GLOMERULAR FILTRATION RATE IN LIVER CIRRHOSIS

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ABSTRACT

Liver cirrhosis (LC) is often accompanied by functional renal failure. The mortality was significantly greater in LC patients with creatinine clearance less than 50 ml/min. Indicators of moderately impaired renal function are of great clinical importance. Serum creatinine concentration, the best establish simple parameter of glomerular filtration rate (GFR), has some disadvantages: its concentration depends on sex and muscle mass and shows marked increases only at severely reduced creatinine clearance values. Cystatin C has recently been suggested as a sensitive marker of GFR and as early indicator of impaired renal function. Cystatin C serum concentration appears to be independent of sex and muscle mass. The determination of cystatin C is not affected by billirubun or haemolysis. The objective of this study was to investigate the correlation between GFR (based on cystatin C levels) and hepatic index in patients with LC at Dr. Soetomo Hospital.This study used cross-sectional design, involving population of liver cirrhosis patients who had eligible inclusion and exclusion criteria. It was found that GFR (based on cystatin C levels) in patients with LC with mild hepatic failure is 60.625 ± 17.631, moderate hepatic failure is 50.231 ± 12.029, and severe hepatic failure 16.960 ± 8.438. There was a strong negative correlation between GFR (based on cystatin C levels) and hepatic index based on score levels (r -0.646; 0.0001) and based on stadium levels (r -0.636; p 0.001) in LC patients. In conclusion, based on cystatin C serum level, GFR in patients LC with mild hepatic failure higher than those in moderate hepatic failure and severe hepatic failure. GFR does not play a major role in determining hepatic index. Nevertheless, GFR in patients LC with mild hepatic failure higher than those in moderate hepatic failure and severe hepatic failure.

Keyword: *glomerular filtration rate, cystatin C, liver cirrhosis*

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INTRODUCTION

Cirrhosis of the liver is often accompanied by functional renal failure. This is due to haemodynamic alterations, mainly peripheral vasodilatation followed by activation of vasoconstricting hormones and neurohumoral system such as renin-aldosterone, vasopressin, endothelin, and increased activity of the sympathetic nervous system (Møller 1997, Schrier et al. 1998) These alterations induce renal retention of water and sodium, and a decrease in glomerular filtration rate (Møller 1997, Arroyo et al. 1999) Typically, these impairments in renal function in cirrhosis are of a functional nature which means that they are not accompanied by morphological changes and in the early stages can be reversed by medical intervention (Arroyo et al. 1996, Gerbes 1996, Gerbes et al. 1998). The extreme stage of this renal failure however, the hepatorenal syndrome, is rarely reversible, and liver transplantation is the only established therapy. Patients with functional renal failure of cirrhosis are particularly sensitive to decreases in plasma volume (Bernardi et al 1993). Therefore, monitoring renal function is pivotal. On diagnosis of deterioration in renal function, appropriate measures such as volume expansion can be taken to avoid further impairment and development of hepatorenal syndrome. Thus indicators of moderately impaired renal function are of great clinical importance. Serum creatinine concentration, the best established simple parameter of glomerular filtration rate, has some disadvantages: its concentration depends on sex and muscle mass and shows marked increases only at severely reduced creatinine clearance values (Papadakis & Arieff 1987, Whelton et al. 1994). Thus while sufficient for the diagnosis of hepatorenal syndrome (Arroyo et al. 1996) serum creatinine determination can miss less severely impaired renal function. Similar limitations apply for serum urea concentration. Therefore, rather than determination of serum parameters, measurement of clearance rates of exogenous or endogenous substances has been introduced. Among these, inulin clearance is considered the gold standard but is rarely used becauseof costs and inconvenience, except in experimental protocols. Creatinine clearance is the most widely used parameter for in hospital patients. It requires 24 hour urine collection and may be inaccurate

on an outpatient basis. Thus a simple serum parameter is needed which is sensitive for slight deterioration since renal function and not influenced by the factors mentioned above. Recently, the protease inhibitor cystatin C has been suggested as a sensitive marker of glomerular filtration rate and as an early indicator of impaired renal function, possibly superior to serum creatinine (Jung et al. 1995, Stickle et al. 1998). Cystatin C is a non-glycosylated low molecular weight protein produced by nucleated cells at a constant rate, freely filtered by the glomeruli, and catabolised in the tubuli. Its renal clearance was found to be very similar to that of exogenous substances such as 51Cr-EDTA (Tenstad et al. 1996). Cystatin C serum concentration appears to be independent of sex or muscle mass and determination is not affected by hyperbilirubinaemia or haemolysis (Randers et al. 1998, Keevil et al. 1998). Furthermore, very low intraindividual variation of cystatin C in healthy controls (Finney et al. 1997) argues against a significant impact of diet on serum cystatin C concentrations. The aim of this study was to investigate the correlation between GFR (based on cystatin C levels) and hepatic index in patients with liver cirrhosis at Dr. Soetomo Hospital, Surabaya.

