The Open Biomarkers Journal

Content list available at: https://openbiomarkerjournal.com

RESEARCH ARTICLE

Role of Serum Cystatin C as a Diagnostic Tool for Renal Function in Cirrhotic Patients

Fathia Elsayed Asal[1], Mohamed Yousef[1], Hend Atteya Abdelkhalek Abdraboh[1], Sherief Abd-Elsalam[1,*], Ahmed Abdelaziz Abdelaziz Shama[2], Mohamed Elbahnasawy[3], Mohammed H Elnaggar[4], Hesham Ahmed Alsrogy[5] and Heba Elashry[1]

[1]*Department of Tropical Medicine and Infectious Diseases, Faculty of Medicine, Tanta University, Tanta, Egypt*
[2]*Department of Anesthesia, Surgical Intensive Care and Pain Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt*
[3]*Department of Emergency Medicine and Traumatology, Faculty of Medicine, Tanta University, Tanta, Egypt*
[4]*Department of Internal Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt*
[5]*Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt*

Abstract:

Background:

Assessment of cystatin C levels could be valuable in the early detection of renal dysfunction because they increase faster than the creatinine levels as the GFR decreases. The aim of this work was to evaluate serum cystatin C as a diagnostic tool for renal dysfunction in cirrhotic patients with and without hepatorenal syndrome (HRS).

Methods:

This case-control study was conducted on 60 patients from the Tropical Medicine Department of Tanta University Hospitals and 10 people served as healthy control volunteers. Serum cystatin C was measured in the three groups.

Results:

A significant difference was observed among the three groups as cystatin C was higher in patients with HRS compared to the cirrhotic group and healthy controls.

Conclusion:

Serum cystatin C is a good predictor for hepatorenal syndrome with a good correlation with serum creatinine, blood urea, GFR, and creatinine clearance.

Keywords: Cirrhosis, Kidney, Liver, Renal functions, Liver failure, Marker.

Article History	Received: October 7, 2021	Revised: December 13, 2021	Accepted: January 20, 2022

1. INTRODUCTION

Cirrhosis refers to a nodular disorder that affects the normal functioning of the liver due to the main preventable cases attributed to viral hepatitis, NAFLD, or extreme alcohol consumption [1]. Patients with progressive liver cirrhosis are at an increased hazard of developing renal dysfunction as they frequently use intravenous radiocontrast mediators and diuretics, undergo paracentesis, and suffer from gastrointestinal hemorrhages, such as variceal bleeding, or infection as spontaneous bacterial peritonitis [2 - 35].

Moreover, renal dysfunction usually progresses to hepatorenal syndrome with the development of liver cirrhosis and portal hypertension [3]. The progress of renal dysfunction is one of the greatest important prognostic features in these patients [4]. The prognosis is mostly poor once HRS develops [5].

An accurate assessment of renal function in these patients is essential to estimate the prediction and determine the

* Address correspondence to this author at the Department of Tropical Medicine and Infectious Diseases, Faculty of Medicine, Tanta University. El-Giash Street 31527, Tanta, Egypt; Tel: +2-01147773440;
E-mails: sherif.abdelbaky@med.tanta.edu.eg, sherif_tropical@yahoo.com

accurate therapeutic interference (including drug dosing) and reaction [6]. Hepatorenal syndrome (HRS) is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure, in the absence of a pre-existing renal pathology [7, 8].

Cystatin C is a nonglycosylated 13 kDa protein that is one of the cystatin superfamilies of cysteine protease inhibitors [10]. It is produced at a constant degree in all nucleated cells and spontaneously crosses the glomerular membrane, being reabsorbed and broken down in the proximal tubular cells of the kidney, without extrarenal elimination. Contrasting creatinine levels, cystatin C levels do not depend on muscle mass, age, and gender, and are not influenced by inflammatory disorders or malignancy [11 - 20].

