Study of serum Cystatin C and Resistive Index as predictors of hepato-renal syndrome in Egyptian patients with advanced liver disease

Elsayed G. Ammar[1], Mahmoud B. Ismail[2] Mahmoud Elsayed morsy[3], Ismail M. El mansy[3] and khaled S. Karam[4]

Tropical Medicine Departement[1], Clinical Pathology Departement[2], General Medicine Departement[3] Radiodiagnosis Department[4] Faculty of Medicine Al Azhar Univerisity
drsaidammar@yahoo.com

Abstract: Background: Liver cirrhosis is a common problem in Egypt due to prevalence of hepatitis C virus**,** hepatorenal syndrome(HRS)is one of major complications of cirrhosis.Serum cystatin C concentration is a reliable and accurate marker of GFR so Cystatin c is a more specific than serum creatinine in detection of impaired renal function in patients with (HRS).also Duplex Doppler can be used to assess vascular resistance in the small renal intraparenchymal vessels through simple analysis of the Doppler waveform by a parameter termed the resistive index (RI)*an* elevated RI (reflecting intrarenal vasoconstriction)has been observed in various conditions associated with elevated renal vascular resistance should be detectable in liver disease related Intense intracranial vasoconstriction is an early hallmark of this functional kidney failure. **The aim of this work** was Study of serum Cystatin C and Resistive index as predictors of hepato-renal syndrome in Egyptian patients with advanced liver disease. **Method**: this study was conducted on 30 patients with advanced liver disease admitted at Tropical medicine department, Al-Azhar university hospitals during the interval between September 2013 – May 2014. All patients were subjected to the followings. Full history taking, clinical examination, laboratory investigations, Serum Cystatin c at day 0 and 2 month. Abdominal U.S, Renal Doppler U.S**. Results**: From this study Serum cystatin c is statistically significant in both groups at 0 day in comparison with serum creatinine which elevated only in control group. Serum Cystatin c is significantly elevated in both groups (Mean is 2.040 ± SD 0.676) for the study group and (Mean is 2.073 ± SD 0.632) for control group.There is a highly significant elevation of serum Cystatin c either at 0 day or at 2m with (Mean 2.0 ± SD0.7) at baseline and (Mean 2.4± SD 0.5) at 2m.in the study group but with no statistically significant difference in serum Cystatin c during follow up from 0 day to 2m.,renal Doppler ultrasound in both groups shows Increased Resistive Index (RI) was detected in about 10 patients = 66.67%, in study group and11 patients = 73.33% in control group **Conclusion:** Cystatin c is a more specific than serum creatinine in detection of impaired renal function in patients with (HRS),Renal Duplex Doppler ultrasonography used as noninvasive predictor of kidney dysfunction and hepatorenal syndrome in advanced liver disease.

[Elsayed G. Ammar, Mahmoud B. Ismail Mahmoud Elsayed morsy, Ismail M. El mansy and khaled S. Karam. **Study of serum Cystatin C and Resistive Index as predictors of hepato-renal syndrome in Egyptian patients with advanced liver disease.** *J Am Sci* 2014;10(11):64-70]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 10

Keywords: cystatin c, resistive index and hepatorenal syndrome

1. Introduction

Major complications of cirrhosis include ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy(HE), portal hypertension, variceal bleeding and hepatorenal syndrome(HRS)**(17).** Hepatorenal syndrome (HRS) is the development of renal failure in patients with severe liver disease in the absence of any identifiable renal pathology. It is a functional rather than structural disturbance in renal function. The histology of the kidney is virtually normal. **(35)** The hallmark change is intense intrarenal vasoconstriction (**10**, **15**, **and 12**). Thi's vasoconstriction is associated with a reduced renal plasma flow and an elevated renal arterial vascular resistance that may precede clinically recognized kidney dysfunction by weeks or months. Although the precise cause of the renal vasoconstriction remains elusive and is likely multifactorial (ll), a state of elevated renal vascular resistance is present in many nonazotemic patients with liver disease. These patients may be at greater risk for subsequent development of overt hepatorenal syndrome. In ***1969*** serum creatinine was introduced to assess renal function. However, its blood concentration is affected by muscle mass, age and gender (**14),** in addition, creatinine is secreted in small amounts by renal tubules thus it overestimates GFR in moderate to severe decrease in GFR (**23**). Also, serum creatinine is insensitive for detection of small changes in GFR because of non linear relationship between its plasma concentration and GFR (**30**). Cystatin C is a low molecular weight protein that is produced at a constant rate by all nucleated cells and widely distributed in all biological fluids **(26).** It is freely filtered by renal glomeruli and not secreted or reabsorbed as intact molecule by renal glomeruli

