

Detection of the Imbalance of Procoagulant versus Anticoagulant Factors in Egyptian Cirrhotic patients

Thesis

*Submitted for partial fulfillment of Master Degree in Internal
Medicine*

By

Ahmad Nady Abd-Al-Aziz Abd-Al-Azim Elneairy

M.B.B.Ch

Faculty of Medicine-Ain Shams University

Under supervision of

Prof. Mohamed Abd El-Hamid El-bokl

Professor of Internal Medicine & Gastroenterology

Faculty of Medicine-Ain Shams University

Ass.Prof. Amal Shawky Mohamed Bakir

Assistant Professor of Internal Medicine & Gastroenterology

Faculty of Medicine-Ain Shams University

Ass.Prof. George Safwat Riad

Assistant Professor of Internal Medicine & Gastroenterology

Faculty of Medicine-Ain Shams University

**Faculty of Medicine
Ain Shams University
2012**

Acknowledgements

First of all, all gratitude is to **Allah** almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.

Really I can hardly find the words to express my gratitude to **Prof. Dr. Mohamed Abd El-Hamid El-bokl**, Professor of internal medicine, faculty of medicine, Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the revision of the whole work. It is a great honor to work under his guidance and supervision.

I am also indebted to **Ass.Prof. Dr. Amal Shawky Mohamed Bakir** Assistant Professor of internal medicine, faculty of medicine, Ain Shams University for her guidance, continuous assistance and sincere supervision of this work.

I would like also to express my sincere appreciation and gratitude to **Ass.Prof.Dr. George Safwat Riad** Assistant Professor of internal medicine, faculty of medicine, Ain Shams University, for his continuous directions and support throughout the whole work.

Last but not least, I dedicate this work to **my family** (my mother, my father, my brothers & sister), my beloved sincere relatives & friends, my senior & junior colleagues, including doctors, workers, nurses & medical staff whom without their sincere emotional support, help & pushing me forward; this work would not have ever been completed.

Ahmad Nady Elneairy

2012

Contents

	<i>Page</i>
<i>Introduction</i>	1
<i>Aim of the work</i>	5
<i>Review of literature:</i>	
<i>Chapter 1: Liver Cirrhosis.....</i>	6
<i>Chapter 2: Normal Hemostasis.....</i>	70
<i>Chapter 3: Coagulopathy in chronic liver disease....</i>	111
<i>Patients & methods.....</i>	135
<i>Results</i>	141
<i>Discussion</i>	182
<i>Summary & Conclusion</i>	200
<i>Recommendations</i>	204
<i>Chapter 10: References</i>	206
<i>Arabic Summary</i>	-

List of Tables

<i>Table</i>	<i>Subject</i>	<i>Page</i>
I	The Child-Pugh classification.	29
II	Different Prognostic models for urgency-based allocation systems.	31
III	Methods to assess liver fibrosis.	33
IV	Fibrosis markers.	35
V	The Multicomponent indirect serologic markers for liver fibrosis.	36
VI	Grading of ascites and suggested treatment.	40
VII	Definition and diagnostic criteria for refractory ascites in cirrhosis.	46
VIII	Criteria for diagnosis of hepatorenal syndrome in cirrhosis.	47
IX	Proposed nomenclature for hepatic encephalopathy.	58
X	Precipitating factors for HE development.	58
XI	West Haven classification for grading mental status in HE.	59
XII	The portal-systemic encephalopathy score.	60
XIII	Patterns of Prohemostatic and Antihemostatic Drivers in the Different Phases of Hemostasis in Patients with Chronic Liver Disease.	116

XIV	Underlying conditions that explain the bleeding tendency in patients with decompensated chronic liver disease.	120
1	Age comparison among the study groups.	144
2	Gender distribution among the study groups.	145
3-a	The main demographic characteristics of the study population.	146
3-b		147
4	The main ultrasonographic findings of the study population.	148
5	The main upper gastrointestinal endoscopic findings of the study population.	149
6	The laboratory findings of the study population.	150
7	The main haemostatic parameters & events of the study population.	151
8	Comparison between patient groups separated according to Child-Pugh Classification as regard MELD-UNOS & MELD-XI.	152
9	Comparison between control group Vs all patients with cirrhosis; as regard Factor VIII %.	153
10	Comparison between control group Vs all patients with cirrhosis; as regard Protein C %.	154
11	Comparison between control group Vs all patients with cirrhosis; as regard PICI %.	155

12	Comparison between control group Vs all patients with cirrhosis; as regard Factor VIII/Protein C ratio.	156
13	Comparison between control group Vs all patients with cirrhosis; as regard prothrombin time.	157
14	Comparison between control group Vs all patients with cirrhosis; as regard partial thromboplastin time.	158
15	Comparison between control group Vs all patients with cirrhosis; as regard international normalization ratio.	159
16	Comparison between control group Vs all patients with cirrhosis; as regard platelets count.	160
17	Comparison between control group & patient group separated according to Child-Pugh Classification.; as regard Factor VIII %.	161
18	Comparison between control group & patient group separated according to Child-Pugh Classification.; as regard Protein C %.	162
19	Comparison between control group & patient group separated according to Child-Pugh Classification.; as regard PICI%.	163
20	Comparison between control group & patient group separated according to Child-Pugh Classification.; as regard Factor VIII/Protein C ratio.	164

