(MELD) and (MELD-Na) Score as Predictors of Systemic Vascular Resistance in Cirrhosis in Patients with and without Renal Impairment

Thesis

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Wael salah El-Din Hagmagid

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List of Abbreviations

Abbrev.	Full-term
AC	: Adenylyl cyclase
ALD	: Alcoholic liver disease
ALT	: Alanine aminotransferase
APRI	: AST-to-platelet ratio index
APRI	: AST-to-platelet ratio index
AST	: Aspartate aminotransferase
CBDL	: Common bile duct ligation
cGMP	: Cyclic guanosine monophosphate
CNS	: Central nervous system
CO	: Carbon monoxide
CPA	: Collagen proportionate area
CTP	: Child-Turcotte-Pugh
ELF	: European Liver Fibrosis score
EET	: Epoxyeicosatrienoic acid
FIB4	: Fibrosis 4 index
GFR	: Glomerular filtration rate
HBV	: Hepatitis B virus
HCC	: Hepatocellular carcinoma
HCV	: Hepatitis C virus
HE	: Hepatic encephalopathy
HVPG	: Hepatic-vein pressure gradient

INR : International normalized ratio

LT : Liver transplantation

MELD : Model for End-Stage Liver Disease

MR : Magnetic resonance

NAFLD : Non-alcoholic fatty liver disease

NO : Nitric oxide

PBC : Primary biliary cirrhosis

PELS : Parenchymal extinction lesions

PIIINP : N-terminal peptide of type III procollagen

PSC : Primary sclerosing cholangitis

RAAS : Rennin-angiotensin-aldesterone system

RCT : Random controlled trial

RES : Reticuloendothelial system

SOD : Superoxide dismutase

SVR : Systemic vascular resistance

TIMP-1 : Metallopeptidase inhibitor 1

TNF- α : Tumor necrosis factor alpha

UNOS : United Network of Organ Sharing

VEGF : Vascular endothelial growth factor

yGT : Yglutamyltranspeptidase

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Abstract

Background: The aim of this study was to investigate whether systemic vascular resistance (SVR) correlates with validated prospective scoring systems such as Model for End-stage Liver Disease (MELD) and its modification MELD Sodium.

Methods : Patients with cirrhosis, who were admitted to hospital with decompensation (as defined by development of ascites, hepatic encephalopathy, and variceal bleeding) with and without renal failure and underwent echocardiography were included in this study.Compensated cirrhosis patients were also included. Laboratory data required for computing MELD score, serum bilirubin, serum creatinine, international normalized ratio, and serum sodium were collected for every patient. We tabulated hemodynamic and echocardiography parameters that enabled calculation of SVR. We analyzed the correlation between SVR and each of the individual prognostic scores.

Results : A total of 60 patients with a diagnosis of decompensated cirrhosis were included in the study in which 30 have renal failure. 30 patients were found to have a low sodium level (<135 mEq/L) and 30 were found to have a normal sodium level (>135 mEq/L). In the patients with hyponatremia, we found statistically significant inverse correlations between SVR and validated liver severity models. However, these correlations were not seen in patients with normonatremia.

CONCLUSION: We observed a statistically significant inverse correlation between SVR and all the validated liver disease severity models used in this study among patients with hyponatremia but not in those with normonatremia.

KEYWORDS: Model for End-stage Liver Disease; cirrhosis; scoring systems; systemic vascular resistance

Introduction

Cirrhosis is the end stage in the spectrum of chronic liver disease, characterized by advanced fibrosis and formation of regenerative nodules with distortion of underlying normal hepatic architecture. The most commonly implicated causes of cirrhosis include viral agents (hepatitis B and hepatitis C), alcohol, and nonalcoholic fatty liver disease ***(Heidlbaugh et al., 2006).***

Cirrhosis of the liver is more common than previously thought, affecting more than 633,000 adults yearly worldwide, according to a study published in the ***(Journal of Clinical Gastroenterology, 2015).*** There are multiple prognostic scores that predict the mortality from chronic liver disease, of which the Child-Pugh score and MELD score are the most commonly used. MELD is a validated scoring system used to predict mortality and is a composite of the patient's laboratory values for serum bilirubin and serum creatinine, and the international normalized ratio (INR) for prothrombin time. The MELD scoring system is used by the United Network for Organ Sharing to stratify and prioritize patients for liver transplantation. According to the MELD- based policy, patients with the highest score have a priority for organ allocation ***(Younossi et al., 2014)***. The MELD score has been shown to be at least equivalent to the Child-Pugh score ***(Shaikh et al., 2010)*** in predicting survival of patients with cirrhosis.