(37). Its serum level is not affected by age, sex, muscle mass, any medications or pathologies as inflammation or cancer **(21)**. So, serum cystatin C concentration is a reliable and accurate marker of GFR ***(3).*** Duplex Doppler ultrasonography is a widely used noninvasive method to assess vascular patency and blood flow in many sites. Duplex Doppler can be used to assess vascular resistance in the small renal intraparenchymal vessels through simple analysis of the Doppler waveform by a parameter termed the resistive index (RI) (**31**). ***An*** elevated RI (reflecting intrarenal vasoconstriction) has been observed in various conditions associated with elevated renal vascular resistance such as kidney obstruction, acute tubular necrosis, renal vein thrombosis **(27)** and the hemolytic-uremic syndrome **(28)** and should be detectable in liver disease related Intense intrarenal vasoconstriction is an early hallmark of this functional kidney failure, although the precise causes are poorly defined and clinical assessment of the vasoconstriction has up to now been difficult (**15-25**).

2. Patients and Methods

This study was conducted on 30 patients with advanced liver disease admitted at Tropical medicine department, Al-Azhar university hospitals during the interval between September 2013 – May 2014. Thirty patients were selected from inpatients and divided into two groups:

Fifteen patients with advanced liver disease and impaired renal function (Control group). Fifteen patients with advanced liver disease and tense ascites but with normal renal functio**n** (studied group).

Inclusion criteria

Cirrhotic patients with tense ascites, Egyptian patients**.** Age: 18-60 year old,Patients with normal urine analysis(no proteinur**ia),** Patients with normal kidney by ultrasoun,Patients not receiving any nephrotoxic drugs.

Exclusion criteria

Congestive heart failure, Coronary heart diseas, Nephrotic syndrom. All patients were subjected to the followings.

Full history taking, clinical examination, laboratory investigations including: Urine analysis, CBC. Liver function tests (AST), (ALT), total and direct bilirubin, serum albumin and prothrombin time (PT), Random blood sugar, HCV Ab, HBs Ag., Renal function tests.(serum creatinine, blood urea) Abdominal U.S, Renal Duplex Doppler ultrasonography, Serum Cystatin C at day 0 and 2 month.Serum cystatin C assay was made by latex particle enhanced turbi-dimetric immunoassay, Creatinine assay Serum and urinary creatinine concentrations were determined by Jaffe reaction. Statistical tests used in this study are: Student t test, Chi-square test**:**

3. Results

There is no statistically significant difference between two groups as regard to age distribution.

Table I: Shows age distribution in both groups.

Group	Age/ year					T-test	
	Range			Mean	± SD	t	P-value
Study	35.0	-	68.0	51.733	± 8.022	1.603	0.120
Control	37.0	-	58.0	47.400	± 6.727		

Mean of age in the study group is 51.733± SD 8.022 and Mean of age in the control group is 47.400 ± SD 6.727.