21	Comparison between control group & patient group separated according to Child-Pugh Classification.; as regard prothrombin time.	165
22	Comparison between control group & patient group separated according to Child-Pugh Classification.; as regard partial thromboplastin time.	166
23	Comparison between control group & patient group separated according to Child-Pugh Classification.; as regard international normalization ratio.	167
24	Comparison between control group & patient group separated according to Child-Pugh Classification.; as regard platelets count.	168
25	Correlation of PICI % versus procoagulant and anticoagulant factors in the entire study group.	169
26	Correlation of MELD-UNOS & MELD-XI versus procoagulant and anticoagulant factors in the entire study group.	170
27	Chi square test for bleeding events (including hematemesis & melena) distribution in patients Vs control group.	171
28	Chi square test for bleeding events (including hematemesis & melena) distribution in control group Vs patient groups stratified according to Child-Pugh class.	172
29	Distribution of thromboembolic events (including portal vein thrombosis) in patients Vs control group.	173

30	Distribution of thromboembolic events (including portal vein thrombosis) in control group Vs patient groups stratified according to Child-Pugh class.	174
31	The relation between bleeding events (including hematemesis & melena) & the main study parameters in the whole study groups.	175
32	The relation between thromboembolic events (without portal vein thrombosis) & the main study parameters in the whole study groups.	176
33	The relation between thromboembolic events (including portal vein thrombosis) & the main study parameters in the whole study groups.	177
34	The relation between bilharziasis & the main study parameters in the whole study groups.	178
35	The relation between bleeding events (including hematemesis & melena) and thromboembolic events (including PVT) in the whole study group.	179
36	The relation between Age (years), smoking (pack/years), CLD duration (months) & splenic bipolar diameter (cm) Vs the main study parameters in the whole study groups.	180
37	Comparison between the main study parameters in all patients as regard the degree of oesophageal varices.	181

List of Figures

<i>Fig</i>	<i>Subject</i>	<i>Page</i>
I	Suggested algorithm for the management of hepatic encephalopathy.	67
II	Events of haemostasis at the site of vascular injury.	72-73
III	Anti- and procoagulant activities of endothelium.	75
IV	Schematic diagram of hemostasis.	80
V	Platelet adhesion and aggregation.	83
VI	Model of platelet aggregation under laminar flow conditions.	85
VII	Aggregation under conditions of localized alterations in blood flow.	86
VIII	Picture of the classic coagulation cascade incorporating extrinsic and intrinsic pathways of coagulation.	91
IX	Schematic representation of the initiation and propagation of blood coagulation.	95
X	Clot formation at vascular injury site.	97
XI	The extrinsic and intrinsic pathways in the cell-based model of coagulation.	102
XII	Principal mediators of fibrinolysis.	104

XIII	Thrombin on an endothelial cell has antithrombotic function by activating protein C.	108
XIV	Thrombin generation & inhibition.	112-113
XV	A & B: Protein C Activation by Thrombin on the Membrane of Endothelial Cells. C: The balance of antihemostatic and prohemostatic drivers in the different phases of hemostasis in patients with chronic liver disease.	117-118
XVI	Fibrinolysis activation and inhibition.	122
1	Pie chart showing gender distribution among all the study subjects.	141
2	Pie chart showing gender distribution among patients group.	142
3	Number of subjects in control group & patients groups stratified according to the Child-Turcotte-Pugh score.	143
4	Bar chart showing the mean rank difference for Age (Years) for control group & patient groups stratified according to Child-Pugh Class.	144
5	Box plots of the distribution of values (median, lower, and upper quartile & outliers identified as dots) for Age (Years) for control group & patient groups stratified according to Child-Pugh class.	144

6	Bar chart showing gender distribution among the study groups.	145
7	Box plots of the distribution of values (median, lower, and upper quartile, and outliers identified as dots) for Factor VIII % for control group Vs all patients with cirrhosis.	153
8	Box plots of the distribution of values (median, lower, and upper quartile, and outliers identified as dots) for Protein C % for control group Vs all patients with cirrhosis.	154
9	Box plots of the distribution of values (median, lower, and upper quartile, and outliers identified as dots) for PICI % (protac induced coagulation inhibition percentage) for control group Vs all patients with cirrhosis.	155
10	Box plots of the distribution of values (median, lower, and upper quartile, and outliers identified as dots) for Factor VIII/Protein C ratio for control group Vs all patients with cirrhosis.	156
11	Box plots of the distribution of values (median, lower, and upper quartile, and outliers identified as dots) for prothrombin time for control group Vs all patients with cirrhosis.	157
12	Box plots of the distribution of values (median, lower, and upper quartile, and outliers identified as dots) for partial thromboplastin time for control group Vs all patients with cirrhosis.	158

