Key words

liver cirrhosis, renal function, glomerulal filtration rate, cystatin C

Słowa kluczowe

marskość wątroby, funkcja nerek, wskaźnik przesączania kłębuszkowego, cystatyna C

Summary

Introduction. Progressive renal function impairment is a pitfall of chronic liver disorders. Routinely used estimates of glomerular filtration rate (GFR) based on serum creatinine may potentially lead to the overdiagnosis of chronic kidney dysfunction. In recent years, serum cystatin C (cys C) has been proposed as an early marker of kidney dysfunction.

Aim. The aim of current study was to assess value of serum cystatin C in liver cirrhotics with subclinical kidney dysfunction and its possible usefulness in liver cirrhosis progression prediction.

Material and methods. Cystatin C was measured in sera of 77 patients with liver cirrhosis (48 males; age 52 yrs) by ELISA (BioVendor GmbH, Germany). Cys C was correlated with creatinine based GFR but also markers of liver dysfunction. Moreover, in 62 patients follow-up information on future decompensation or death was available.

Results. Serum cystatin C was independent of age, weight, bilirubin concentration, ALT, INR, hemoglobin and platelets count. We observed a positive correlation with serum creatinine (B = 0.83, $P < 0.001$) but also negative with albumins (B = -0.48, $P = 0.01$). Interestingly, cys C levels were higher in patients who developed liver decompensation (351.6 ± 73.3 vs. 794.1 ± 234.3 ng/mL, $P = 0.005$) or died due to its complications (359.2 ± 62.7 vs. 1.235 ± 486.6 ng/mL, $P = 0.04$) in the follow-up period.

Conclusions. This study showed the increase of serum cystatin C in liver cirrhotics with subclinical renal function impairment, but also suggests its association with the level of liver impairment. Our results point towards cystatin C as potential, clinical marker useful in predicting the development of liver cirrhosis complications.

Streszczenie

Wstęp. Postępująca dysfunkcja nerek jest jedną z istotnych cech przewlekłych chorób wątroby. Rutynowo stosowane sposoby obliczania wskaźnika przesączania kłębuszkowego (GFR) oparte na kreatyninie mogą prowadzić do zawyżania rozpoznania przewlekłej dysfunkcji nerek. W ostatnich latach podkreśla się przydatność oznaczania cystatyny C (cys C) w surowicy krwi jako wczesnego wskaźnika upośledzenia wydolności nerek.

Cel pracy. Celem pracy była ocena przydatności pomiaru stężenia cys C u chorych z marskością wątroby oraz subklinicznym upośledzeniem funkcji nerek, jak również jej przydatności jako wskaźnika rokowniczego progresji marskości wątroby.

Materiał i metody. Stężenie cystatyny C oznaczono w surowicy 77 chorych z marskością wątroby o różnej etiologii za pomocą zestawu ELISA (BioVendor GmbH, Niemcy). Stężenia korelowano z GFR, jak również ze wskaźnikami upośledzenia funkcji wątroby. Sześćdziesięciu dwóch chorych poddano dalszej obserwacji celem ustalenia progresji choroby wątroby.

Wyniki. Stężenie cys C było niezależne od wieku, wagi, stężenia bilirubiny, aktywności ALT, INR, HgB oraz liczby płytek krwi. Stwierdzono dodatnią zależność ze stężeniem kreatyniny (B = 0,83; $P < 0,001$), ale też negatywny związek ze stężeniem albumin (B = -0,48; $P = 0,01$). Co więcej, zaobserwowano wyższe wyjściowe stężenia cys C u chorych, którzy w dalszej obserwacji rozwinęli niewydolność wątroby (351,6 ± 73,3 vs. 794,1 ± 234,3 ng/mL; $P = 0,005$) lub zmarli z jej powodu (359,2 ± 62,7 vs. 1,235 ± 486,6 ng/mL; $P = 0,04$).

Wnioski. Przeprowadzone badania wskazują na podwyższone stężenia cystatyny C w surowicy krwi chorych z marskością wątroby oraz na związek ze stopniem wydolności wątroby. Dodatkowo stężenie cystatyny C może wiązać się z niekorzystnym rokowaniem w marskości wątroby, co powinno być uwzględnione w skalach rokowniczych.