MATERIALS AND METHODS

This study used cross-sectional design, involving population of liver cirrhosis patients who had eligible inclusion and exclusion criteria. Twenty five out and in hospital patients with liver cirrhotic at Dr. Soetomo Hospital Surabaya were investigated. There were 15 male and 10 female with age between 39 to 70 years old. Clinical criteria of cirrhosis of the liver based on Soeharjono-Soebandiri criteria, where the diagnoses of cirrhosis of the liver were based on at least five from seven following criteria: Palmar erytheme, collaterals of the vessels both in chest, abdominal, esophageal varises; ascites, pedal oedema; spider angioma; enlargement of the spleen; haematemesis and/or melena; and inverse of albumin/globulin ratio. The inclusion criteria were male and female and the eligibility to diagnosis of liver cirrhotic based on clinical criteria (Soeharjono-Soebandiri criteria), laboratory and ultrasonography. The exclusion criteria were hematemesis and or melena; circulatory shock; sepsis; hypertension, diabetes mellitus, coronary heart disease; consumption of nephrotoxic drugs, diuretics, and or beta blockers; urinalysis, with erythrocyte of more than 50/high power field and or proteinuria more than 500 mg/24 hours, and obstruction of urinary tract and or kidney disease on ultrasonography examination.

Cystatin was determined with the Dade Behring N Latex Cystatin C assay (Dade Behring Diagnostics, Marburg, Germany) (Finney et al. 1997, Erlandsen et al. 1999) a particle enhanced nephelometric immunoassay implemented on the Dade Behring Nephelometer II. Intra and interassay coefficients of variation were always below 5% in accordance with earlier reports (Erlandsen et al. 1999). Normal level of cystatin-C 0.57-0.96 mg/l (male) and 0.50-0.96 mg/l (female). In this study we use cutoff point 1.4 based on Halilintar's study (Halilintar 2004), which is level of cystatin C less than 1.4 mg/l is normal. Glomerular filtration rate based on cystatin C level can estimate from table of Arnal's study (Table 1). Correlation between GFR based on Cystatin C and hepatic index based on score levels and based on stadium level were analyzed with Spearman Correlation Analysis.

Table 1. Estimation of GFR based on Cystatin C level

Cystatin C (mg/L)	GFR estimation (ml/min)	Inulin clearance Mean ± SD (ml/min)	N
0.6	145	125 ± 34	14
0.7	119	111 ± 26	31
0.8	99	93 ± 16	21
0,9	85	84 ± 27	17
1.0	74	79 ± 15	21
1.1	65	68 ± 12	15
1.2	58	61 ± 16	9
1.3	52	55 ± 13	15
1.4	47	55 ± 14	12
1.5 – 1.6	41	40 ± 19	12
1.7 – 1.8	35	42 ± 10	9
1.9 – 2.0	30	32 ± 7	7
2.1 – 2.3	26	34 ± 6	7
2.4 – 2.6	22	28 ± 11	5
2.7 – 3.0	18	24 ± 7	5

Kaniawati M, Gantini L (2002)

RESULTS

There were twenty five patients who eligible of inclusion and exclusion criteria were enrolled in this study. There were 15 (60%) male and 10 (40%) female with age between 39 and 77 year olds (57.48 ± 11.78). Hepatic index based Child McDermott Modification reveal that 8 (32%) patients had mild hepatic failure, 13 (52%) patients had moderate hepatic failure and 4 (16%) patients had severe hepatic failure. Liver function test of these patients showed albumin level 2.80 ± 0.58 g/dl, globulin 3.95 ± 1.57 g/dl, total billirubin 4.93 ± 9.15, with alanine tranferase 77.25 ± 124. 49 IU/l. Renal function test: blood urea nitrogen 30.66 ± 27.82 g/dl, creatine serum 1.31 ± 1.09 mg/dl, and GFR (based on Cockroft-Goult formula) 65.37 ± 37.82 ml/minute.