Evaluation of cystatin C levels could be valued in the early prediction of renal dysfunction as they increase faster than creatinine levels as the GFR declines [12]. Thus in this study, we investigated the role of serum cystatin C as a diagnostic tool for renal dysfunction in cirrhotic patients with and without the hepatorenal syndrome.

2. METHODS

After approval of the Research Ethical Committee and written consent from participants involved in the study, this case-control study was conducted on 60 patients admitted to the Tropical Medicine Department of Tanta University Hospital and 10 healthy volunteers from January 2018 till June 2019. The participants were divided into 3 groups. Group 1 included 30 patients with liver cirrhosis and normal kidney function, group 2 included 30 cirrhotic patients with hepatorenal syndrome type 2 according to the criteria for diagnosis of the hepatorenal syndrome [13], and group 3 included 10 people who served as healthy control volunteers.

The diagnosis of cirrhosis was based on a combination of physical examination, laboratory tests, and using imaging [14]. Cirrhotic patients with and without hepatorenal syndrome were included in the study. Patients with the following features were excluded from the study, such as patients with chronic renal failure or other causes of renal dysfunction apart from the hepatorenal syndrome, patients with heart failure, patients with metabolic syndrome diagnosed when the fasting glucose is ≥ 100 mg/dl (or receiving drug therapy for hyperglycemia), blood pressure ≥140/90 mm Hg (or receiving drug therapy for hypertension), triglycerides ≥ 150 mg/dl (or receiving drug therapy for hypertriglyceridemia), HDL-C <40 mg/dl in men or <50 mg/dl in women (or receiving drug therapy for reduced HDL-C), and waist circumference ≥102 cm (40 inches) in men or ≥88 cm (35 inches) in women.

All individuals were subjected to thorough history taking, with emphasis on the history of liver disease and drug history, including NSAIDs. Complete clinical examination with detection of signs of shock and hypotension was done. Laboratory investigations included CBC, blood urea, creatinine, liver function tests (total bilirubin, serum ALT, serum AST, and serum albumin), hepatitis markers (HCV-antibody, HBs-ag), blood electrolytes (sodium and potassium), blood sugar, glomerular filtration rate (GFR), and calculation of the scores were carried out. The Child-Pugh score was classified according to total serum bilirubin, serum albumin, INR, ascites status, and degree of hepatic encephalopathy [15].The MELD score was calculated according to the following formula; MELD score = 3.78 × ln (total bilirubin, mg/dl) + 11.2 × ln (INR) + 9.57 × ln (Cr, mg/dl) + 6.43 [16].

Estimation of cystatin C was performed using about 5 ml of the random blood sample taken from each patient and put into plan tubes and then centrifugated for about 2 minutes. The serum was collected and stored at -20°C till the time of analysis. Estimation of cystatin C by automated chemistry using Roche/Hitachi MODULAR analyzers and Cobas c. The C.f.a.s cystatin C is a liquid ready-to-use calibrator based on pooled human serum enriched with recombinant human cystatin C produced in E. coli. The concentration of the calibrator component had been adjusted to ensure optimal calibration of the appropriate Roche method on clinical chemistry analyzers. The calibrator values were determined using the method stated in the electronically available or enclosed value sheets. Determinations were performed under strictly standardized conditions on Roche analyzers using Roche system reagents and the Roche master calibrator.

Abdominal ultrasound was done on all participants using Toshiba Nemio XG apparatus by B-mode ultrasound at the Tropical Medicine Department; the patients were fasting at least for 6 hours and were asked to be in the supine position to assess liver echogenicity, surface, edge, size, portal vein diameter, attenuation of hepatic veins, size of the spleen, and presence of ascites.

In cases of hepatorenal syndrome, no pre-existing intrinsic renal disease should be reported. The kidneys should be in normal size with no evidence of atrophy, and good differentiation between cortex and medulla. Normal appearing kidneys on ultrasound are required for the diagnosis of hepatorenal syndrome according to the Hepatorenal Syndrome-AKI Guidelines issued by the International Club of Ascites.