Table II: Shows difference in hepatitis markers in both groups:

Hepatitis markers		Group		
		Study	Control	Total
HCV	N	13	15	28
	%	86.67	100.00	93.33
HBV	N	2	0	2
	%	13.33	0.00	6.67
Total	N	15	15	30
	%	100.00	100.00	100.00
Chi-square	X^2	2.916		
	P-value	0.088		

In the study group number of the patients with positive HCV Ab was 13 = 86.67% & number of the patients with positive HBs Ag was 2 = 13.33%.In control group number of the patients with positive HCV Ab was 15 = 100% & number of the patients with positive HBs Ag was 0= 0 %. Total number of patients with positive HCV Ab was 28 = 93.33% & Total number of patients with positive HBs Ag was 2 = 6.67%

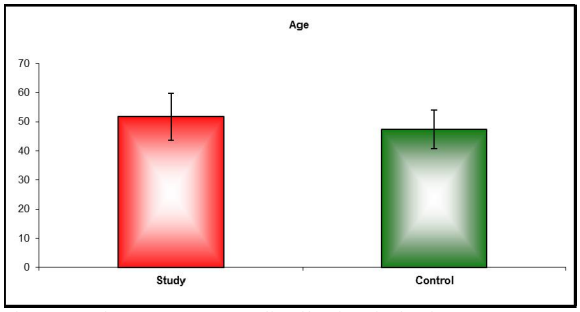

Figure I: Shows mean age distribution in both groups:

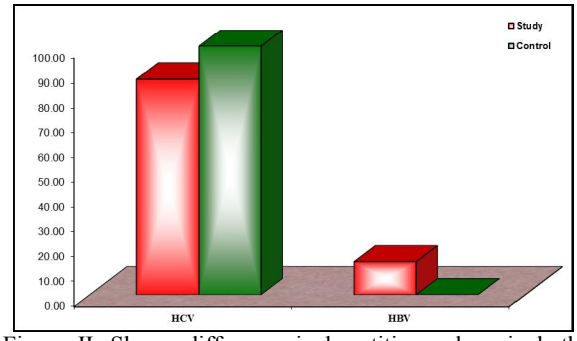

Figure II: Shows difference in hepatitis markers in both groups

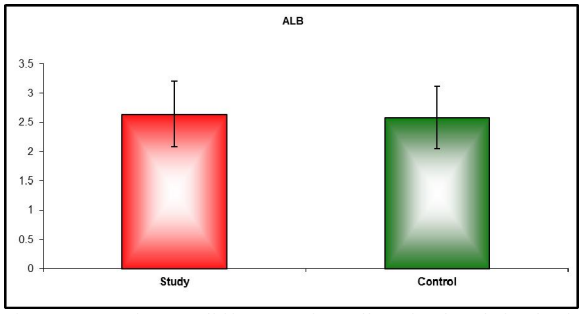

Figure III: Shows difference in Albumin level in both groups

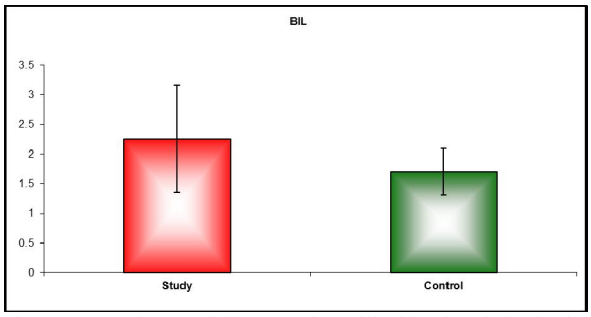

Figure IV: Shows difference in Bilirubin level in both groups

Table III: Shows difference in Albumin level in both groups:

Group	ALB					T-test	
	Range			Mean	± SD	t	P-value
Study	1.8	-	3.4	2.640	± 0.555	0.304	0.763
Control	1.8	-	3.4	2.580	± 0.525		

Mean of Albumin level in the study group is 2.640 ± SD 0.555 and Mean of Albumin level in the control group is 2.580 ± SD 0.525.

There is no statistically significant difference between two groups as regard to Albumin level.

Table IV: Shows difference in Bilirubin level in both groups:

Group	BIL					T-test	
	Range			Mean	± SD	T	P-value
Study	1.3	-	3.8	2.253	± 0.906	2.168	0.039
Control	1.2	-	2.6	1.700	± 0.395		

Mean of Biliirubin level in the study group is 2.253 ± SD 0.906 and Mean of Bilirubin level in the control group is 1.700 ± SD 0.395.

There is no statistically significant difference between two groups as regard to Bilirubin level.

