ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

DISSIMINATED INTRAVASCULAR COAGULATION IN CHRONIC LIVER DISEASE AND ITS IMPACT ON ACUTE VARICEAL BLLEDING

Hassan M.A. ELSanhoty.,[1] Mahmoud A. Ashour.,[1] Mohamed Z. Hafez.,[1] Mohamed H. Ibrahim.,[1] Asmaa M.H. Esh.[2] , Soumaia A. M. Kassem.[1]

1. Internal Medicine Department **(**Gastroenterology & Hepatology unit) Faculty of Medicine, Zagazig University, Egypt.

2. Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt.

Manuscript Info

Manuscript History:

Received: 14 October 2015
Final Accepted: 22 November 2015
Published Online: December 2015

Key words:

Disseminated intravascular coagulation; chronic liver disease; Varecial bleeding; Acute; Impact.

Corresponding Author

Hassan M.A. ELSanhoty

Abstract

The liver plays a central role in the maintenance of haemostasis as the site of protein synthesis required for regulation of coagulation and fibrinolysis. So, impairment of liver parenchymal cell function can disturb haemostasis resulting in the development of multiple coagulation abnormalities. Disseminated intravascular coagulation (DIC) is characterized by activation of the clotting cascade by a magnitude overpowering the anticoagulation pathway, resulting in widespread intravascular fibrin deposition and ultimately, arterial or venous thrombosis and multiorgan failure Disseminated intravascular coagulation in patients with liver disease involves multiple triggering mechanisms. **Patients & Methods:** 60 patients with chronic liver disease were classified into two main groups : group I 30 patient non bleeder and group II 30 patient presented by haemetemesis and / or melena precipitated by endoscopically evident oesophageal variceal rupture each group subdivided according to Child's–Pugh classification into A,B &C. laboratory investigation and clinical evaluation were done then calculation of DIC score according to international society of thrombosis and haemostasis (ISTH) Diagnostic Scoring System for DIC. **Results:** Combined HCV&HBV represent 52.4%among child class C. As regard to DM no significant differences but there was significant association between hypertension and child class A, 50%of patients in child class A were hypertensive. Significant association between portal vein thrombosis in bleeder group and increasing child class, 7 patients had PVT were child class C. By ANOVA significant association between increasing child class and decrease platelet count, increase fibrinogen, prolongation of PT, and DIC **Conclusion: DIC** correlated with advanced cirrhosis with increasing Child's–Pugh score from A to C.

INTRODUCTION

Hemostasis enables the body to 1) close off damaged blood vessels, 2) keep the blood in a fluid state, and 3) remove blood clots after restoration of vascular integrity**[1].** Hemostasis can be devided into primary hemostasis, secondary hemostasis, and fibrinolysis **[2].**

The liver plays a central role in the maintenance of haemostasis as the site of synthesis for the vast majority of proteins required for regulation of coagulation and fibrinolysis**.** So, impairment of liver parenchymal cell function can disturb haemostasis resulting in the development of multiple coagulation abnormalities that can predispose the

patient to bleeding or thrombosis formation. **[3]** Liver disease is associated with a variety of haemostatic abnormalities that disrupt the delicate balance between clotting and fibrinolysis **[4]**. Haemostatic abnormalities in liver disease include decrease in clotting factors syntheses, excessive fibrinolysis, thrombocytopenia**,** platelet function defect, DIC and thrombosis. [5-8]

DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes leading to damage the microvasculature, which if sufficiently severe, can produce organ dysfunction. DIC occurs secondary to sepsis, trauma, malignancy, liver disease, obstetric disorders, envenomation, vascular anomalies and major transfusion reactions. **[9]** Common laboratory features of DIC include low platelet count, prolonged PT, prolonged thrombin time, decreased fibrinogen concentration, and elevation of D-dimer. **[10]**

The ISTH Sub-Committee of the Scientific and Standardization Committee (SSC) has recommended the use of scoring system based on the Japanese Ministry of Health and Welfare score a cumulative score of five or more from prolonged PT, reduced platelets and fibrinogen, and elevated fibrin related markers (e.g. D-dimer or FDP) was proposed. **[11-12]**

This study is designed to evaluate the possible association between DIC and chronic liver disease and the impact of DIC on acute variceal bleeding.

Patients and methods

This work has been carried out in Internal Medicine Department, Gastroenterology and Hepatology Unit, Faculty of Medicine, Zagazig University Hospital during the period from March 2013 to March 2014.