2.1. Statistical Analysis

Once data were collected, a code sheet was developed. Organization, tabulation, presentation, and analysis of data were performed using SPSS V25 (IBM©, USA). Normal distribution was checked using the Shapiro Wilks test. Quantitative parametric data (*e.g*., age) were presented as mean and standard deviation (SD) and compared by ANOVA (one-way Analysis Of Variance) or F test (in the case of 3 groups). Quantitative non-parametric data (*e.g*., platelet) were presented as the median and interquartile range (IQR) and compared by the Kruskal-Wallis test (in the case of 3 groups). Categorical data (*e.g*., sex) were presented as numbers and percentages and compared by chi-square test.

3. RESULTS

All cases of group 1 and group 2 were of post hepatitis C cirrhosis. Considering lower limb edema, a significant difference was found among the three groups, which was found to be more prevalent in group 1 and group 2. Regarding ascites, there was a significant difference among the studied groups, 25 cases of moderate to severe in group 1 and 24 cases in group 2. In terms of hepatic encephalopathy, there were 5 cases in group

1 and 12 cases in group 2 with a significant difference between groups 1 and 2. The baseline demographic and clinical data are demonstrated in Tables **1** and **2**. Kidney function tests and electrolytes in the studied groups are demonstrated in Table **3**.

Table 1. Demographic data in the studied groups.

		Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=10)	Test	P-value
Age	Mean ±SD	52.1± 11.2	53.8± 11.4	45.6± 11.6	F= 1.853	0.165
	Range	26–76	33–80	23–60		
Gender	Male	20(66.7%)	20(66.7%)	6 (60%)	X^2 =0.169	0.919
	Female	10(33.3%)	10(33.3%)	4 (40%)		
Weight	Mean ±SD	81.9±7	87.8± 10.6	84.6± 12.3	F= 1.74	0.183
	Range	70–102	66–110	65–105		

X^2=chi-square test, F=one-way ANOVA.

Table 2. Clinical data of the three studied groups.

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=10)	$x2$	P-value
HCV	30 (100%)	30 (100%)	0	56.86	**<0.001***
Lower limb edema					
No	7	1	10	42.49	**<0.001***
Mild	17	13	0		
Moderate	5	15	0		
Marked	1	1	0		
Ascites					
No	2	0	10	48.02	**<0.001***
Minimal	3	6	0		
Moderate	19	15	0		
Marked	6	9	0		
Hepatic encephalopathy					
No	25	18		14.19	**0.028***
Grade I	2	1			
Grade II	1	10			
Grade III	0	0			
Grade IV	2	1			

Table 3. Kidney function tests and electrolytes in the studied groups.

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=10)	F Test	P-value		
Serum creatinine (mg/dL)	1.139 ±0.29	2.58 ± 0.93	0.91 ± 0.13	47.4	**<0.001***	P 1	**<0.001***
						P 2	0.331
						P 3	**<0.001***
BUN (mg/dL)	85.1 ± 30.9	146.4 ±93.9	48.4 ± 13.5	32.6	**<0.001***	P 1	**<0.001***
						P 2	0.87
						P 3	**<0.001***
GFR (mL/min)	68.5 ± 29.9	27.2 ± 9.47	111.3 ±22.1	35.6	**<0.001***	P 1	**<0.001***
						P2	**<0.001***
						P 3	**<0.001***

(Table 3) contd.....