Table V: Shows difference in INR in both groups:

Group	INR					T-test	
	Range			Mean	± SD	T	P-value
Study	1.0	-	2.0	1.440	± 0.336	0.000	1.000
Control	1.0	-	2.0	1.440	± 0.336		

Mean of INR in the study group is 1.440 ± SD 0.336 and Mean of INR in the control group is 1.440 ± SD 0.336.

There is no statistically significant difference between two groups as regard to INR.

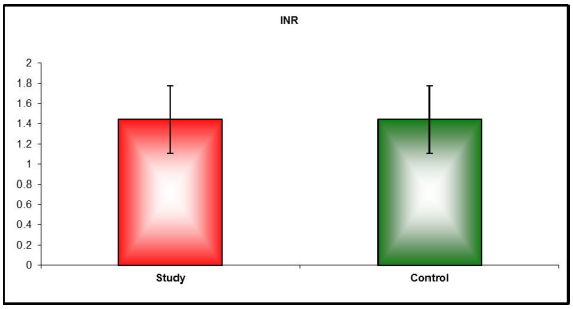

Figure V: Shows difference in INR in both groups

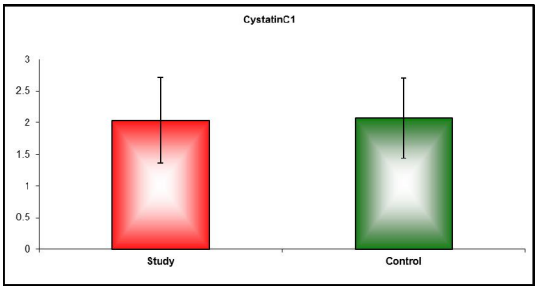

Figure VII: Shows the level of serum Cystatin C in both groups at day 0

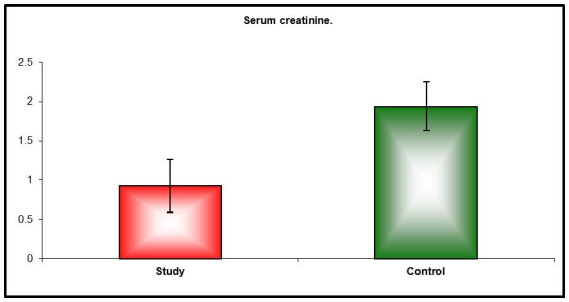

Figure VI: Shows difference in serum creatinine in both groups

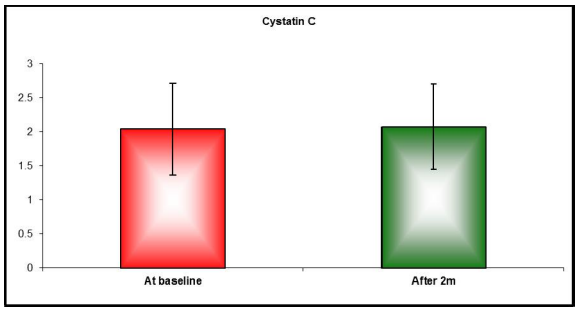

Figure VIII: Shows difference in serum Cystatin C at day 0 and day 60 in study group

Table VI: Shows difference in serum creatinine in both groups:

Group	Serum creatinine.			T-test	
	Range	Mean ± SD		T	P-value
Study	0.1 - 1.4	0.927 ± 0.335		-8.645	0.000
Control	1.5 - 2.5	1.940 ± 0.307			

As regard study group serum creatinine level shows no statistically significant difference. (Mean is 0.927 ± SD 0.335**).**

As regard control group serum creatinine level shows very high statistically significant difference. (Mean is 1.940 ± SD 0.307).

Table VII: Shows the level of serum Cystatin c in both groups at day 0:

Group	Cystatin C at baseline			T-test	
	Range	Mean ± SD		T	P-value
Study	1.0 - 2.9	2.040 ± 0.676		-0.140	0.890
Control	1.0 - 2.9	2.073 ± 0.632			

Serum cystatin c is statistically significant in both groups at day 0 in comparison with serum creatinine which elevated only in control group.