Address/adres:

*Jerzy Jaroszewicz
Department of Infectious Diseases and Hepatology
Medical University of Białystok
ul. Żurawia 14, 15-540 Białystok
tel./fax +48 (85) 741-69-21
jerzy.jaroszewicz@umb.edu.pl

INTRODUCTION

Progressive renal function impairment is a pitfall of chronic liver disorders. Hepatorenal syndrome in liver cirrhotics yields high mortality despite of novel treatment possibilities: terlipressin and albumins (1-3). Progressive renal dysfunction may eventually lead to acute tubular necrosis, interstitial fibrosis and tubular atrophy which remain irreversible. In fact, the diagnosis and cause of renal failure is independently associated with prognosis in liver cirrhosis, together with MELD score (Model For End-Stage Liver Disease), serum sodium, and hepatic encephalopathy (4). On the other hand, renal function impairment is not solely confined to end stage liver disease. In chronic hepatitis C a variety of kidney disorders can be observed, including the most common cryoglobulinemic glomerulopathy, and also other types of immune globulin associated nephropathies, membranoproliferative glomerulonephritis, diabetic nephropathy or focal glomerular sclerosis (5, 6).

MELD score including serum bilirubin and creatinine levels and International Normalized Ratio (INR) for prothrombin time is a current gold standard in prognosis assessment (7, 8) and replaces Child-Pugh classification of liver cirrhosis (9). On the other hand, routinely used estimates of glomerular filtration rate (GFR) which are based on serum creatinine may potentially lead to the overdiagnosis of chronic kidney dysfunction. First, several chromogens, among them bilirubin, glucose, uric acid and certain antibiotics interfere with creatinine quantity (10). Second, serum creatinine may be influenced by several factors unrelated to renal function: creatinine dietary intake, state of hydration as well as total pool body creatinine – muscle mass (11).

In recent years, serum cystatin C (cys C) has been proposed as a marker of early detection of kidney dysfunction (12). Cystatin C is a nonglycosylated low molecular weight (13 kDa) basic protein that is a member of the cystatin superfamily of cysteine protease inhibitors. It is a secreted protein ubiquitously expressed in all tissues. Therefore, it has a stable production rate even if there is an inflammatory response and is freely filtered by the glomeruli. Moreover, as opposed to serum creatinine, serum cystatin C concentration is not affected by dietary protein intake, and there is no interference of proteins and bilirubin present in serum during the estimation process.

Several investigators have previously reported that serum cystatin C correlates well with GFR and is especially useful in diagnosis of early, subclinical renal function impairment (13-15). We showed that serum cystatin C may reflect mild renal dysfunction in HIV-infection (16). Significant experience on the association between cys C levels and creatinine estimated GFR (Cr-GFR) was gained in another persistent viral disease, HIV-infection. Results from two large studies by Odden et al. (17) including 1008 participants and Jones et al. (18) including 250 subjects agreeably showed that serum creatinine levels may overestimate GFR in HIV-infection and kidney dysfunction is more prevalent than previously expected.

AIM

The aim of our study was to assess serum concentrations of cystatin C in liver cirrhosis of various aetiologies with early, subclinical kidney dysfunction. Moreover we addressed the possible usefulness of cystatin C measurement as a prognostic marker of in liver cirrhosis progression and its complications development.

MATERIAL AND METHODS

Patients

Cystatin C was measured in sera of 77 Caucasian patients with liver cirrhosis (29 females and 48 males; median age: 52.0, min. 21, max. 82). Alcohol-related liver cirrhosis (ALC) was diagnosed in 37, primary biliary cirrhosis (PBC) in 14, hepatitis C virus related liver cirrhosis (HCV-LC) in 12, whereas role of hepatitis B virus (HBV-LC) as an etiologic factor was established in 14 subjects. None of patients included had HRS diagnosed, based on criteria proposed by Salerno et al. (19), nor pre-existing renal disorders detected by use of urinalysis or ultrasonography. Degree of liver insufficiency was established according to Child-Pugh classification (9). Ascites, encephalopathy, prothrombin index, as well as concentrations of bilirubin and albumin were evaluated for this purpose. Patients were scored as follows: 5-6 points as class (group) A, 7-9 points as class (group) B, and 10-15 points as class (group) C. Moreover, MELD score based on serum creatinine, albumins and bilirubin concentration was calculated (7). Clinical characteristic of studied population is presented in table 1. In the group of 62 patients with liver cirrhosis follow-up information was available (median 25 months) and clinically significant events, including liver cirrhosis decompensation or death due to the liver disease were recorded.

