Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 10, ISSUE 01, 2019

Role of Cystatin C and Renal Resistive Index in Assessment of Renal Function in Patients with Liver Cirrhosis

Ahmed Samir Abo Halima, Ahmed Ali Moines Yassen, Engy Yousry El Sayed Ashour, Mohammed Anwar Abd Elaziz

Department of Internal Medicine, Faculty of Medicine, Ain Shams University, Egypt

ABSTRACT

Objective: To evaluate the clinical significance of cystatin C and renal resistive index for the determination of renal function in patients with liver cirrhosis.

Settings: Hepatology department, Ain Shams University Hospital

Subjects: Male and female patients with Liver cirrhosis

Measurements and main results: We confirmed significant differences in values of cystatin C between patients with different stages of liver cirrhosis according to Child-Pugh and positive correlation was noticed between GFR_{cr} and GFR_{cys} and significant positive correlation was noticed between Cystatin c and RRI and this is support our recommendation of using of serum cystatin c and renal resistive index for evaluation of renal status in liver cirrhotic patients.

Conclusion: Cystatin C can be used as reliable marker for assessment of liver insufficiency. Additionally, cystatin C and renal resistive index represent sensitive indicators of renal dysfunction in patients with liver cirrhosis.

Keywords: Liver cirrhosis, Cystatin C, Renal resistive index

INTRODUCTION

Renal impairment is considered as public complication of liver cirrhosis. This may be linked to the odd hemodynamics of systemic and splanchnic arterial vasodilatation and extra-hepatic vasoconstriction distinct to advanced cirrhosis **[1].**

Renal impairment may present either acutely, or may be as a result of pre-existing chronic kidney disease (CKD). In any condition, it is associated with amplified mortality and morbidity **[2].**

Whereas patients with a significantly impaired glomerular filtration rate can be diagnosed easily by elevated serum creatinine (Cr) concentrations, moderately reduced renal function may go unnoticed by this conventional parameter. Nevertheless, the protease inhibitor cystatin C (CysC) has been proposed as a specific marker of glomerular filtration rate (GFR) and an early indicator of impaired renal function **[3].**

Serum cystatin C is 122-amino acid a non-glycosylated protease inhibitor with a low molecular weight 13.3-kDa. The Cystatin C gene is a so named "housekeeping gene "It is produced at a constant rate by all nucleated cells; it is spontaneously filtered across the glomerular membrane and is reabsorbed and metabolized in the proximal tubule **[4].**

Opposed to Creatinine, cystatin C is not affected by gender, age, and muscle mass and fair influenced by serum bilirubin, inflammation, or malignancy **[5]**.

The intra-renal resistive index (RI) is the most frequently used parameter to assess intra-renal resistance and is calculated based on intra-renal duplex ultrasound measurements. Renal arterial RI was reported to be higher in cirrhotic patients than in healthy controls and also it is higher in cirrhotic patients with ascites than in cirrhotic patients with-out ascites **[6].**

The resistive index (RI) measures the degree of intrarenal arterial impedance and is

ISSN: 0975-3583, 0976-2833 VOL 10, ISSUE 01, 2019

calculated using the following formula: ([peak systolic velocity – end-diastolic velocity]/ peak systolic velocity) **[7].**

AIM OF THE WORK

The aim of the study was to evaluate the clinical significance of CysC and renal blood flow for the determination of renal function in patients with liver cirrhosis.

PATIENTS AND METHODS

This study was conducted on seventy patients with liver cirrhosis admitted in Hepatology Department, Ain Shams University Hospital and thirty healthy subjects served as control between December 2015 and October 2016.

Written informed consent was obtained from all participants. The study was approved by the local ethical committee.

Exclusion criteria:

- Patients suffering from any evident malignancies.
- Patients with serum creatinine ≥ 1.5.
- Patients with Diabetes mellitus.
- Patients with hypertension.
- Patient with Obstructive uropathy.
- Patients on nephrotoxic drugs.

The patients were divided into four groups according to the following criteria:

1. Group **A**: 25 patients with liver cirrhosis with Child-Pugh score ≤ 6.
2. Group **B**: 24 patients with liver cirrhosis with Child-Pugh score 7-9.
3. Group **C**: 21 patients with liver cirrhosis with Child-Pugh score ≥ 10.
4. Control group: 30 healthy persons without liver cirrhosis.