In patients with mild hepatic failure, cystatin C level were 1.24 ± 0.357 mg/l (0.91 – 2.02 mg/l), 7 patients (87.5%) had normal Cystatin C level and 1 (12.5%)

patient had abnormal Cystatin C level. Glomerular filtration rate based on cystatin C level were 60.63 ± 17.63 ml/min (range 30 – 85 ml/min);4 (50%) patients has GFR 60 – 89 ml/min and 4 (50%) patients has GFR 30 – 59 ml/min. In patients with moderate hepatic failure, cystatin C level were 1.39 ± 0.25 mg/l (1.04 – 1.89 mg/l), 6 patients (46.15 %) had normal Cystatin C level and 7 (53.85%) patients had abnormal Cystatin C level.

Table 2. Patients' Data

No.	Age (yrs)	Sex	Child McDermot Modification Criteria		Cystatin -C (mg/l)	GFR (ml/min)
			Hepatic Index Score	Hepatic Index Stage		
1	40	M	3	Moderate	1.29	52
2	40	M	3	Moderate	1.04	74
3	50	M	7	Severe	4.13	11.84
4	62	M	6	Severe	2.57	22
5	52	F	5	Moderate	1.55	41
6	62	F	2	Mild	1.35	47
7	45	F	6	Severe	2.18	26
8	67	M	5	Moderate	1.12	65
9	64	F	4	Moderate	1.15	58
10	56	F	3	Moderate	1.6	41
11	58	M	0	Mild	1.09	65
12	56	M	3	Moderate	1.36	47
13	49	M	2	Mild	2.02	30
14	39	F	0	Mild	0.91	85
15	56	F	0	Mild	0.95	74
16	60	F	2	Mild	1.21	58
17	62	F	2	Mild	1.33	52
18	41	M	6	Severe	5.61	8
19	68	M	4	Moderate	1.49	41
20	77	M	3	Moderate	1.89	35
21	72	M	4	Moderate	1.67	41
22	65	M	3	Moderate	1.54	41
23	50	M	3	Moderate	1.29	52
24	85	F	3	Moderate	1.16	65
25	61	M	2	Mild	1.02	74

Note: M = male; F = female, GFR = glomerular filtration rate

Glomerular filtration rate based on cystatin C level were 50.23 ± 12.03 ml/min (range 35 – 74 ml/min);3 (23.08%) patients has GFR 60 – 89 ml/min and 10 (76.92%) patients has GFR 30 – 59 ml/min. In patients with severe hepatic failure, cystatin C level were 3.62 ± 1.57 mg/l (2.18 – 5.61 mg/l), all patients had abnormal Cystatin C level. Glomerular filtration rate based on cystatin C level were 16.96 ± 8.44 ml/min (range 8 – 26 ml/min);2 (50%) patients has GFR 15 – 29 ml/min and 2 (50%) patients has GFR < 15 ml/min.

GFR (based on cystatin C levels) in patients with LC with mild hepatic failure is 60.625 ± 17.631, moderate hepatic failure is 50.231 ± 12.029, and severe hepatic failure 16.960 ± 8.438. There was a strong negative correlation between GFR (based on cystatin C levels) and hepatic index based on score levels (r -0.646; 0.0001) and based on stadium levels (r -0.636; p 0.001) in LC patients.

DISCUSSION

Cystatin C has recently been introduced as an excellent marker of glomerular filtration rate (Stickle et al. 1998) that is not influenced by several physiological and pathophysiological conditions. While patients with severely impaired renal function exhibit increased serum creatinine concentrations, detection of slightly or moderately decreased glomerular filtration rate by serum parameters is rather difficult (Papadakis & Arieff 1987). Creatinine clearance, widely used in inhospital patients for estimation of glomerular filtration rate, requires 24 hour urine collection and lacks sufficient reliability in outpatients. Early diagnosis of impaired renal function is particularly important in patients with cirrhosis of the liver. We therefore investigated the correlation between glomerular filtration rate (based on cystatin C serum concentration) and hepatic index based on score levels and based on stadium levels in LC patients. It was found that the average cystatin C serum concentrations are higher in the patients with severe hepatic failure than patients with moderate or mild hepatic failure.

