Predictive value of non invasive markers in the Assessment of complications of hepatic cirrhosis

Thesis submitted for partial fulfillment of

Master Degree in Internal Medicine

By

MOHAMED EL SAYED ABASS

M.B.B.CH

Under supervision of

PROF DR.MOHAMED A .M. MAKHLOUF

Professor of Internal Medicine&Hepatology

Faculty of Medicine-Ain shams university

PROF DR.HATEM ABD EL LATIF MOHAMED

Professor of Internal Medicine&Hepatology

Faculty of Medicine-Ain Shams university

DR.AHMED EL SAADY MOHAMED

Lecturer of Internal Medicine&Hepatology

Faculty of Medicine-Ain Shams university

Faculty of Medicine

Ain shams university

2015

ABSTRACT

OBJECTIVE:

To determine whether Model for End-stage Liver Disease (MELD) Child-Turcotte-Pugh (CTP) classification, AST to platelet ratio index (APRI), and laboratory tests could predict the presence of esophageal varices (EV) or varices which need prophylactic therapy (medium or large size EV).

METHODS:

Between January 2012 and May 2013, we prospectively enrolled 60 consecutive patients suffering from hepatitis C virus liver cirrhosis at Internal Medicine Department of determined Hospitals , cairo and They were 22 females and 38 males with a mean age 49.0±8.883 years. The presence of EV (any size and medium or large EV) was correlated with patients' characteristics (MELD, CTP classification, APRI, platelets count, and liver tests).

RESULTS:

Forty four patients (73%) had EV, of whom 54% (24) had varices which need prophylactic therapy (VPT). INR ≥ 1.4 sec(sensitivity: 80%; specificity: 55%; AUC: 0.867) and platelet count lower than 110x10³ (sensitivity: 85%; specificity: 54%; AUC: 0.856) had the best sensitivity for prediction of OV. The VPT could be predicted by platelet count lower than 99.9x10³ (sensitivity: 65%; specificity: 44%; AUC: 0.342) and total bilirubin higher than 2.34 mgldl(sensitivity: 83%; specificity: 63%; AUC: 0.674).). In this study the presence of OV could be predicted by MELD score higher than 8.5 (sensitivity: 82%; specificity: 60%; AUC: 0.683). the VPT could be predicted by MELD score higher than 9.1(sensitivity: 81%; specificity: 62%; AUC: 0.657).

CONCLUSION:

High values on MELD are associated with EV and thrombocytopenia, with varices which need prophylactic therapy. As a result of their low sensitivity and specificity, it is suggested to maintain the recommendation of upper gastrointestinal endoscopy for all patients with cirhosis.

KEYWORDS: cirrhosis, esophageal varices, MELD,INR, platelets.

ACKNOWLEDGEMENT

First of all, thanks to "Allah" who granted me the ability to accomplish this work.

I would like to express my deepest gratitude and highest appreciation to Prof Dr. Mohamed A.M. Makhlouf Professor of Internal Medicine & Hepatology for his continuous encouragement, generous support and unlimited help.

I am extremely grateful to Dr. Hatem Abd El Latif Mohamed Assistant Professor of Internal Medicine & Hepatology, for his continuous guidance and suggestions, saving no effort or time to make this work better.

I am greatly honored to express my deepest appreciation to Dr. Ahmed El Saady Mohamed Lecturer of Internal Medicine & Hepatology for his outstanding guidance and kind support throughout the work.

Mohamed El sayed Abass

DEDICATIONS

I dedicate this work to my beloved family especially my parents &wife who always show so much care, aid, support and patience.

I dedicate this work also to all dear professors from whom I learned as well as my sincere friends who support me.