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=10)	F Test	P-value		
Creatinine clearance (mL/min)	94.7 ± 32.2	43.8 ± 11.5	104.7 ± 15.04	46.4	**<0.001***	P1	**<0.001***
						P2	0.462
						P3	**<0.001***
Serum Sodium (mmol/dL)	131.7 ±9.27	127.7 ±4.76	136.7 ±3.62	1.063	**0.029***	P1	**0.031***
						P2	0.054
						P3	**0.001***
Serum Potassium (mmol/dL)	4.11 ± 0.61	4.48 ± 0.96	3.71 ± 0.14	5.205	**0.015***	P1	0.063
						P2	0.138
						P3	**0.006***

Data are presented as Mean ± SD or median and IQR, F= one-way ANOVA * denotes statistically significant p<0.05, P1: P-value between group 1 and group 2, P2: P-value between group 1 and group 3, P3: P-value between group 2 and group 3

Child score was significantly worse in group 2 compared to group 1 (P = 0.011). The MELD score was significantly higher in group 2 compared to group 1 (P < 0.001), as shown in Table **4**.

Regarding cystatin C, there was a significant difference among the three groups (P <0.001). A significant difference between group 1 and group 2 (P1 <0.001), between group 1 and group 3 (P2 = 0.029), and between group 2 and group 3 (P3 <0.001), was observed, as shown in Table **5**.

The diagnostic performance of cystatin C for diagnosis of hepatorenal syndrome was evaluated using the ROC curve. The cutoff value of cystatin C was 1.9 mg/L, which showed a diagnostic sensitivity of 90%, specificity of 97.5%, positive predictive value (PPV) of 96.4%, and negative predictive value (NPV) of 92.9%. The area under the curve (AUC) was 0.972 and the P-value was <0.001 (*i.e*. good predictor for hepatorenal syndrome) (Tables **6** and **7**).

Table 4. Child score and MELD score in group 1 and group 2.

		Group 1 (n=30)	Group 2 (n=30)	Test	P value
Child score	**A**	2 (6.67%)	0	$X^2 = 8.98$	**0.011***
	B	16 (53.33%)	7 (23.33%)		
	C	12 (40%)	23 (76.67%)		
MELD score		14.4 (11.4-17.7)	26.75 (23-30.5)	K= 874	**<0.001***

Table 5. Cystatin C in the studied groups.

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=10)	F Test	P value		
Cystatin C (mg/L)	1.61 ± 0.85	3.50 ± 1.22	0.93 ± 0.63	19.2	**<0.001***	P1	**<0.001***
						P2	**0.029***
						P3	**<0.001***

Table 6. Correlation between cystatin C and creatinine, urea, GFR, and creatinine clearance.

		Creatinine	Urea	GFR	Creatinine clearance
CystatinC	r	0.820	0.718	-0.654	-0.703
	P value	**<0.001***	**<0.001***	**<0.001***	**<0.001***

Table 7. Diagnostic performance of cystatin C for diagnosis of hepatorenal syndrome.

Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	P value
>1.9	90%	97.5%	96.4%	92.9%	0.972	**<0.001***

PPV: positive predictive value, NPV: negative predictive value, AUC: Area under the curve.

There was a positive statistically significant correlation between cystatin C and MELD (r = 0.766, P <0.001). An insignificant correlation was found between cystatin C and Child score, and AST/ALT ratio.

4. DISCUSSION

Diagnosing HRS requires exclusion of other kidney disorders, absence of shock, no current or recent treatment with nephrotoxic drugs, and no improvement in serum creatinine after at least two days of diuretic withdrawal and volume expansion with albumin. HRS has a high mortality rate; therefore, early identification is important [17]. New biomarkers, including CysC, are known to be more accurate in estimating GFR and better correlate with the gold standard method of GFR estimation, such as DTPA scan or iohexol-based clearance [18]. In this study, GFR was found to be decreased in HRS patients (group 2) than cirrhotic patients (group 1). This may be due to severe renal vasoconstriction and decreased vasodilator factors acting on renal circulation. Our results were in agreement with the findings of a study conducted by Markwardt *et al*. [19], who showed that GFR was significantly lower in patients with HRS. Considering creatinine clearance, our results demonstrated that it was decreased in patients with HRS more than the cirrhotic patients compared to its normal level in controls. This met the alternative definition of HRS which is characterized by slow and progressive worsening of renal function, with serum creatinine clearance of > 40 ml/min{Arroyo, 1996 #1479}. Regarding the Child–Pugh score, we found that the score was worse in patients with HRS (most of them were Child class C) compared to cirrhotic patients (most of them were Child class B). In terms of cystatin C, a significant difference was found among the three groups as cystatin C was higher in patients with HRS compared to the cirrhotic group and healthy controls.