All patients of the four groups were subjected to the following:

- Full history taking.
- Full physical examination for manifestations of liver cirrhosis and any possible complications.
- Laboratory investigations will include:
  - Complete blood count (C.B.C).
  - Fasting blood sugar (FBS).
  - Liver function tests (serum albumin and PT).
  - Liver enzymes [Alanine Transaminase (ALT), Aspartate Transaminases (AST)].
  - Serum bilirubin (total, direct).
  - Viral markers (HCV Abs, HCV PCR, HBsAg and HBcAb).
  - Scoring system by child-Pugh classification to assess the severity of liver cirrhosis.
  - Urine analysis.
  - Renal function tests (urea and creatinine).
  - Blood Na, blood K.
  - Collecting 24h urine for Cr clearance.
  - Serum Cystatin C.
- Estimated GFR was calculated from Serum CysC using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
- Renal color Doppler ultrasonography was used to evaluate renal resistive index (RRI).
- **Cystatin C**:

Cys C serum concentration was determined by the PENIA method (Particle-Enhanced Nephelometric Immuno-Assay), using the SIEMENS (Marburg, Germany) tests, on laser nephleometer (BNIIDadeBehring) by using (BioVendor R&D) kits.

Assay format: Sandwich ELISA, HRP-labelled antibody.

Calibration range: 200 to 10000 ng/ml.

Limit of detection: 0.25 ng/ml.

ISSN: 0975-3583, 0976-2833 VOL 10, ISSUE 01, 2019

Applications: serum, plasma, urine, cerebrospinal fluid.

Sample requirements: 10 µl/ well.

Storage/Shipping: 2–8 °C/Wet ice.

Estimated GFR was calculated from serum Cr using the Modification of Diet in Renal Disease (MDRD) equation:

$eGFR = 186 \times sCr^{-1.154} \times age^{-0.203} \times 1.212$ (if African American) × 0.742 (if female)

Estimated GFR was calculated from cystatin C using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [8]:

Serum cystatin C (Scys; mg/L) ≤ 0.8

$GFR=133 \times (Scys/0.8)^{-0.499} \times 0.996^{Age}$[× 0.932 if female]

Serum cystatin C (Scys; mg/L) >0.8

$GFR=133 \times (Scys/0.8)^{-1.328} \times 0.996^{Age}$[× 0.932 if female]

- **Abdominal and renal Doppler ultrasonography:**

Ultrasonography (Toshiba Core Vision, with Doppler duplex convex probe, 3.5 MHz) was performed to examine the liver size, echo structure of the hepatic parenchyma and possible focal changes, spleen diameter, and presence of ascites.

Renal color Doppler duplex ultrasonography was used to evaluate renal resistive index (RRI). The renal arteries were evaluated bilaterally of the distal arcuate branches. RRI equals peak systolic velocity minus the final diastolic velocity divided by the peak systolic velocity. RRI less than 0.7 is considered normal **[9].**

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0.Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. Chi-square test for categorical variables, to compare between different groups. Fisher's Exact or Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than 5. F-test (ANOVA) for normally quantitative variables, to compare between more than two studied groups, and Post Hoc test (LSD) and (Tukey) for pairwise comparisons. Pearson coefficient to correlate between two normally quantitative variables. P value < 0.05 was considered significant.

RESULTS

The patient group comprised 74 (74%) males and 26(26%) females. The average age of the patients was 58 ± 11. The main etiology of liver cirrhosis was HCV in 56 patients (80%) and Non-alcoholic steatohepatitis (NASH) in 11 patients (15.7%) and HBV in 3 patients (4.3%).

The average value of serum creatinine in patients of group (A) was 0.76 ± 0.17 and in patients of group (B) was 0.70 ± 0.14 and in group (C) was 0.82 ± 0.21 while in control group was 0.76 ± 0.16. The average value of blood urea in patients of group (A) was 30.96 ± 4.76 and in patients of group (B) was 31.21 ± 4.63and in group (C) was 30.14 ± 3.85 while in control group was 29.87 ± 4.13. According GFR_{cr} there were statistically differences between the four groups as median value in group (A) was 92.78 mL/min/1.73 m^2 and in group (B) was 65 mL/min/1.73 $m^2$and in group (C) was 60.2 while in control group was 121 mL/min/1.73 m^2 (Table 1).

