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

Thesis

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Mohammed Anwar Abd Elaziz

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List of Abbreviations

ACEIs	**:**	Angiotensin-converting-enzyme inhibitors
AKI	**:**	Acute kidney injury
ALT	**:**	Alanine transaminase
AST	**:**	Aspartate transaminases
ATN	**:**	Acute tubular necrosis
C.B.C	**:**	Complete blood count
CKD	**:**	Chronic kidney disease
CKD-EPI	**:**	Chronic kidney disease epidemiology
CPT	**:**	Child pugh turcotte
CysC	**:**	Serum cystatin C
DN	**:**	Diabetic nephropathy
DUS	**:**	Doppler ultrasound
$eGFR_{cys}$	**:**	Estimated glomerular filtration rate $_{cys}$
ESRD	**:**	End-stage renal disease
FBS	**:**	Fasting blood sugar
GFR	**:**	Glomerular filtration rate
HRS	**:**	Hepatorenal syndrome
KIM-1	**:**	Kidney injury molecule-1
L-FABP	**:**	Liver type fatty acid-binding protein
LVP	**:**	Large volume paracentesis
MAP	**:**	Mean arterial pressure
MARS	**:**	Molecular adsorbent recirculating system

MDRD	**:**	Modification of diet in renal disease
NASH	**:**	Non-alcoholic steatohepatitis
NGAL	**:**	Neutrophil gelatinase-associated lipocalin
NSAIDs	**:**	Non steroid anti-inflammatory drugs
OLT	**:**	Orthotopic liver transplantation
RRI	**:**	Renal resistive index
SBP	**:**	Spontaneous bacterial peritonitis
TIPS	**:**	Transjugular intrahepatic portosystemic shunt

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Introduction

Cirrhosis of the liver is often accompanied by functional renal failure particularly in advanced stages of liver disease. Hemodynamic alterations with reduced effective arterial blood volume and peripheral vasodilation are followed by activation of vasoconstrictive hormones (renin-aldosterone, vasopressin, and endothelin) and neurohumoral systems (including increased activity of nervous system) ***(Salerno et al., 2007).***

The most common functional renal abnormalities in patients with cirrhosis are an impaired ability to excrete sodium and water and a reduction of renal blood flow and glomerular filtration rate, the latter two being secondary to vasoconstriction of the renal circulation ***(Arroyo et al., 2008).***

Hence renal failure is directly linked 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 ***(Kim et al., 2011).***

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 ***(Zeller et al., 2008).***

The resistive index (RI) measures the degree of intrarenal arterial impedance and is calculated using the following formula: ([peak systolic velocity – end-diastolic velocity]/ peak systolic velocity) ***(Krumme et al., 2006).***

Serum cystatin C could be proposed as a marker of liver disease stage and a more sensitive indicator of renal function in patients with cirrhosis than serum Cr level ***(Chung et al., 2010).***

Serum cystatin C level was useful marker for predicting the prognosis of cirrhotic patients ***(Seo et al., 2009)***

CysC is a non-glycosylated 13 kDa protein, produced at a constant rate by all nucleated cells, freely filtered by the glomeruli and subsequently metabolized in the proximal tubules ***(Chew et al., 2008).***

Opposed to creatinine, CysC is independent of gender, age, and muscle mass and not influenced by serum bilirubin, inflammation, or malignancy ***(Zahran et al., 2007).***

Aim of the work

The aim of the present work is to evaluate the Role of cystatin C and renal resistive index in assessment of renal function in patients with liver cirrhosis

Renal Dysfunction in liver Cirrhosis

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 ***(Wong et al., 2012).***

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 ***(Mindikoglu et al., 2013).***

Etiology of renal Failure in liver cirrhosis

The most common causes of kidney injury in liver cirrhotic patients: ***(Carvalho GC et al., 2012)***

(1) Sepsis which may complicated with circulatory dysfunction

(2) Pre-renal cause like Hypovolemia secondary to gastrointestinal bleeding, large volume paracentesis or excessive diuretic use.

(3) Drug-induced or contrast induced nephropathy.

(4) Chronic kidney diseases.

(5) Hepatorenal syndrome.

Chronic kidney diseases like IgA nephropathy, glomerulonephritis or nephrosclerosis are frequently seen in cirrhotic patients. In most cases, the original reasons of both conditions are alcoholic liver disease, hepatitis B and C and non-alcoholic steatohepatitis with associated diabetes and/or hypertension ***(Hartleb et al., 2012).***

Hepatorenal syndrome (HRS) is a functional form of renal failure overstated especially in end stage of liver cirrhotic patients particularly with ascites. It can be reversed either with orthotopic liver transplantation (OLT) or with pharmacological treatment with splanchnic vasoconstrictors and albumin ***(Angeli et al., 2015).***

HRS is the eventual result of arterial underfilling due to splanchnic and systemic vasodilation commonly with high cardiac output. When the circulatory dysfunction is insufficient to restore hemodynamics, vasoconstrictor mediators are released, resulting in severe renal vasoconstriction ***(Angeli et al., 2015).***

Pathophysiology of Hepatorenal syndrome

The main cause of HRS is thought to be due to extreme circulatory dysfunction. Several local acting vasodilators factors such as cannabinoids and nitric oxide are created from Hepatocytes and stellate cells in a cirrhotic liver. These vasodilators act locally on the splanchnic circulation which represents an essential part of the circulation of the body leading to splanchnic arterial vasodilation. Thus, splanchnic vasodilation cause a reduction in mean arterial pressure (MAP), which prompts the activation of the sympathetic nervous system, which in turn leading to release of noradrenaline in high levels into circulation, which lead to increase in cardiac output as an early circulatory compensating mechanisms that keep MAP constant ***(Iwakiri et al., 2014).***

The worse splanchnic vasodilation becomes, the more vasoconstrictor systems get activated and released in circulation as vasopressin and the renin-angiotensin-aldosterone system ***(Iwakiri et al., 2014).***

Aldosterone prompts sodium and water retention by the kidneys leading to progress of ascites. Vasopressin augments free water retention leading to hyponatremia. The splanchnic vascular bed is insensitive to the action of all