Our results were in agreement with the study conducted by Lei *et al*. [20] demonstrating that serum Cys C levels in the AKI group (2.4 ± 1.0 mg/L) were significantly higher than those in the non-AKI group (0.8 ± 0.1 mg/L) and the control group (0.7 ± 0.1 mg/L). Gomaa *et al*. [21] showed that the mean values of Cys C were higher in HRS patients than in the control group (2.62±0.45 and 0.74±0.08 mg/l, respectively) and cirrhotic patients with normal renal function (0.93±0.10 mg/l). Also, Markwardt *et al*. [19] in a study determining the plasma levels of CysC in 429 patients hospitalized for acute decompensation of cirrhosis in acute-on-chronic liver failure in cirrhosis (CANONIC) showed that CysC was significantly higher in patients with HRS. Our results were in agreement with the findings of Sharawey *et al*. [22], who found that cystatin C was higher in the HRS group than other cirrhotic patients (p < 0.001).

We found that the cut-off value of cystatin C, *i.e*., 1.9 mg/L, can be used for diagnosis of hepatorenal syndrome with a diagnostic sensitivity of 90%, specificity of 97.5%, PPV of 96.4%, and NPV of 92.9% with AUC of 0.972 and P-value <0.001 (*i.e*., good predictor for hepatorenal syndrome). These results were in agreement with the study conducted by Sharawey *et al*. [22], who revealed that the area under the curves (AUCs) for CysC was 0.86 with an optimal cut-off value of 1.8 mg/L CysC. The sensitivity and specificity for predicting the development of HRS were 88.8% and 67.6%, respectively. Near to our results were the findings of a study conducted by Gomaa *et al*. [21], who showed that Cys C at a cut-off value of 1.6 mg/l had a sensitivity of 73.3% and a specificity of 63.33%, PPV of 50%, NPV of 82.6, and AUCs of Cyst C was 0.72 (95% CI: 0.581–0.870; P=0.015). Also, Omar *et al*. [23] demonstrated that Cys C at a cut-off value of 1.2 mg/L had 89.6% sensitivity and 63.6% specificity in detecting early HRS. AUC was found to be 0.785. Also, Chung *et al*. [24] revealed that the sensitivity, specificity, PPV, and NPV of the cystatin C reference value in regard to a renal injury that occured within three months were found to be 66.7%, 86.4%, 50%, and 92.7%, respectively. The area under the ROC curve was 0.809 (95% CI, 0.671-0.947, p<0.001) in serum cystatin C. Also, Lei *et al*. [20] showed that the AUC of serum Cys C was 0.816 and P was < 0.001. Moreover, a cutoff value of serum Cys C concentration was 0.93 mg/L, and the sensitivity and specificity were 76.1% and 78.6%, respectively. Wang *et al*. [25] found that the optimal cut-off value of Cys C was 1.24 mg/l in the diagnosis of kidney impairment in hepatic cirrhosis patients with a sensitivity of 87.6% and a specificity of 93.1%. In our study, there was a positive significant correlation between cystatin C and serum creatinine, urea, GFR, and MELD score [25 - 28].

Orlando *et al*. [28] stated that, unlike creatinine, the plasma cystatin C concentration is not affected by decompensated cirrhosis and is a reliable GFR marker in such patients. Studying cirrhotic patients, creatinine failed to detect reduced renal function, with sensitivity being only 23%, whereas cystatin C exhibited good diagnostic sensitivity (88%). Also, Kim *et al*. [26] showed that serum CysC level was the only independent predictor for significantly decteting a renal impairment.