Serum Cystatin c is significantly elevated in both groups (Mean is 2.040 ± SD 0.676) for the study group and (Mean is 2.073 ± SD 0.632) for control group.

Table VIII: Shows difference in serum Cystatin c at 0 day and day 60 in study group:

	Cystatin C		Difference		Paired t-test	
	Mean ± SD		Mean ± SD		T	P-value
At baseline	2.0 ± 0.7		-0.360 ± 0.253		-5.511	<0.001*
At day 60	2.4 ± 0.5					

There is a highly significant elevation of serum Cystatin c either at day 0 or at day 60 with (Mean 2.0 ± SD0.7) at baseline and (Mean 2.4± SD 0.5) at day 60.

But with no statistically significant difference in serum Cystatin c during follow up from day 0 to day 60.

Table IX: Shows difference in renal Duplex **Doppler ultrasound in both groups:**

Renal Doupler		Group		
		Study	Control	Total
Normal	N	2	2	4
	%	13.33	13.33	13.33
Increase Resitivity index No renal artery stenosis"	N	10	11	21
	%	66.67	73.33	70.00
Bilateral grade one intra parenchymal nephropathy	N	3	2	5
	%	20.00	13.33	16.67
Total	N	15	15	30
	%	100.00	100.00	100.00
Chi-square	X^2	0.249		
	P-value	0.883		

In the study group: Increased Resisitive Index (RI) was detected in about 10 patients = 66.67%, normal renal Doppler ultrasound was detected in 2 patients = 13.33 and bilateral grade one intra parenchymal nephropathy was detected in 3 patients = 20.00%.

In control group: Increased Resisitive Index (RI) was detected in about 11 patients = 73.33%, normal renal Doppler ultrasound was detected in 2 patients = 13.33 and bilateral grade one intra parenchymal nephropathy was detected in 2 patients = 13.33%.

Total number of patients with Increased Resistive Index (RI) was 21= 70.00 %, total number of patients with normal renal doupler ultrasound was 4 patients = 13.33% and total number of patients with bilateral grade one intra parenchymal nephropathy was 5 patients = 16.67%.

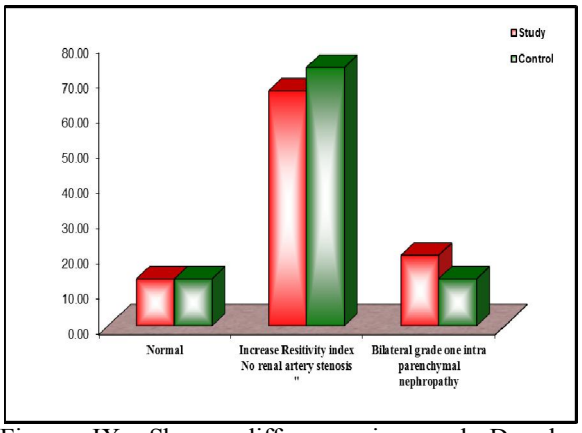

Figure IX: Shows difference in renal Doppler ultrasound in both groups

4. Discussion

In clinical practice, serum creatinine is the most widely used method for non- invasive estimation of GFR to diagnose patients with hepatorenal syndrome) **(9).** Using serum creatinine and creatinine clearance seems not to be satisfactory to assess renal function in hepatorenal syndrome. Thus, it is clear that new and more specific tests are required **(24)**. The constancy of GFR under physiological conditions and the fast that it is affected by the majority of disease processes involving the kidney have led to its wide acceptance as one of the best indices for the measurement of renal function (**2**). When we evaluated the tests for renal function the best correlation of GFR (Tc DTPA), which is gold standard for this study, was found with serum Cystatin C. This agrees with **(5).** It has been known that there are some difficulties in applying the GFR (Tc-DTPA) test in advanced cirrhotic patients. By contrast, cystatin C may be measured automatically on various analyzers in sera in several minutes with a great precision (**16**). Also, GFR measurement by radionuclide method provides an accurate method, but their use is limited by the inherent restriction associated with the clinical use of radioisotopes,the aim of this study was to detect predictors of hepatorenal syndrome in advanced liver disease.In the present study, the cause of liver disease was HCV infection with percentage 93.33% and HBV infection with percentage 6.67%. In Egypt the main cause of decompensated liver disease is HCV infection, because Egypt developed the world's highest rates of HCV infection over a hort period of time.**(36)** In the present study, Mean values of serum Cystatin c was 2.040 ± SD 0.676 for the study group and 2.073 ± SD 0.632 for control group. **(18)** reported that children over one year age had 1.33±0.63 mg/L level and similar to that for adults. Also, in the present study, serum Cystatin C levels showed no significant correlation with age**.** In the present study, Cystatin C showed high sensitivity than creatinine in detection of reduced GFR in hepatorenal patients. These results are similar to those reported with **(4)**. On the other hand, **(13)** reported no difference between Cystatin C and creatinine for estimating GFR.This controversy