Cystatin C serum concentration was measured by sandwich enzyme immunoassay (BioVendor GmbH, Heidelberg, Germany). According to manufacturer information cystatin C assay limit of detection is 0.2 ng/mL, intra-assay CV is 5.0-9.6% and inter-assay CV is 4.8-6.2%. Creatinine, urea, albumin concentrations were measured in serum from the same sample. The glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault and Modification of Diet in Renal Disease Study (MDRD) formula: GFR=170 x [serum creatinine concentration (mg/dL)] - 0.999 x [Age] - 0.176 x [0.762 if subject is female] x [serum urea nitrogen (mg/dL)] - 0.17 x [serum albumin concentration (g/dL)] + 0.318 with normal range of 90-120 mL/min per 1.73 m^2 (11). Serum cystatin C concentrations in liver cirrhosis were compared with those obtained in 15 healthy volunteers (5 females and 10 males; median age: 42.0, min. 27, max. 62). The procedures followed

Table 1. Characteristics of studied population.

Age (median, min.-max.), years	52.0 (21-82)
Men/Women	48/29
Liver cirrhosis etiology	ALD, n = 37 HBV-LC, n = 14 HCV-LC, n = 12 PBC, n = 14
Child-Pugh class	A, n = 19 B, n = 28 C, n = 30
Child-Pugh score, pts. (median, min.-max.)	9 (5-13)
ALT [U/L], mean ± SE	92.1 ± 23.2
Bilirubin [mg/dL], mean ± SE	5.6 ± 0.9
INR, mean ± SE	1.7 ± 0.3
Albumin [g/dL], mean ± SE	3.0 ± 0.1
RBC [10^6/uL], mean ± SE	3.9 ± 0.1
WBC [10^3/uL], mean ± SE	7.1 ± 0.8
PLT [10^3/uL], mean ± SE	120.3 ± 9.2
Creatinine [mg/dL], mean ± SE	0.9 ± 0.1
GFR by Cockroft-Gault formula[1] [mL/min], mean ± SE	86.7 ± 6.3
GFR by MDRD[2] [mL/min], mean ± SE	104.6 ± 5.8

were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. The study was approved by the Bioethical Committee of the Medical University of Białystok. Informed consent was obtained from each patient.

Statistical analyses

Values were expressed as median (min., max.) and mean ± standard error of mean (SE). The significance of differences was calculated by non-parametric Mann-Whitney U test. For correlation analysis, the Spearman non-parametric correlation was used. Moreover multiple, stepwise regression with serum cystatin as dependant variable was performed. A $P < 0.05$ was considered statistically significant. Statistical analyses were performed with Statistica 5.0 for Windows software (Statsoft Inc., Tulsa, USA).

RESULTS

Mean serum cystatin C in healthy individuals was 78.1 ± 25.9 ng/mL (min. 5.0, max. 260 ng/mL). In liver cirrhosis the mean concentration of serum cystatin C was 536.6 ± 93.5 ng/mL ($P = 0.001$ in comparison to control group) and significantly increased with Child-Pugh class (A: 232.0 ± 72.6 ng/mL; B: 377.5 ± 85.2 ng/mL; C: 947.2 ± 232.6 ng/mL, $P = 0.01$ by Kruskal-Wallis ANOVA test).

Serum cystatin C values did not differ significantly among individuals with various liver cirrhosis aetiology (ALC: 421.8 ± 76.9; PBC: 592.1 ± 252.5; HCV-LC: 215.8 ± 63.4; HBV-LC: 1.063 ± 387 ng/mL; $P = 0.29$ by Kruskal-Wallis ANOVA test). Moreover there were no differences in respect to sex (544.9 ± 155.5 vs. 531.8 ± 118.2 ng/mL, $P = 0.45$). In multiple regression analysis serum cystatin C was independent of age, weight serum bilirubin concentration, ALT activity, INR, haemoglobin concentration and platelets count. We observed the strong positive correlation with serum creatinine (B = 0.83, $P < 0.001$). Among other laboratory parameters only serum albumins were associated negatively with cystatin C levels (B = -0.48, $P = 0.01$) (tab. 2). Moreover, we observed the significant, negative correlations between cystatin C levels and GFR estimated by Cockcroft-Gault (R = -0.43, $P = 0.001$) and MDRD (R = -0.53, $P < 0.001$) formulas.