This study revealed that cystatin C is a very good predictor for hepatorenal syndrome. This study recommends adding cystatin C as an important part of the evaluation of cirrhotic patients with hepatorenal syndrome.

CONCLUSION

From our results, serum cystatin C is a good predictor for hepatorenal syndrome with a good correlation with serum creatinine, blood urea, GFR, and creatinine clearance.

AUTHORS' CONTRIBUTION

Fathia El Sayed Asal designed the methodology of the study. Fathia El Sayed Asal, Mohamed Yousef, and Hend

Atteya Abdelkhalek Abdraboh contributed to providing the study materials, recruiting patients, and collecting laboratory samples. Ahmed Abdelaziz Abdelaziz Shama and Mohamed Elbahnasawy analyzed the statistics of the study. Sherief Abd-Elsalam, Mohamed Elbahnasawy, Mohammed H Elnaggar, Hesham Ahmed Alsrogy, and Heba Elashry wrote the manuscript. Sherief Abd-Elsalam revised the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study has been approved by the institutional review board of the Tanta University Faculty of Medicine Research.

HUMAN AND ANIMAL RIGHTS

No animals were used in the studies that are the basis of this research. Human participation was in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Informed consent was obtained from all the participants of this study.

STANDARDS OF REPORTING

STROBE guidelines and methodologies were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Dr. Sherief Abd-Elsalam is the Associate Editorial Board Member of The Open Biomarkers Journal.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Friedman LS, Martin P. Handbook of Liver Disease E-Book. Elsevier Health Sciences 2017.

[2] Ginès P, Guevara M, Arroyo V, Rodés J. Hepatorenal syndrome. Lancet 2003; 362(9398): 1819-27. [http://dx.doi.org/10.1016/S0140-6736(03)14903-3] [PMID: 14654322]

[3] Ng CKF, Chan MH, Tai MH, Lam CW. Hepatorenal syndrome. Clin Biochem Rev 2007; 28(1): 11-7. [PMID: 17603637]

[4] Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009; 361(13): 1279-90. [http://dx.doi.org/10.1056/NEJMra0809139] [PMID: 19776409]

[5] Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology 2008; 48(6): 2064-77. [http://dx.doi.org/10.1002/hep.22605] [PMID: 19003880]

[6] Barakat M, Khalil M. Serum cystatin C in advanced liver cirrhosis and different stages of the hepatorenal syndrome. Arab J Gastroenterol 2011; 12(3): 131-5. [http://dx.doi.org/10.1016/j.ajg.2011.07.006] [PMID: 22055590]

[7] Diaconescu D, Pantea Stoian A, Socea LI, *et al.* Hepatorenal syndrome: a review. Arch Balk Med Union 2018; 53(2): 239-45. [http://dx.doi.org/10.31688/ABMU.2018.53.2.10]

[8] Angeli P, *et al.* Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015; 64(4): 531-7.

[9] Martín-Llahí M, Pépin MN, Guevara M, *et al.* Terlipressin and albumin *vs* albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology 2008; 134(5): 1352-9. [http://dx.doi.org/10.1053/j.gastro.2008.02.024] [PMID: 18471512]

[10] 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(116): 1168-73. [PMID: 22057374]

[11] Seo YS, Jung ES, An H, *et al.* Serum cystatin C level is a good prognostic marker in patients with cirrhotic ascites and normal serum creatinine levels. Liver Int 2009; 29(10): 1521-7. [http://dx.doi.org/10.1111/j.1478-3231.2009.02105.x] [PMID: 19725889]

[12] Sjöström P, Tidman M, Jones I. Determination of the production rate and non-renal clearance of cystatin C and estimation of the glomerular filtration rate from the serum concentration of cystatin C in humans. Scand J Clin Lab Invest 2005; 65(2): 111-24. [http://dx.doi.org/10.1080/00365510510013523] [PMID: 16025834]