in results could be due to difference in selection of patients and various nephropathies covered. Moreover, **(19)** reported that higher sensitivity and negative predictive value of Cystatin C are equivalent in patients with glomerular or tubular impairment.In the present study, Cystatin C showed higher increment above control than serum creatinine in early stages of kidney affection of hepatorenal syndrome.This results was similar to that noticed by *(7)*.**(6)** found that Cystatin C is a more sensitive marker than creatinine in evaluation of renal toxicity induced by cisplatin therapy in oncologic patients. **(26)** have suggested cystatin C as the best endogenous GFR marker.**(8)** reported that Serum Cystatin C level may be considered a predictor of HRS and mortality in patients with liver cirrhosis and ascites. **(1)** reported that The 'early' HRS identified by a rise in Cystatin C in cases with advanced cirrhosis was found to be common and can be added to the already classified two types, as type-3 HRS. In the present study, serum Cystatin c showed statistical significance at 0 day and two month respectively, with no statistically significant difference in serum Cystatin c during the follow up.So, In conclusion, serum Cystatin C concentration is independent of age or body mass index. Cystatin C may be a useful marker for early detection of renal insufficiency in hepatorenal syndrome for which early treatment is important. Thus, Cystatin C might be a superior marker of GFR evaluation compared to creatinine and might be added to routine renal tests for hepatorenal syndrome. Also, the increase in Cystatin C is higher in decompansated cirrhotic patients.

Regarding Renal Doppler ultrasound We have applied renal duplex Doppler ultrasonography, a widely available noninvasive modality,to the identification of this early kidney vasoconstriction in patients with established liver disease. Through use of a simply measured and easily obtained parameter, the RI, patients with probable kidney vasoconstriction can be quickly identified. We hypothesized that these patients with an elevated RI (presumably reflecting intrarenal vasoconstriction) would be at greater risk for development of overt hepatorenal syndrome. We have found renal RI to be a useful new noninvasive predictor of subsequent kidney status in patients with liver disease.We analyzed showed that: 1-In the study group: Increased Resisitive Index (RI) was detected in about 10 patients = 66.67%, normal renal Doppler ultrasound was detected in 2 patients = 13.33 and bilateral grade one intra parenchymal nephropathy was detected in 3 patients = 20.00%.2- In control group: Increased Resisitive Index (RI) was detected in about 11 patients = 73.33%, normal renal Doppler ultrasound was detected in 2 patients = 13.33 and bilateral grade one intra parenchymal nephropathy was detected in 2 patients = 13.33%. 3-Total number of patients with Increased Resisitive Index (RI) was 21= 70.00 %, total number of patients with normal renal doupler ultrasound was 4 patients = 13.33% and total number of patients with bilateral grade one intra parenchymal nephropathy was 5 patients = 16.67%.These data were in agreement with **(31)** who reported that Abnormal results of Doppler examinations (elevated resistive index) were seen in 76 (42%) of the 180 patients. Kidney dysfunction developed in 55% (42/76) of the patients with an elevated resistive index and 6% (6/104) of those with normal results of Doppler study ($p < 0.00005$). So, Renal Duplex Doppler ultrasonography can noninvasively identify a subgroup of patients with liver disease that is at significantly higher risk for subsequent development of kidney dysfunction and the hepatorenal syndrome.