Table 3. Cystatin - C level in Liver Cirrhotic patients

Liver Index	Cystatin C level		Total
	Normal (< 1.4 mg/l)	High (≥ 1.4 mg/l)	
Mild	7	1	8
Moderate	6	7	13
Severe	0	4	4
Total	13	12	25

Table 4. GFR based on Cystatin C

Liver Index	Glomerular Filtration Rate (ml/minute)				Total
	60-89	30-59	15-29	< 15	
Mild	4	4	0	0	8
Moderate	3	10	0	0	13
Severe	0	0	2	2	4
Total	7	14	2	2	25

In patients with mild hepatic failure only 12.5% patient have high serum cystatin C level, but in patients with moderate hepatic failure the percentage of high cystatin C serum concentrations (> 1.4 mg/l) is 53.85 % and all of patients with severe hepatic failure have high cystatin C serum concentrations. It was also found that the glomerular filtration rate (based on cystatin C serum level) in patients with mild hepatic failure (60.625 ± 17.631 ml/min) higher than those in moderate hepatic failure (50.231 ± 12.029 ml/min) and severe hepatic

failure (16.960 ± 8.438 ml/min). There was a strong negative correlation between GFR (based on cystatin C levels) and hepatic index based on score levels (r -0.646; 0.0001) and based on stadium levels (r -0.636; p 0.001) in LC patients.

Throughout the literature, creatinine-based GFR estimates have been reported to overestimate GFR in patients with liver cirrhosis (Caregaro et al. 1994, Papadakis & Arieff 1987). Various factors contribute to reduce the creatinine serum levels to lower than expected from a known GFR level. Besides malnutrition and reduced muscle mass, it has been shown that creatinine synthesis itself may be reduced by 40–50% in liver cirrhosis (Papadakis & Arieff 1987, Sherman et al. 2003). Tubular creatinine secretion additionally reduces serum creatinine concentration (Caregaro et al. 1994).

Cystatin C has a low molecular weight (13 kD) and is a member of the family of cysteine protease inhibitors, which are produced by all nucleated cells. A structural analysis of the cystatin C gene and its promoter has shown this gene to be a house-keeping type, which is compatible with a stable production rate by most cells, even under inflammatory conditions (Filler et al. 2005). Because of its small size and basic pH, cystatin C is freely filtered by the glomerulus. It is not secreted, but is reabsorbed by tubular epithelial cells and subsequently catabolized so that it does not return to the blood flow (Laterza et al. 2002). Because of these properties, cystatin C bears some advantages over serum creatinine. Cystatin C is independent of muscle mass, age, or sex. Most significantly, on average, GFR declines with age by approximately 1 ml /min/1.73 m2/year over the age of 40 years, and the rate of decline in GFR accelerates after 65 years of age 24. Serum creatinine alone is an unacceptable measure of renal function in the elderly. Possible reasons for this include reduced muscle mass and poor nutrition. However, serum cystatin C concentrations increase with advancing age. Therefore, the measurement of cystatin C is useful, especially in the elderly and chronic diseases (Tanaka et al. 2007).

Some formulas using the serum cystatin C concentration based on the particle-enhanced immunonephelometric assay (PENIA) or immunoturbidimetric assay (PETIA) in order to estimate GFR have recently been reported (Hoek et al. 2003, Sjöström et al. 2005, Grubb et al. 2005a,b). The diagnostic accuracy of three cystatin C-based formulas (Larson, Hoek, and Filler formulae) that used an immunonephelometric method was evaluated in liver transplant recipients (Gerhardt et al. 2006) and in kidney transplant recipients (Poge et al. 2006). In both reports, the Hoek formula showed the best overall performance for GFR with respect to bias, precision, and accuracy

In our study formula using the serum cystatin C concentration based on the particle-enhanced immunonephelometric assay (PENIA) and showed that average cystatin C serum concentrations are higher in the patients with severe hepatic failure than patients with moderate or mild hepatic failure; and percentage of patients who have abnormal cystatin C serum concentrations increased with the severity of the disease. Glomerular filtration rate (based on cystatin C serum level) in patients with mild hepatic failure higher than those in moderate hepatic failure and severe hepatic failure.

CONCLUSION

based on cystatin C serum level, GFR in patients LC with mild hepatic failure higher than those in moderate hepatic failure and severe hepatic failure. GFR does not play a major role in determining hepatic index. Nevertheless, GFR in patients LC with mild hepatic failure higher than those in moderate hepatic failure and severe hepatic failure.

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