The study included 60 patients of chronic liver disease (child A, B & C) group I: 30patient non bleeder taken from out patient clinic(19 male and 11 female) with age ranged from 40 to 59 years, that group was subdivided into three subgroups (A,B,and C) according to Child- Pugh classification.GroupII:30patient (19 males and 11 females) their age ranged from 40 to 59 years presented by haemetemesis and / or melena precipitated by endoscopically evident oesophageal variceal rupture taken from intensive care unite, subdivided into (A,B,and C) according to Child- Pugh classification. Patients were selected according to the following criteria:

Inclusion criteria all patients with chronic liver disease in which no criteria of exclusion.

Exclusion criteria

- recent trauma or surgical intervention for at least 2 weeks prior to the study. Patients undergo any diagnostic or therapeutic invasive procedures for at least 2 weeks prior to the study.
- Patients receive blood or any blood component therapy for at least 2 weeks prior to the study.
- history of taken drugs, which have any effect on haemostasis for at least 2 weeks prior to the study.
- Acute hepatic failure.
- Cirrhotic patients with malignant liver.
- Hepatic patients with renal impairment.
- Severe infection & sepsis.

Written consents were taken from all patients included in the study

Methods : All subjects of the study were subjected to

A- Thorough history and full clinical examination:

According to the included work sheet with special emphasis on

History of upper GIT bleeding, hepatic encephalopathy or ascites

History of infection ,sepses ,blood transfusion,invasive procedure or any drug affecting coagulation

History of DM or hypertension

B- Routine investigations:

I-Laboratory investigations They were all done according to the methods applied in the laboratories of zagazig university hospitals and included:

1- Complete blood picture (by automated blood counter).
2- Liver function tests: serum bilirubin (total and direct), serum albumin, serum ALT and AST measured by kinetic method
3- Renal function tests: serum creatinine , urea .
4- coagulation profile : PT,PTT and INR.
5- alfa fetoprotein
6-Ascetic fluid sample for total and differential WBCs**,**glucose and protein**.**
7-HCV Ab\HBsAg
II-Pelvi- abdominal ultrasound for all patients at radiology department zagazig university hospitals**.**

C- Special Investigation : included
1-D-DIMER.
2-FIBRONGEN.
3- Upper GIT endoscopey: in groupII (Oesphageal varices, gastric varices or portal hypertensive gastropathy).
4-Diagnosis of liver cirrhosis : was done by physical signs, laboratory and ultrasound findings and severity of the liver disease was scored according to Child–Pugh's classification.
5-Confermation for diagnosis of portal vein thrombosis in sussibtable patients : was done by doppler ultrasound in all patients and contrast enhanced triphasic CT in some cases(to exclude HCC)
6-Exclusion of hepatocellularr cacinoma: was done by abdominal ultrasound, contrast enhanced triphasic CT and alpha fetoprotein .
7- diagnosis of DIC according to ISTH
Score the test results
• Platelet count (>100 ×109/l = 0, <100 × 109/l = 1,<50 × 109/l = 2)
• Elevated fibrin marker (e.g. D-dimer, fibrin degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)
• Prolonged PT (<3 s = 0, >3 but <6 s = 1, >6 s = 2)
• Fibrinogen level (>1 g/l = 0, <1 g/l = 1)
Calculate score:
≥5 compatible with overt DIC

Statistical analysis:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis.

Results:

Table (1): describes demographic data of the studied groups and it demonstrates that no significant differences among the groups as regard to sex (p > 0.05), Total female represent 36.7%, male 63.3% .Table (2,3): Co morbidities in the studied groups as regard to D.M and hypertension it demonstrates that no significant in both groups as regard to DM. and HTN association (P>0.05). In group I DM represent 50%, hypertension 26.7% and in group II DM 36.7%, hypertension 33.3% .Table (4): describes HE in the studied groups, it demonstrates that no significant difference as regard to HE in the studied groups (P > 0.05) in group I 16.7%of patients have history of hepatic encephalopathy, 16.7% were in hepatic encephalopathy and 66.6 were normal, in group II the results was 16.7 %, 10% and 73.3% respectively. Table (5): etiology of chronic liver disease in the studied groups it demonstrates that no significant difference between both groups as regard to etiology (P > 0.05). In group I HBV represents 20%, HCV 65.7% combined B&C23.3%. In group II the results was13.3%,60% &26.7% respectively . Table (6-10): describes U.S data in the studed groupes as regard to liver appearance, spleen size, ascits and abscenc of focal lesion demonstrate that no significant difference in both group (P > 0.05). But as regard to portal vein thrombosis in the bleeder group there was significant difference in bleeder group. In group I(70%cirrhotic, 30%early cirrhotic ,marked acites 20%,mild acites 33.3%modrat acites 16.7% &no acites 30%) , in group II(73.3% ,26.7% ,30% ,30% ,0.0%&40%) respectively .portal vein thrombosis represents 23.3% in group II confermed by Doppler U.S&triphasic CT without underlying focal lesion . In both group focal lesion was excluded by alpha feto protein and CT. As regard endoscopic findings represented in Table (11): grade I OV 36.7% grade II OV 63.3%.