Table 2. The association between serum cystatin (dependent variable) and selected clinical and biochemical parameters in studied population obtained by use of step-wise multiple regression analysis (R = 0.83, $P < 0.001$).

Parameter	Beta	Beta error	*P*
Age [yrs]	0.77	0.13	0.56
Weight [kg]	0.04	0.12	0.75
ALT [U/L]	0.05	0.12	0.96
Bilirubin [mg/dL]	-0.16	0.14	0.27
Albumins [g/dL]	-0.48	0.17	0.01*
INR	-0.08	0.12	0.49
Creatinine [mg/dL]	0.83	0.15	< 0.001*
WBC [10^3/uL]	-0.33	0.16	0.05
HgB [g/dL]	-0.11	0.14	0.42
PLT [10^3/uL]	-0.03	0.13	0.78

*denotes statistical significance calculated by use step-wise multiple regression analysis

Cystatin C concentrations showed significant association with liver function impairment as assessed by Child-Pugh score (R = 0.31, $P = 0.01$) and MELD (R = 0.27, $P = 0.03$). Interestingly, baseline cystatin C levels were significantly higher in patients, who developed further liver cirrhosis decompensation (351.6 ± 73.3 vs. 794.1 ± 234.3 ng/mL, $P = 0.005$) or died due to its complications (359.2 ± 62.7 vs. 1.235 ± 486.6 ng/mL, $P = 0.04$) in the follow-up period (tab. 3). Furthermore, we observed the negative association between baseline serum cystatin C and time of decompensation development after initial visit (R = -0.56, $P = 0.01$).

DISCUSSION

The usefulness of cystatin C monitoring as a marker of GFR was validated in many disorders including subjects undergoing cardiac catheterization, diabetes or critically ill patients (20-22). It was shown particularly valuable, more sensitive than serum creatinine in the detection of early renal insufficiency in a variety of renal disorders. Nevertheless, some reports suggest that serum cystatin C might be influenced by factors other than renal function alone in healthy individuals. Knight et al. (23) among potential biasing factors indicated: older age, male gender, greater weight, greater height, current

Table 3. The association between baseline concentrations of selected parameters and liver cirrhosis complications during follow-up period.

Parameter	Death		*P*	Decompensation		*P*
	Yes (n = 9)	No (n = 53)		Yes (n = 20)	No (n = 42)	
Age [years]	62.3 ± 4.9	53.4 ± 1.7	0.09	54.9 ± 12.4	54.7 ± 2.0	0.72
Child-Pugh score [pts.] (median, min., max.)	10.0 ± 0.9	8.5 ± 0.3	0.14	9.6 ± 0.6	8.2 ± 0.3	0.06
MELD score	17.3 ± 2.7	15.8 ± 1.1	0.56	17.1 ± 1.5	15.0 ± 1.1	0.18
Bilirubin [mg/dL]	5.2 ± 1.4	5.7 ± 1.1	0.33	5.8 ± 1.5	4.5 ± 0.8	0.26
Albumin [g/dL]	2.6 ± 0.1	3.1 ± 0.1	0.14	2.7 ± 0.6	3.2 ± 0.1	0.08
INR	1.4 ± 0.1	1.8 ± 0.3	0.58	1.5 ± 0.3	1.8 ± 0.4	0.02*
PLT [10^3/uL]	76.7 ± 16.4	126.5 ± 10.2	0.02*	83.2 ± 9.7	137.8 ± 12.1	0.01*
Creatinine [mg/dL]	1.1 ± 0.3	0.9 ± 0.1	0.41	0.9 ± 1.2	0.9 ± 0.1	0.77
GFR by Cockroft-Gault [ml/min]	59.4 ± 18.6	91.3 ± 6.6	0.03*	82.2 ± 10.7	89.1 ± 8.1	0.53
GFR by MDRD [ml/min]	89.8 ± 26.3	107.9 ± 5.4	0.06	105.4 ± 11.6	105.3 ± 6.7	0.68
Cystatin C [ng/mL]	1.235 ± 486.6	359.2 ± 62.7	0.04*	794.1 ± 234.3	351.6 ± 73.3	< 0.01*

*denotes statistical significance calculated by use of Mann-Whitney U test

cigarette smoking, and higher serum C-reactive protein.