References

1. Barakat M, Khalil M.(2011): Serum cystatin C in advanced liver cirrhosis and different stages of the hepatorenal syndrome. 2011 Sep;12(3):131-5. doi: 10.1016/j.ajg.2011.07.006. Epub 2011 Aug 30.
2. Bauer JH, Brooks CS, Burch RN.(1982) Clinical approach of creatinine clearance as a measurement of GFR. Is J Kidney Dis 1982;2:337-46.
3. Challot-Dallon E., Stoermann-Chopard C. and Martin P.Y. (2006)*:* Could Cystatin C replace creatinine as a market of glomerular filtration rate?. Rev. Med. Suisse. Mar.1;2(55): 582-5.
4. Coll E., Alvarez I., Poch E., Quinto L., Saurina A.,et al (2000): Serum cystatin C as a new marker for noninvasive estimation of glomerular filteration rate and as a marker for early renal impairment. Am. J. Kidney Dis. 36: 29-34.
5. Demirtas S, Bozbas A, Akbay A,Yavuz Y, Karaca L. (2001): Diagnostic value of serum cystatin C for evaluation of hepatorenal syndrome. Clinica Chimica Acta 2001;311:81 9.
6. Demirtas S, Ayyildiz A, Yavuz Y.(1998): The evaluation of renal toxicity induced by cisplatin therapy in oncologic patients. Klin Lab Arastirma Derg;2(1):17-21.
7. El-Agroudy et al.(2004): serum Cystatin c:Agood marker for evaluation of glomerular filtration rate in hepatorenal syndrome. Eur J Gen Med 2004; 1(4): 29-35.
8. El-sharawy et al. (2011): Cystatin C: a predictor of hepatorenal syndrome in patients with liver cirrhosis. Hepatology International, December 2011, Volume 5, Issue 4, pp 927-933.
9. Issue 4, pp 927-933.*9-Epstein M.(1999):Hepatorenal syndrome In: Epstein M, editor. The kidney in liver disease 4th edition. Philadelphia: Hanley and Belfus, 1996 p:75-108.
10. Epstein M. Hepatorenal syndrome. In: Epstein M, ed. The hdneyin liver disease. 3rd ed. Baltimore: Williams & Wilkins, 1988:89-118.