LIST OF CONTENTS:

Topic		page
List of tables		**1**
List of figures and diagrams		**2**
List of abbreviations		**3**
Introduction and aim of work		**6**
Review of Literature	**Chapter one (liver cirrhosis)**	**10**
	Chapter two (esophageal varices)	**33**
	Chapter three (prediction of esophageal varices)	**46**
Patients and methods		**75**
Results		**82**
Discussion		**99**
Summary and conclusion		**111**
References		**114**
Arabic summary		**136**

LIST OF TABLES:

Table number	Title	Page
1	North Italian endoscopic club (NIEC) index for prediction of variceal bleeding.	43
2	Bleeding risk at one year according to North Italian endoscopic club (NIEC) index.	43
3	Doppler sonoscore for the risk assessment of variceal bleeding in patient with liver cirrhosis.	51
4	Child-Pugh classification of severity of liver disease	79
5	Descriptive data of the study group	83
6	Description of the presenting symptoms among the studied cases	84
7	Description of local examination results among the studied cases	85
8	Description of different sonographic findings among the studied cases	85
9	Descriptive laboratory data of the study group	86
10	Comparison between patients with and without OV regarding descriptive data	87
11	Comparison between group 1 and group 2 regarding laboratory data	88
12	Comparison between group 1 and group 2 regarding MELD & APRI	89
13	Multi-regression analysis of Predictors of the presence of esophageal varices OV	90
14	Sensitivity, specificity and predictive values in prediction of the presence of esophageal varices OV	91
15	Comparison between group 2 A and group 2 B regarding descriptive data	92
16	Comparison between group 2A and group 2B regarding laboratory data	93
17	Comparison between group 2A and group 2B regarding MELD & APRI	94
18	Multi-regression analysis of Predictors of the presence of VPT	95
19	Sensitivity, specificity and predictive values in prediction of presence of VPT	95

20	Correlation between OV grade and laboratory data	97
21	Correlation between OV grade and MELD & APRI	97
22	Relation between endoscopic parameters versus Child classification	98

LIST OF FIGURES AND DIAGRAMS:

Figure number	Title	Page
1	*Pathogenic mechanisms in hepatic fibrosis*	13
2	*Cirrhosis with architectural alteration resulting from fibrosis and nodular hepatocellular regeneration*	14
3-4	Macro and Micro nodular cirrhosis	15
5	Progressive *liver fibrosis showed histologically*	16
6	Spider angiomas.	21
7	Clubbing of the fingers.	21
8	Dupuytren's contracture.	22
9	Examination for Gynecomastia.	22
10	Clinical manifestation and complication of cirrhosis.	27
11	Extension of esophageal varices	35
12	Size of varices	38
13	Cherry red spots and red wale markings in esophageal varices	40
14	Signs of reflux disease	40
15	Barium swallow in the left lateral decubitus position	45
16	CT sections demonstrate esophageal varices protruding into the lumen	55
17	Maximum intensity projection magnetic resonance image of the portal venous system	56

18	Fibroscan device, probe and method of application	57
19	Pillcam Eso Device and Parameters	59
20	Child Pugh Score of the study group	84
21	Child Pugh Score in the studied group	88
22	Comparison between group 1 and group 2 regarding APRI	90
23	Sensitivity, specificity and predictive values in prediction of OV	91
24	Comparison between group 2 A and group 2 B regarding descriptive data	93
25	Comparison between group	94
26	Sensitivity, specificity and predictive values in prediction of VPT	96

LIST OF ABBREVIATIONS:

ALP	Alkaline phosphatase.
ALT	Alanine aminotransferase
APRI	AST-to-platelet ratio index.
AST	Aspartate aminotransferase
AUROC	Areas under the ROC curve.
BaEs	Barium esophagography
BUN	Blood urea nitrogen
CBC	Complete blood count
CLD	Chronic liver disease
CPS	Child-pugh score
CSPH	clinically significant portal hypertention
CT	Computerized tomography