In liver cirrhosis the exact assessment of renal function is of a great importance, since its possible prognostic value. Commonly used GFR estimation formulas: Cockcroft-Gault and MDRD have been shown to overestimate and underestimate renal function in liver cirrhosis (24). On the contrary, the "gold standard" methods, like inulin, [^{99}Tcm]-DTPA, ^{51}Cr-EDTA are expensive and impractical for routine use. Limited studies validated the usefulness of serum cystatin C as a marker of renal dysfunction in liver cirrhosis. Gerbes et al. (25) showed that serum cystatin C determination could be a valuable tool in patients with cirrhosis, particularly with Child-Pugh class C or in female patients. More recently, Ustundag et al. (26) found that serum cystatin C, but not serum creatinine or RRI measurement, correlated with GFR ($r = -0.877$, $P < 0.05$) measured by use of by technetium(99m) renal scintigraphy in patients with liver cirrhosis in different stages of liver failure.

In our research, multiple regression analysis confirmed that serum cystatin C concentrations in liver cirrhosis were independent of sex, age, weight, serum bilirubin concentration, ALT activity, INR, haemoglobin concentration and white blood as well as platelets counts. This suggests its practical usefulness in individuals with liver dysfunction. More interestingly, we found the significantly higher baseline concentrations of cystatin C in patients who developed further liver complications or died during the median 25 months of follow-up. Other parameters associated with disadvantageous prognosis in studied population, but to lesser extent than cystatin C, were platelet count and INR, on the contrary the serum creatinine did not vary significantly.

Our data suggest that cystatin C is not just a simple marker of renal impairment in chronic liver disorders but additionally might reflect liver dysfunction. This observation can be further support by recent reports that cystatin C levels may reflect fibrogenic and necroinflammatory activities in chronic HCV-induced liver disease (27). Furthermore it was shown by Ahn et al. (28) that cystatin C was a good predictor of hepatorenal syndrome in liver cirrhosis prediciting survival in such patients. These observations raise the question of possible incorporating the serum cystatin C concentration in liver insufficiency risk scoring systems. In fact, Pöge et al. (29) found that cys C-based equations showed significantly lower bias and higher precision than the creatinine-based formulae in renal function assessment in liver cirrhosis. Possible prognostic usefulness of cystatin C measurement were suggested in patients with heart failure (30) or after the heart surgery (31). We are aware that small sample of studied population and relatively short observation period does not allow to draw firm conclusions. However these preliminary data strongly suggest the need of further studies assessing the possible prognostic usefulness of serum cystatin C in liver cirrhosis.

CONCLUSIONS

In conclusion, our study showed the increase of serum cystatin C in liver cirrhotics with sublinical renal function impairment but also with the level of liver insufficiency. Moreover, our results point towards cystatin C as potential, clinical marker useful in predicting the development of liver cirrhosis complications.

BIBLIOGRAPHY

1. Sanyal AJ, Boyer T, Garcia-Tsao G et al.: A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 2008; 134: 1360-1368.