[13] 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(5): 1360-8. [http://dx.doi.org/10.1053/j.gastro.2008.02.014] [PMID: 18471513]

[14] Ratib S, West J, Crooks CJ, Fleming KM. Diagnosis of liver cirrhosis in England, a cohort study, 1998-2009: a comparison with cancer. Am J Gastroenterol 2014; 109(2): 190-8. [http://dx.doi.org/10.1038/ajg.2013.405] [PMID: 24419483]

[15] Brown RS Jr, Kumar KS, Russo MW, *et al.* Model for end-stage liver disease and Child-Turcotte-Pugh score as predictors of pretransplantation disease severity, posttransplantation outcome, and resource utilization in United Network for Organ Sharing status 2A patients. Liver Transpl 2002; 8(3): 278-84. [http://dx.doi.org/10.1053/jlts.2002.31340] [PMID: 11910574]

[16] Alessandria C, Ozdogan O, Guevara M, *et al.* MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology 2005; 41(6): 1282-9. [http://dx.doi.org/10.1002/hep.20687] [PMID: 15834937]

[17] Koola JD, Chen G, Malin BA, *et al.* A clinical risk prediction model to identify patients with hepatorenal syndrome at hospital admission. Int J Clin Pract 2019; 73(11)e13393 [http://dx.doi.org/10.1111/ijcp.13393] [PMID: 31347754]

[18] Maiwall R, Sarin SK, Moreau R. Acute kidney injury in acute on chronic liver failure. Hepatol Int 2016; 10(2): 245-57. [http://dx.doi.org/10.1007/s12072-015-9652-y] [PMID: 26471272]

[19] Markwardt D, Holdt L, Steib C, *et al.* Plasma cystatin C is a predictor of renal dysfunction, acute-on-chronic liver failure, and mortality in patients with acutely decompensated liver cirrhosis. Hepatology 2017; 66(4): 1232-41. [http://dx.doi.org/10.1002/hep.29290] [PMID: 28545169]

[20] Lei L, Li LP, Zeng Z, *et al.* Value of urinary KIM-1 and NGAL combined with serum Cys C for predicting acute kidney injury secondary to decompensated cirrhosis. Sci Rep 2018; 8(1): 7962. [http://dx.doi.org/10.1038/s41598-018-26226-6] [PMID: 29784944]

[21] Gomaa SH, Shamseya MM, Madkour MA. Clinical utility of urinary neutrophil gelatinase-associated lipocalin and serum cystatin C in a cohort of liver cirrhosis patients with renal dysfunction: a challenge in the diagnosis of hepatorenal syndrome. Eur J Gastroenterol Hepatol 2019; 31(6): 692-702. [http://dx.doi.org/10.1097/MEG.0000000000001347] [PMID: 30601335]

[22] Sharawey MA, Shawky EM, Ali LH, Mohammed AA, Hassan HA, Fouad YM. Cystatin C: a predictor of hepatorenal syndrome in patients with liver cirrhosis. Hepatol Int 2011; 5(4): 927-33. [http://dx.doi.org/10.1007/s12072-011-9266-y] [PMID: 21484118]

[23] Omar M, Abdel-Razek W, Abo-Raia G, Assem M, El-Azab G. Evaluation of Serum Cystatin C as a Marker of Early Renal Impairment in Patients with Liver Cirrhosis. Int J Hepatol 2015; 2015309042 [http://dx.doi.org/10.1155/2015/309042] [PMID: 26550493]

[24] Chung MY, Jun DW, Sung SA. Diagnostic value of cystatin C for predicting acute kidney injury in patients with liver cirrhosis. Korean J Hepatol 2010; 16(3): 301-7. [http://dx.doi.org/10.3350/kjhep.2010.16.3.301] [PMID: 20924213]