However, the MELD score does not suffer from subjective scoring differences (such asthose that could occur with the Child-Pugh scoring system while estimating the degree of ascites and encephalopathy) (***Bedreli et al., 2016)*** and has a greater discriminatory continuous scoring capacity. Hyponatremia is a common laboratory finding in patients with decompensated liver disease. It has been noted in several studies that inclusion of the serum sodium level, especially in hyponatremic patients, increases the predictive accuracy of MELD in chronic liver disease ***(Biselli et al., 2010).*** Hyponatremia mirrors the underlying primary changes in hemodynamic parameters, such as vasodilation with decreased systemic vascular resistance (SVR) and subsequent compensatory neurohumoral adaptations ***(Ginès and Guevara, 2008)***, such as increased antidiuretic hormone secretion. The severity of vasodilation increases with progression of liver disease, leading to renal hypoperfusion and hepatorenal syndrome in some patients. It has been postulated that the marked reduction in SVR results from inability of the liver to metabolize circulating vasodilators such as nitric oxide, eicosanoids, bile salts, adenosine, and tachykinins (***Ginès and Schrier,, 2009).*** Therefore, SVR could theoretically be a single predictor for severity of liver disease. In this study, we aim to determine the correlation of SVR with validated liver disease severity scoring systems like MELD and MELD-Na (MELD sodium score).

Aim of the Work

To identify the prognostic value of Systemic Vascular Resistance as a single entity, according to its correlation with prospectively validated scoring systems such as Model of End stage Liver Disease & its modification as predictors of severity in cirrhosis and also their correlation with renal impairment.

Liver Cirrhosis and associated renal dysfunction

Introduction

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterised by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture ***(Schuppan et al., 2008)***. This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic dysfunction. Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for oesophagealvarices and hepatocellular carcinoma. Lately, this perception has been challenged, because 1-year mortality in cirrhosis varies widely, from 1% to 57%, depending on the occurrence of clinical decompensating events ***(Tsochatzis et al., 2014)***. Histopathologists have proposed that the histological term cirrhosis should be substituted by advanced liver disease, to underline the dynamic processes and variable prognosis of the disorder ***(Hytiroglou et al., 2012)***. Moreover, fibrosis, even in the cirrhotic range, regresses with specific therapy if

available, such as antiviral treatment for chronic hepatitis B ***(Marcellin et al., 2013)*** or C ***(Morgan et al., 2010)***.

Epidemiology

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries. It is the 14th most common cause of death in adults worldwide, but the fourth in central Europe; it results in 103 million deathsper year worldwide, 8 170 000 per year in Europe ***(Blachier et al., 2013)***, and 33 539 per year in the USA ***(Hoyert et al., 2012)***. Cirrhosis is the main indication for 5500 liver transplants each year in Europe ***(Blachier et al., 2013)***.

Pathophysiology

The transition from chronic liver disease to cirrhosis involves inflammation, activation of hepatic stellate cellswith ensuing fibrogenesis, angiogenesis, and parenchy-malextinction lesions caused by vascularocclusion ***(Wanless et al., 2011)***. This process leads to pronounced hepatic microvascular changes, characterised by sinusoidal remodelling (extracellular matrix deposition from proliferating activated stellate cells resulting in capillarisation of hepatic sinusoids), formation of intrahepatic shunts (due to angiogenesis and loss of parenchymal cells), and hepatic endothelial dysfunction ***(Fernandez et al., 2009)***. The endothelial dysfunction is characterised by insufficient release of vasodilators, of which the most important is nitric oxide.Release of nitric oxide is inhibited by low activity of endothelial nitric oxide synthetase (as a result of insufficient protein-kinase-B-