2. Ortega R, Ginès P, Uriz J et al.: Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002; 36: 941-948.

3. Martín-Llahí M, Guevara M, Torre A et al.: Prognostic importance of the cause of renal failure in patients with cirrhosis. Gastroenterology 2011; 140: 488-496.
4. Kamath PS, Wiesner RH, Malinchoc M et al.: A model to predict survival in patients with end-stage liver disease. Hepatology 2001; 33: 464-470.
5. Sumida K, Ubara Y, Hoshino J et al.: Hepatitis C virus-related kidney disease: various histological patterns. Clin Nephrol 2010; 74: 446-456.
6. Lapinski TW, Parfieniuk A, Rogalska-Plonska M et al.: Prevalence of cryoglobulinaemia in hepatitis C virus and hepatitis C virus/human immunodeficiency virus-infected individuals: implications for renal function. Liver Int 2009; 29: 1158-1161.
7. Wiesner RH, McDiarmid SV, Kamath PS et al.: MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001; 7: 567-580.
8. Londoño MC, Cárdenas A, Guevara M et al.: MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation. Gut 2007; 56: 1283-1290.
9. Pugh RN, Murray-Lyon IM, Dawson JL et al.: Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-649.
10. Cholongitas E, Marelli L, Kerry A et al.: Different methods of creatinine measurement significantly affect MELD scores. Liver Transpl 2007; 13: 523-529.
11. Levey AS, Bosch JP, Lewis JB et al.: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modiffication of Diet in Renal Disease study Group. Ann Intern Med 1999; 130: 461-470.
12. Inker LA, Schmid CH, Tighiouart H et al.: Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367: 20-29.
13. Herget-Rosenthal S, Pietruck F, Volbracht L et al.: Serum cystatin C a superior marker of rapidly reduced glomerular filtration after uninephrectomy in kidney donors compared to creatinine. Clin Nephrol 2005; 64: 41-46.
14. Grubb A, Bjork J, Lindstrom V et al.: A cystatin C-based formula without anthropometric variables estimates glomerular filtration rate better than creatinine clearance using the Cockcroft-Gault formula. Scand J Clin Lab Invest 2005; 65: 153-162.
15. Gabutti L, Ferrari N, Mombelli G et al.: Does cystatin C improve the precision of Cockcroft and Gault's creatinine clearance estimation? J Nephrol 2004; 17: 673-678.
16. Jaroszewicz J, Wiercinska-Drapalo A, Lapinski TW: Does HAART improve renal function? An association between serum cystatin C concentration, HIV viral load and HAART duration. Antivir Ther 2006; 11: 641-645.
17. Odden MC, Scherzer R, Bacchetti P et al.: Cystatin C level as a marker of kidney function in human immunodeficiency virus infection: the FRAM study. Arch Intern Med 2007; 167: 2213-2219.
18. Jones CY, Jones CA, Wilson IB et al.: Cystatin C and creatinine in an HIV cohort: the nutrition for healthy living study. Am J Kidney Dis 2008; 51: 914-924.
19. Salerno F, Gerbes A, Ginès P et al.: Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007; 56: 1310-1318.
20. Artunc FH, Fischer IU, Risler T et al.: Improved estimation of GFR by serum cystatin C in patients undergoing cardiac catheterization. Int J Cardiol 2005; 10: 173-178.
21. Perkins BA, Nelson RG, Ostrander BE et al.: Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. J Am Soc Nephrol 2005; 16: 1404-1412.
22. Villa P, Jimenez M, Soriano MC et al.: Serum cystatin C concentration as a marker of acute renal dysfunction in critically ill patients. Crit Care 2005; 9: R139-143.
23. Knight EL, Verhave JC, Spiegelman D et al.: Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int 2004; 65: 1416-1421.
24. Gonwa TA, Jennings L, Mai ML et al.: Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. Liver Transpl 2004; 10: 301-309.
25. Gerbes AL, Gülberg V, Bilzer M et al.: Evaluation of serum cystatin C concentration as a marker of renal function in patients with cirrhosis of the liver. Gut 2002; 50: 106-110.
26. Ustundag Y, Samsar U, Acikgoz S et al.: Analysis of glomerular filtration rate, serum cystatin C levels, and renal resistive index values in cirrhosis patients. Clin Chem Lab Med 2007; 45: 890-894.
27. Ladero JM, Cárdenas MC, Ortega L et al.: Serum cystatin C: a non-invasive marker of liver fibrosis or of current liver fibrogenesis in chronic hepatitis C? Ann Hepatol 2012; 11: 648-651.
28. Ahn HS, Kim YS, Kim SG et al.: Cystatin C is a good predictor of hepatorenal syndrome and survival in patients with cirrhosis who have normal serum creatinine levels. Hepatogastroenterology 2012; 59: 1168-1173.
29. Pöge U, Gerhardt T, Stoffel-Wagner B et al.: Calculation of glomerular filtration rate based on cystatin C in cirrhotic patients. Nephrol Dial Transplant 2006; 21: 660-664.
30. Djoussé L, Kurth T, Gaziano JM: Cystatin C and risk of heart failure in the Physicians' Health Study (PHS). Am Heart J 2008; 155: 82-86.
31. Ledoux D, Monchi M, Chapelle JP et al.: Cystatin C blood level as a risk factor for death after heart surgery. Eur Heart J 2007; 28: 1848-1853.

received/otrzymano: 05.03.2014
accepted/zaakceptowano: 12.05.2014