CTP	**Child-Turcotte-Pugh score**
ECE	**Esophageal capsule endoscopy**
EGD	**Esophagogastroduodenoscopy**
EGF	**epidermal growth factor**
ET	**Endothelin**
EV-OV	**Esophageal varices**
FSH	**Follicle stimulating hormone**
GGT	**Gamma-glutamyl transpeptidase**
GOV	**Gastroesophageal varices**
HBV	**Hepatitis B virus**
HCC	**Hepatocellular carcinoma**
HCV	**Hepatitis C virus**
HOA	**Hypertrophic osteoarthropathy**
HREV	**High risk esophageal varices**
HVPG	**Portal-hepatic venous pressure gradient**
IGF	**insulin growth factor**
IgG	**Immunoglobulin G**
IGV	**Isolated gastric varices**
IL	**Interleukin.**
INR	**International randomized ratio**
LFTs	**Liver function tests**
LH	**Luteinizing hormone**
MCL	**Midclavicular line**
MELD	**Model for end-stage liver disease**

MMP	**Matrix metalloproteinase**
MSBD	**Mean splenic bipolar diameter**
NIEC	**North Italian endoscopic consortium**
p	**P value**
PDGF	**Platelet-derived growth factor**
PI	**Prothrombin index**
PLT	**Platelet**
PPG	**portal pressure gradient**
PT	**Prothrombin time**
PVD	**Portal vein diameter**
ROC	**Receiver operating characteristic**
ROS	**Reactive oxygen species**
SAAG	**Serum-ascites albumin gradient**
SBP	**Spontaneous bacterial peritonitis**
SD	**Standard deviation**
TGF-β_1	**Transforming growth factor-beta**
TIMP	**Tissue inhibitors for metalloproteinase**
TIPS	**transjugular intrahepatic portosystemic shunt**
UGE	**upper gastrointestinal endoscopy**
ULN	**Upper limit of normal**
UNOS	**United Network for Organ Sharing**
VPT	**varices with indication for prophylactic therapy**

INTRODUCTION

AND

AIM OF THE WORK

INTRODUCTION

Cirrhosis(greek kirrhos=yellow) implies irreversible liver damage.histollogically,there is loss of normal architecture with fibrosis and nodular regeneration.most commonly causes are HBV, HCV infction, chronic alcohol abuse and drugs:eg amiodarone. **(Longmore et al., 2008)**

Portal hypertention one of the complications of hepatic failure leading to ascites ,splenomegaly,portosystemic shunt including oesophygeal varices(life threatening upper GIT bleed) and caput medusa(enlarged superficial peri umbilical veins. **(Madhotra et al., 2002)**

Portal hypertention causes dilated collateral veins(varices) at sites of portosystemic anastomosis.varices most commonly occur in the lower oesophages,but may also be found in the stomach and rectum. Varices develop in patients with cirrhosis once portal pressure(measured by hepatic venous pressure gradient) is more than 10 mmhg :if more than 12 mmhg variceal bleeding may develop associated with amortality of 30-50% per episode.**(Chang et al., 2007)**

The Child-Pugh classification (sometimes the Child-Turcotte-Pugh score) is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation. **(Cholongitas et al., 2005)**

Model for End-Stage Liver Disease, or MELD, is a The scoring system for assessing the severity of chronic liver disease. It was initially developed to predict death within three months of surgery in patients who had undergone a transjugular intrahepatic portosystemic shunt (TIPS) .This score is now used by the United Network for Organ Sharing (UNOS) and Eurotransplant for prioritizing allocation of liver transplants. **(Kamath et al., 2007)**

Among non-invasive liver fibrosis tests, APRI has the highest diagnostic value in discriminating liver transplanted patients with progression to significant liver fibrosis, although its accuracy is influenced by recipient sex. **(Lin et al., 2011)**

AIM OF WORK

The aim of work to determine whether model for End-stage liver disease(MELD) Child-Turcotte-Pugh (CTP) classification, AST to platelet ratio index(APRI),and laboratory tests could predict the complications of hepatic Cirrhosis such as oesophageal varices which impend upper GIT bleeding, ascites,hepatic encephalopathy .

REVIEW OF LITERATURE

CHAPTER ONE

LIVER CIRRHOSIS