13	Box plots of the distribution of values (median, lower, and upper quartile, and outliers identified as dots) for international normalization ratio for control group Vs all patients with cirrhosis.	159
14	Box plots of the distribution of values (median, lower, and upper quartile, and outliers identified as dots) for platelets count for control group Vs all patients with cirrhosis.	160
15	Bar chart showing the mean rank difference for factor VIII for control group & patient groups stratified according to Child-Pugh Class.	161
16	Box plots of the distribution of values (median, lower, and upper quartile & outliers identified as dots) for factor VIII for control group & patient groups stratified according to Child-Pugh class.	161
17	Bar chart showing the mean rank difference for Protein C % for control group & patient groups stratified according to Child-Pugh Class.	162
18	Box plots of the distribution of values (median, lower, and upper quartile & outliers identified as dots) for Protein C % for control group & patient groups stratified according to Child-Pugh class.	162
19	Bar chart showing the mean rank difference for PIC1% for control group & patient groups stratified according to Child-Pugh Class.	163

20	Box plots of the distribution of values (median, lower, and upper quartile & outliers identified as dots) for PICT% for control group & patient groups stratified according to Child-Pugh class.	163
21	Bar chart showing the mean rank difference for Factor VIII/Protein C ratio for control group & patient groups stratified according to Child-Pugh Class.	164
22	Box plots of the distribution of values (median, lower, and upper quartile & outliers identified as dots) for Factor VIII/Protein C ratio for control group & patient groups stratified according to Child-Pugh class.	164
23	Bar chart showing the mean rank difference for prothrombin time for control group & patient groups stratified according to Child-Pugh Class.	165
24	Box plots of the distribution of values (median, lower, and upper quartile & outliers identified as dots) for Factor prothrombin time for control group & patient groups stratified according to Child-Pugh class.	165
25	Bar chart showing the mean rank difference for partial thromboplastin time for control group & patient groups stratified according to Child-Pugh Class.	166
26	Box plots of the distribution of values (median, lower, and upper quartile & outliers identified as dots) for partial thromboplastin time for control group & patient groups stratified according to Child-Pugh class.	166

27	Bar chart showing the mean rank difference for (INR) international normalization ratio for control group & patient groups stratified according to Child-Pugh Class.	167
28	Box plots of the distribution of values (median, lower, and upper quartile & outliers identified as dots) for (INR) international normalization ratio for control group & patient groups stratified according to Child-Pugh class.	167
29	Bar chart showing the mean rank difference for platelet count for control group & patient groups stratified according to Child-Pugh Class.	168
30	Box plots of the distribution of values (median, lower, and upper quartile & outliers identified as dots) for platelet count for control group & patient groups stratified according to Child-Pugh class.	168
31	Bar chart showing bleeding events (including hematemesis & melena) distribution in patients Vs control group.	171
32	Bar chart showing bleeding events (including hematemesis & melena) distribution in control group Vs patient groups stratified according to Child-Pugh class.	172
33	Bar chart showing thromboembolic events (including portal vein thrombosis) distribution in patients Vs control group.	173
34	Bar chart showing thromboembolic events (including portal vein thrombosis) distribution in control group Vs patient groups stratified according to Child-Pugh class.	174

List of Abbreviations

AAA	: Aromatic Amino Acids.
Ab	: Antibody.
ADAMTS 13:	Disintegrin & metalloproteinase with thrombospondin type 1 motif 13.
ADP	: adenosine diphosphate.
ADPase	: Adenosine diphosphatase.
Ag	: Antigen.
AIH	: Autoimmune hepatitis.
ALD	: Alcoholic Liver Diseases.
ALP	: Alkaline phosphatase.
ALT	: Alanine aminotransferase.
aPC	: Activated Protein C.
aPTT	: Activated Partial thromboplastin time.
AST	: Aspartate aminotransferase.
AT	: Antithrombin.
ATP	: Adenosine triphosphate.
BCAA	: Branched chain amino acids.
BUN	: Blood urea nitrogen.
cAMP	: Cyclic adenosine monophosphate.
CD39	: Cluster of differentiation 39.
CLD	: Chronic liver disease.
CO	: Carbon monoxide.
COAT	: <u>C</u> ollagen <u>A</u> nd <u>T</u> hrombin stimulated.
COX	: Cyclooxygenase.
CP classification	: Child-Pugh classification.
CT	: Computed tomography.
CTP score	: Child-Turcotte-Pugh score.
CVS	: Cerebrovascular stroke.
DB	: Direct bilirubin.
DM	: Diabetes Mellitus.
DNA	: Deoxyribonucleic acid.
DVT	: Deep venous thrombosis.
ECM	: Extracellular matrix.