Table (1): Comparison between the four studied groups according to GFR_{Cr}

	Group A (n=25)	Group B (n=24)	Group C (n=21)	Control (n=30)	F	p
GFR_{Cr}						
Min. – Max.	80.13 – 99.16	55.23 – 73.8	49.89 – 69.08	100.0 – 138.0		
Mean ± SD	90.88 ± 7.63	65.24 ± 6.29	59.31 ± 5.76	120.17 ± 11.34	178.56*	0.019*
Median	92.78	65.0	60.2	121.0		
$p_{Cont.}$	0.993	0.012*	<0.017*			
Sig. bet. grps	p_1= 0.036*, p_2<0.001*, p_3=0.040*					

ISSN: 0975-3583, 0976-2833 VOL 10, ISSUE 01, 2019

As regarding to Cystatin c the mean value in group (A) was 0.87 ± 0.05 and in group (b) was 1.16 ± 0.09 and in group (C) was 1.26 ± 0.11 and in control group was 0.75 ± 0.11. There were statistically differences between the three groups as regards to GFR_{CysC} as groups as median value in group (A) was 93.4 mL/min/1.73 m^2 and in group (B) was 66.2 mL/min/1.73 m^2 and in group (C) was 61.95 mL/min/1.73 m^2 and in control group was 117 mL/min/1.73 m^2 (Table 2).

Table (2): Comparison between the four studied groups according to Cystatin c and GFR Cys

	Group A (n=25)	Group B (n=24)	Group C (n=21)	Control (n=30)	F	p
Cystatin c						
Min. – Max.	0.81 – 0.97	1.04 – 1.33	1.10 – 1.45	0.60 – 0.90		
Mean ± SD	0.87 ± 0.05	1.16 ± 0.09	1.26 ± 0.11	0.75 ± 0.11	164.610	<0.001*
Median	0.86	1.15	1.23	0.70		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig.bet. groups	p_1<0.001*, p_2<0.001*, p_3=0.003*					
GFR_{Cys}						
Min. – Max.	81.35 – 100.43	56.5 – 75.20	51.3 – 70.48	87.0 – 140.0		
Mean ± SD	92.30 ± 5.45	66.46 ± 5.94	60.71 ± 6.08	111.40± 19.55	110.091*	<0.001*
Median	93.4	66.2	61.95	117.0		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig.bet. groups	p_1<0.001*, p_2<0.001*, p_3=0.339					

Number of cases which was staged as stage 1 CKD (>90 mL/min/1.73 m2) according GFR_{Cr} was 20 patients (28.57%) while according GFR_{Cys} stage 1 CKD was filled with only 15 patients (21.43%) and number of cases which was staged as stage 2 CKD (60-89mL/min/1.73 m2) according GFR_{Cr} was 36 patients (51.43%) while according GFR_{Cys} stage 2 CKD was 39 patients (55.71%) and number of cases which was staged as stage 3 CKD (<60 mL/min/1.73 m2) according GFR_{Cr} was 14 patients (20%) but according GFR_{Cys} stage 3 CKD was about 16 patients (22.86%) (Table 3).

Table (3): The stages of CKD of cirrhotic patients according to GFRCr and GFRCys:

Stage	GFRCr mL/min/1.73 m^2	No	%
1	>90	20	28.57
2	60-89	36	51.43
3	<60	14	20
	GFRCys mL/min/1.73 m^2		
1	>90	15	21.43
2	60-89	39	55.71
3	<60	16	22.86

As regarding to renal resistive index the mean value in group (A) was 0.63 ± 0.02 and in group (B) was 0.71 ± 0.02 and in group (C) was 0.80 ± 0.03 and in control group was 0.58 ± 0.07 (Table 4).

Table (4): Comparison between the four studied groups according to RRI

	Group A (n=25)	Group B (n=24)	Group C (n=21)	Control (n=30)	F	p
RRI						
Min. – Max.	0.60 – 0.66	0.68 – 0.73	0.74 – 0.84	0.50 – 0.70		
Mean ± SD	0.63 ± 0.02	0.71 ± 0.02	0.80 ± 0.03	0.58 ± 0.07	133.078*	<0.001*
Median	0.63	0.71	0.81	0.60		
$p_{Cont.}$	<0.001*	<0.001*	<0.001*			
Sig.bet. groups	p_1<0.001*, p_2<0.001*, p_3<0.001*					

There was statistically highly significant positive correlation between GFR_{Cr} and GFR_{Cys} in group (B) and group (C) as (p – value <0.05) (Table 5).