11. Epstein M. The hepatorenal syndrome. Hosp Pract 1989;24:65-76.
12. Epstein M, Berk DP, Hollenberg NK, Adams DF, Chalmero TC.Abrams HL, Merrill JP. Renal failure in the patient with cirrhosis:the role of active vasoconstriction. *Am* J Med 1970;49:175-185.
13. Filler G, With I, Priem F, Ehrich JH, Jungk.(1997): Are cystatin C and beta 2- microglabulin better markers than serum creatinine for prediction of a normal glomerular filtration rate in pediatric subjects. Clin Chem;43:1077-8.
14. Finney H., Newman D.J., Gruber W.,et al (2000*):* Initial evaluation of cystatin c measurement by particle enhanced immunonephelometry on the Behring nephelometer system (BNA, BN II). Clin. Chem. 43:1016-1022.
15. Gentilini P, Laffi G, Buzzelli G, Stefani P, Scarpelli P, Paladini S,Smorlesi C, et al. Functional renal alterations in chronic liver diseases. Digestion 1980;20:73-78.
16. Grubb A.(1992): Diagnostic value of analysis of cystatin C and protein HC in biological fluids. Clin Nephrol 1992;38:20-7.
17. Heidelbaugh J and Sherbondy M (2006): Cirrhosis and Chronic Liver Failure: Part JJ. Complications and Treatment. Am. Fam. Physician.; 74(5):767-76.
18. Helin I, Axenram M, Grubb A.(1998): Serum cystatin C as a determinant of glomerular filtration rate in children. Clin Nephrol 1998;49:221-5.
19. Herget-Rosenthal S., Trabold S., Huesing J., Heemann U., Philipp T. and Kribben A. (2000*):* Cystatin C- an accurate marker of glomerular filteration rate after renal transplantation?. Transplant. Int. 13:285-9.
20. Hojs R., Bevc S., Ekart R., Gorenjak M. and Puklavec L. (2006*):* Serum cystatin C as an endogenous marker of renal function in patients with mild to moderate impairment of kidney function. Nephrol. Dial. Transplant. Jul; 21(7): 1855-62.
21. Keevil B.G., Kilpatrick E.S., Nichols S.P.et al (2001): Biological variation of cystatin C: implication for the assessment of glomerular filteration rate. Clin. Chem. 44: 1535-9.
22. KoppelMH, CoburnJW, Mims MM, Goldstein H, Boyle JD, RubiniME. Transplantation of cadaveric kidneys from patients with hepatorenal syndrome: evidence for the functional nature of renal failure in advanced liver disease. N Engl J Med 1969;280:1367-1371.
23. Levey A.S., Bosch J.P., Lewis J.B., Greene T., Rogers N. and Roth D. (1999): A more accurate method to estimate glomerular filtration rate from serum creatinine. Ann. Intern. Med.130: 461-70.
24. Levy M. Hepatorenal syndrome. Kidney Int 1993;43:737-53.
25. Moore K, Wendon J, Frazer M, Karani J, Williams R, Badr K.Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. N Engl J Med 1992;327:1774-1778.
26. Mussap M., Dalla Vestra M., Fioretto P., Saller A., Varagnolo M., Nosadini R. and Plebani M. (2003*):* Cystatin C is a more sensitive marker than creatinine for estimation of GFR in type 2 diabetic patients. Kidney Int. 61: 1453-61.
27. Newman DJ, Price CP.(1999) Renal function and nitrogen metabolites. In Burts CA, Ashwood ED, eds Tietz textbook of clinical chemistry.3rd Edition. Philadelphia PA: Saunders,;p:1251-4
28. Oyabu C., Hayashi N., Surgiyama D., Umezu M., Mukau M., Kawano S. and Kumagai S (2006): Usefulness of serum cystatin C for the diagnosis of impaired renal function. Rinsho Byori Dec; 54(12): 1204-8. Abstract.
29. Parvey HR, Eisenberg RL. Image-directed Doppler sonography of the intrarenal arteries in acute renal vein thrombosis. JCU J ClinUltrasound 1990;18:512-516.
30. Patriquin HB, O'Regan S, Robitaille P, Paltiel H. Hemolyticuremic syndrome: intrarenal arterial Doppler patterns as a useful guide to therapy. Radiology 1989;172:625-628.
31. Perrone RD, Madias NE and Levey AS (1992): Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 38: 1933-1953.
32. platt JF,Ellin JH, Rubin JM et al.(1994): Renal duplex Doppler ultrasonography: a noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. 1994 Aug;20(2):362-9.
33. Platt JF. Duplex Doppler evaluation of native kidney dysfunction:obstructive and nonobstructive disease. AJR Am J RoentgenolN Engl J Med1992;158: 1035-1042.
34. Platt JF, Rubin JM, Ellis JH. Distinction between obstructive and nonobstructive pyelocaliectasis with duplex Doppler sonography.AJR Am J Roentgenol 1989;153:997-1000.
35. Platt JF, Rubin JM, Ellis JH. Acute renal failure: possible role of duplex Doppler US in distinction between acute prerenal failure and acute tubular necrosis. Radiology 1991;179:419-423.
36. Sherlock S (2011): Ascites, In: Diseases of the Liver and Biliary System, (12th edition), UK. Ch (9), P. 210-228.
37. Strickland GT (2006): Liver Disease in Egypt: Hepatitis C Superseded Schistosomiasis As a result of iatrogenic and biological factors. Hepatology; 43(5):915-22.
38. Thakkar H., Lowe P.A., Price C.P., and Newman D.J. (1998*):* Measurement of the kinetics of protein uptake by proximal tubular cells using an optical biosensor. Kidney Int. 54: 1197-205.