[25] Wang D, Feng JF, Wang AQ, Yang YW, Liu YS. Role of Cystatin C and glomerular filtration rate in diagnosis of kidney impairment in hepatic cirrhosis patients. Medicine (Baltimore) 2017; 96(20)e6949 [http://dx.doi.org/10.1097/MD.0000000000006949] [PMID: 28514315]

[26] Kim DJ, Kang HS, Choi HS, *et al.* Serum cystatin C level is a useful marker for the evaluation of renal function in patients with cirrhotic ascites and normal serum creatinine levels. Korean J Hepatol 2011; 17(2): 130-8. [http://dx.doi.org/10.3350/kjhep.2011.17.2.130] [PMID: 21757984]

[27] Demirtaş S, Bozbaş A, Akbay A, Yavuz Y, Karaca L. Diagnostic value of serum cystatin C for evaluation of hepatorenal syndrome. Clin Chim Acta 2001; 311(2): 81-9. [http://dx.doi.org/10.1016/S0009-8981(01)00546-0] [PMID: 11566167]

[28] Orlando R, Mussap M, Plebani M, *et al.* Diagnostic value of plasma cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. Clin Chem 2002; 48(6 Pt 1): 850-8. [http://dx.doi.org/10.1093/clinchem/48.6.850] [PMID: 12029000]

[29] El-Gebaly F, Abou-Saif S, Elkadeem M, *et al.* Study of serum soluble programmed death ligand 1 as a prognostic factor in hepatocellular carcinoma in egyptian patients. Curr Cancer Drug Targets 2019; 19(11): 896-905. [http://dx.doi.org/10.2174/1568009619666190718141647] [PMID: 31538897]

[30] Abdelfattah AAM, Rizk F, Hawash N, Hanafy A, El-Kalla F, Abd-Elsalam S. Randomized trial of preoperative administration of oral pregabalin for postoperative analgesia in patients scheduled for radiofrequency ablation of focal lesions in the liver. Int J Hyperthermia 2018; 34(8): 1367-71. [http://dx.doi.org/10.1080/02656736.2018.1424946] [PMID: 29308685]

[31] Watany M, Badawi R, Elkhalawany W, Abd-Elsalam S. Study of dickkopf-1 (DKK-1) gene expression in hepatocellular carcinoma patients. J Clin Diagn Res 2017; 11(2): OC32-4. [http://dx.doi.org/10.7860/JCDR/2017/23095.9450] [PMID: 28384913]

[32] Negm O, Abou Saif S, El Gharib M, Yousef M, Abd-Elsalam S. Role of low-molecular-weight heparins in prevention of thromboembolic complication after transarterial chemoembolization in hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2017; 29(3): 317-21. [http://dx.doi.org/10.1097/MEG.0000000000000790] [PMID: 27893491]

[33] Abdelmoemen G, Khodeir SA, Abou-Saif S, Kobtan A, Abd-Elsalam S. Prevalence of occult hepatitis C virus among hemodialysis patients in Tanta university hospitals: a single-center study. Environ Sci Pollut Res Int 2018; 25(6): 5459-64. [http://dx.doi.org/10.1007/s11356-017-0897-y] [PMID: 29214477]

[34] Hanafy AS, Soliman S, Abd-Elsalam S. Rescue therapy for chronic hepatitis C virus infection after repeated treatment failures: Impact on disease progression and risk of hepatocellular carcinoma. Hepatol Res 2019; 49(4): 377-84. [http://dx.doi.org/10.1111/hepr.13303] [PMID: 30570817]

[35] Abdelmoemen G, Khodeir SA, Zaki AN, Kassab M, Abou-Saif S, Abd-Elsalam S. Overexpression of hepassocin in diabetic patients with nonalcoholic fatty liver disease may facilitate increased hepatic lipid accumulation. Endocr Metab Immune Disord Drug Targets 2019; 19(2): 185-8. [http://dx.doi.org/10.2174/1871530318666180716100543] [PMID: 30009716]