Table (5): Correlation between GFR_{Cr} and GFR_{Cys}

	GFR Cr	
	r	p
GFR Cys		
Group A	0.022	0.916
Group B	0.733*	<0.001*
Group C	0.632*	0.002*
Total patients	0.612*	<0.001*

ISSN: 0975-3583, 0976-2833 VOL 10, ISSUE 01, 2019

There was statistically highly significant positive correlation between serum Cystatin c and RRI in group (C) as (p –value <0.05) (Table 6).

Table (6): Correlation between Cystatin c and RRI

	Cystatin c	
	r	p
RRI		
Group A	-0.119	0.571
Group B	-0.031	0.885
Group C	0.111*	<0.001*
Total patients	0.811*	<0.001*

The receiver operating curve (ROC) analysis indicates that the cystatin C more than 1.25 (AUC: 0.978) its sensitivity was 97% and its Specificity was 90.53% (Table 7 & Fig. 1).

Table (7): Diagnostic validity of cystatin c as predictor of renal impairment

	Cut off	Sensitivit	Specificit	PPV	NPV
Cystatin	>1.25	97.0	90.53	35.7	100.0

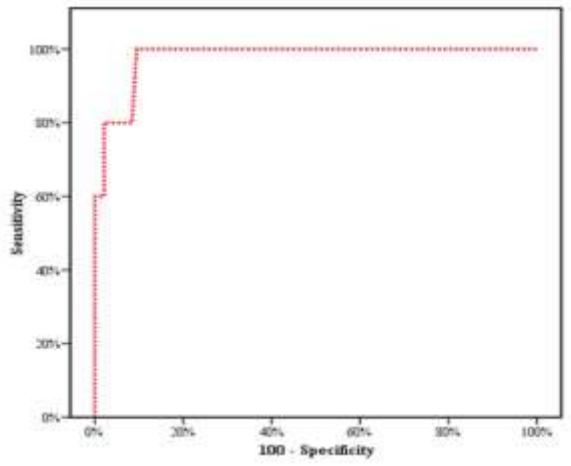

Figure (1): ROC curve for Cystatin c for prediction of renal impairment

While the receiver operating curve (ROC) analysis indicates that the renal resistive index more than 0.8 (AUC: 0. 931) its sensitivity was 97.14% and its Specificity was 86.67% (Table 8 & Fig. 2).

Table (8): Diagnostic validity of RRI as predictor of renal impairment

	Cut off	Sensitivity	Specificity	PPV	NPV
RRI	>0.8	97.14	86.67	94.4	92.9

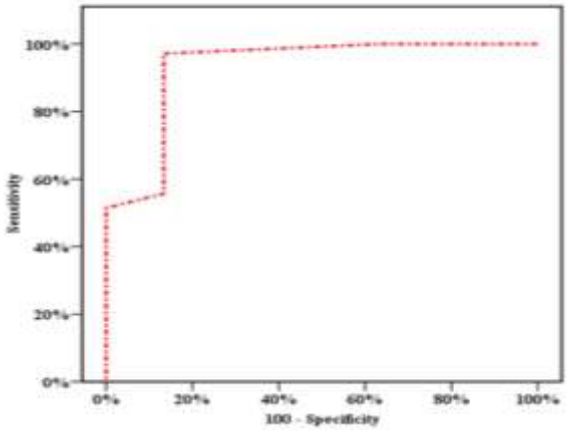

Figure (2): ROC curve for RRI for prediction of renal impairment

DISCUSSION

Cirrhosis of the liver is commonly accompanied by functional renal impairment frequently in advanced stages of liver disease. Hemodynamic changes with decline effective arterial blood volume and peripheral vasodilation are followed by secretion of vasoconstrictive hormones (renin-aldosterone, vasopressin, and endothelin) and neurohumoral systems (including increased activity of nervous system) **[10].**

Hence renal failure is directly related to the mortality rate of cirrhotic patients, it is of a great clinical importance to monitor renal function closely in order to estimate the prognosis and determine the optimal therapeutic option **[13].**

The accurate assess of kidney impairment in hepatic cirrhosis patients is fundamental for the maintenance of favorable kidney function and delaying of disease progression **[12].**

No association was found in this study between the demographic data and renal

ISSN: 0975-3583, 0976-2833 VOL 10, ISSUE 01, 2019

impairment in liver cirrhosis patients. Our results agree with **Ćulafić et al. [13].**

We found that there were no statistically significant differences between the four groups according to blood urea or Serum Cr, our results agree with **Kim et al. [14]** and **El-Shazly et al. [15].**

We report statistically differences between the four groups as regards to GFR_{Cr} as (p =0.019). GFR decline in group (c) with median (60.2 mL/min/1.73 m^2) than group (b) which was (65 mL/min/1.73 m^2), group (a) was (92.78 mL/min/1.73 m^2) and control group. Our results agree with **Chen et al. [16]**.

There were Significant differences were observed in CysC between Child-Pugh class A, B, and C, the median CysC value was significantly higher in Child-Pugh B(1.15)and C(1.23) patients when compared to Child-Pugh A patients (0.86), The finding suggests that CysC may indirectly reflect the degree of liver dysfunction, these results is supported with the study **Ćulafić et al. [13].**

These findings can suggest that CysC may indirectly reflect the degree of liver dysfunction.

By using CKD-EPI_{CysC} equation to estimate GFR_{CysC} there were significant differences observed in our study between the four groups as (p <0.001), there is severe decline in GFR in Child-Pugh C patients if compared with Child-Pugh A and B patients as the median value was in group C (61.95mL/min/1.73 m^2), group B(66.2mL/min/1.73 m^2) and group A(93.4mL/min/1.73 m^2), Our results agree with **Ćulafić et al. [13].**

By comparing GFR_{Cys} and GFR_{Cr} , our study showed that CysC can be used as a predictor of renal impairment as p value of GFR_{Cys} (p <0.001) and p value of GFR_{Cr} (p =0.019), and that agreed with **Kwon et al. [17].**

Moreover, we confirmed a statistically significant positive correlation between GFR_{Cys} and GFR_{Cr} particularly in Child-Pugh B and C, and that agreed with **Ćulafić et al. [13].**

Moreover number of cases which was staged as stage 1 CKD (>90 mL/min/1.73 m^2) according GFR_{Cr} was 20 patients (28.57%) while according GFR_{Cys} stage 1 CKD was filled with only 15 patients (21.43%) and number of cases which was staged as stage 2 CKD (60-89mL/min/1.73 m2) according GFR_{Cr} was 36 patients (51.43%) while according GFR_{Cys} stage 2 CKD was 39 patients (55.71%) and number of cases which was staged as stage 3 CKD (<60 mL/min/1.73 m2) according GFR_{Cr} was 14 patients (20%) but according GFR_{Cys} stage 3 CKD was about 16 patients (22.86%),and this agreed and supported with **Kwon et al. [17].**

According to RRI was significantly higher in Child-Pugh C patients than in Child-Pugh B or A patients and this agreed with **El-Shazly et al. [15].**

There was significant positive correlation between Cystatin c and RRI particularly in Child-Pugh C and this agreed with **Ustundag et al. [18].**

ROC analysis was employed to analyze the diagnostic efficiencies of CysC and RRI for kidney impairment in hepatic cirrhosis patients. Results showed the optimal cutoff value of CysC was >1.25 mg/L its sensitivity was 97% and its Specificity was 90.53% while according to RRI the optimal cutoff value was 0.8 and its sensitivity was 97.14% and its Specificity was 86.67%, our results was agreed with **Wang et al. [19].**

CONCLUSIONS

CysC may be a more reliable marker for liver insufficiency assessment. Additionally, RRI and CysC represent sensitive indicators of renal dysfunction in patients with liver cirrhosis

RECOMMENDATIONS

We recommend that all liver cirrhotic patients should be tested using Serum Cystatin C and calculation of GFR_{Cys} using CKD-EPI_{CysC} equation to accurately assess the renal function.

We recommend using renal resistive index to assess the renal function in all liver cirrhotic

ISSN: 0975-3583, 0976-2833 VOL 10, ISSUE 01, 2019

patients which show high sensitivity and specificity especially in Child-Pugh (C).

Financial support and sponsorship: Nil.

Conflict of interest: Nil.

REFERENCES

1. **Wong F. (2012):** Recent advances in our understanding of hepatorenal syndrome. Nat Rev Gastroenterol Hepatol., 9:382-391.
2. **Mindikoglu AL, Weir MR. (2013):** Current concepts in the diagnosis and classification of renal dysfunction in cirrhosis. Am J Nephrol., 38:345–354.
3. **Gerbes AL, Gülberg V, Bilzer M, Vogeser M. (2002):** Evaluation of serum cystatin C concentration as a marker of renal function in patients with cirrhosis of the liver. Gut, 50: 106-110.
4. **Bevc S, Ekart R, Hojs R. (2014):** Cystatin C – a marker of kidney function and predictor of cardiovascular disease and mortality. Acta Medico–Biotechnica, 7:9–15.
5. **Zahran A, El-Husseini A, Shoker A. (2007):** Can cystatin C replace creatinine to estimate glomerular filtration rate? A literature review. Am J Nephrol., 27: 197-205.
6. **Zeller T, Bonvini RF, Sixt S. (2008):** Color-coded duplex ultrasound for diagnosis of renal artery stenosis and as follow-up examination after revascularization. Catheter Cardiovasc Interv., 71: 995–9.
7. **Krumme B. (2006):** Renal Doppler sonography – Update in clinical nephrology. Nephron Clin Pract., 103: 24–28.
8. **Inker LA, Schmid CH, Tighiouart H, Eckfeldt J, Feldman H. (2012):** Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med;367:20–9.
9. **Viazzi F, Leoncini G, Derchi LE, Pontremoli R. (2014):** Ultrasound Doppler Renal Resistive Index: A Useful Tool for the Management of the Hypertensive Patient. Journal of Hypertension, 32: 149-153.
10. **Karvellas CJ, Durand F, Nadim MK. (2015):** Acute kidney injury in cirrhosis. Crit Care Clin., 31:737–50.
11. **Belcher JM, Parikh CR, Garcia-Tsao G. (2013):** Acute kidney injury in patients with cirrhosis: perils and promise. Clin Gastroenterol Hepatol., 11:1550–1558.
12. **Belcher JM. (2015):** Acute kidney injury in liver disease: role of biomarkers. Adv Chronic Kidney Dis., 22:368–75.
13. **Ćulafić Đ, Štulić M, Obrenović R, Miletić D, Mijač D, Stojković M, Jovanović M, Ćulafić M. (2014):** Role of cystatin C and renal resistive index in assessment of renal function in patients with liver cirrhosis. World J Gastroenterol., 20(21): 6573-6579.
14. **Kim DJ, Kang HS, Choi HS, Cho HJ, Kim ES, Keum B, An H, Kim JH, Seo YS, Kim YS, Yim HJ, Jeen YT, Lee HS, Um SH, Kim CD, Ryu HS. (2011):** 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., 17: 130-138
15. **El-Shazly M, Shayeb AE, Moez P, Sami M, Zaghloul M. (2011):** Diagnostic Value of Serum Cystatin C as an Early Indicator of Renal Impairment in Chronic HCV Egyptian Patients with Liver Cirrhosis. J Am Sci., 7: 75-81.
16. **Chen M, Xia J, Pei G, et al. (2016):** A more accurate method acquirement by a comparison of the prediction equations for estimating glomerular filtration rate in Chinese patients with obstructive nephropathy. BMC Nephrology, 17:150.
17. **Kwon YE, Lee MJ, Park KS, et al. (2017):** Cystatin C is Better than Serum Creatinine for Estimating Glomerular Filtration Rate to Detect Osteopenia in

ISSN: 0975-3583, 0976-2833 VOL 10, ISSUE 01, 2019

Chronic Kidney Disease Patients. Yonsei Medical Journal, 58(2):380-387.

18. **Ustundag Y, Samsar U, Acikgoz S, Cabuk M, Kiran S, Kulah E, Aydemir S. (2007):** Analysis of glomerular filtration rate, serum cystatin C levels, and renal resistive index values in cirrhosis patients. Clin Chem Lab Med., 45: 890-894.
19. **Wang D, Feng JF, Wang AQ, Yang YW, Liu YS. (2017):** Role of Cystatin C and glomerular filtration rate in diagnosis of kidney impairment in hepatic cirrhosis patients. Tripathi. D, ed. Medicine, 96(20): 6949.