Table (12): represents laboratory data in both groups, it demonstrates that no significant difference except in reduction in hemoglobin level in bleeder group. Table (13): demonstrates that's group I contanting 8 Child A, 11 Child B and 11 Child C. Group II containing 8 Child A, 12 Child B and 10 Child C. there is no significant differences among studied groups. Table (14): sex in relation to child class no significant association. Table (15-16) diabetes and hypertension in relation to child class among the studied groups as regard to DM no significant differences but there was significant association between hypertension and child class A, 50% of patients in child class A were hypertensive . Table (17): significant association of combined etiology of hepatitis B and C in relation to increasing child class combined HCV&HBV represent 52.4% among child class C. Table (18-19): significant association between portal vein thrombosis in bleeder group and increasing child class, 7 patients had PVT were child class C. Table (20): Significant association between OV grades and increasing child class. By ANOVA significant association between increasing child class and decrease platelet count, increase fibrinogen, prolongation of PT, and DIC.

Table (1): Demographic data of studied groups as regard to sex.

Crosstab

			Group		**Total**		
			I	II		X^2	P
Sex	**f**	Count	11	11	22		
		% within sample	36.7%	36.7%	36.7%		
	m	Count	19	19	38	0.00	1.00
		% within sample	63.3%	63.3%	63.3%		
Total		Count	30	30	60		
		% within sample	100.0%	100.0%	100.0%		

Table (1): describes demographic data of the studied groups and it demonstrates that no significant differences among the groups as regard to sex ($p > 0.05$).

Table (2-3): Comorbiditis in the studid groups as regard to D.M and hypertension

Table (2): D.M in the studied groups.

Crosstab

			Group		**Total**		
			I	**II**			
DM	**-ve**	Count	15	11	26		
		% within sample	50.0%	36.7%	43.3%		
	+ve	Count	15	19	34	1.08	0.29
		% within sample	50.0%	63.3%	56.7%		
Total		Count	30	30	60		
		% within sample	100.0%	100.0%	100.0%		

Table (3): Hypertension in the studied groups.

Crosstab

			Group		Total		
			I	II			
HTN	-ve	Count	22	20	42		
		% within sample	73.3%	66.7%	70.0%		
	+ve	Count	8	10	18	0.31	0.57
		% within sample	26.7%	33.3%	30.0%		
Total		Count	30	30	60		
		% within sample	100.0%	100.0%	100.0%		

Table (2,3) :- demonstrates that no significant in both groups to DM. HTN association (P>0.05)

Table (4): describes HE in the studied groups.

Crosstab

			Group		**Total**		
			I	II			
HE	**History**	Count	5	5	10		
		% within sample	16.7%	16.7%	16.7%		
	No	Count	20	22	42	0.59	0.74
		% within sample	66.6%	73.3%	70.0%		
	Present	Count	5	3	8		
		% within sample	16.7%	10.0%	13.3%		
Total		Count	30	30	60		
		% within sample	100.0%	100.0%	100.0%		

Table (4) no significant difference as regard to HE in the studied groups. (P >0.05)

Table (5): etiology of chronic liver disease in the studied groups.

Crosstab

			Group		Total		
			I	II			
Virology	B	Count	6	4	10		
		% within sample	20.0%	13.3%	16.7%		
	B\C	Count	7	8	15	0.49	0.78
		% within sample	23.3%	26.7%	25.0%		
	C	Count	17	18	35		
		% within sample	56.7%	60.0%	58.3%		
Total		Count	30	30	60		
		% within sample	100.0%	100.0%	100.0%		

Table (5) describes etiology of chronic liver disease among both groups there are no significant difference between both groups as regard to etiology (P > 0.05).

Table (6-10): ultrasonographic data in the studied groups.

Table (6) Liver appearance in the studied groups

Crosstab

		Group		Total		
		I	**II**			
li cirrhotic	Count	21	22	43		
	% within sample	70.0%	73.3%	71.7%		
Early cirrhosis	Count	9	8	17	0.08	0.77
	% within sample	30.0%	26.7%	28.3%		
Total	Count	30	30	60		
	% within sample	100.0%	100.0%	100.0%		

Table (7): Spleen size in the studied groups.

Crosstab

			Group		Total
			I	II	
spleen	**Enlarged**	Count	30	30	60
		% within sample	100.0%	100.0%	100.0%
Total		Count	30	30	60
		% within sample	100.0%	100.0%	100.0%

Table (8): Portal vein patency in the studied groups

Crosstab

			Group		Total		
			I	**II**			
PV	**Patent**	Count	30	23	48		
		% within sample	100.0%	76.6%	80.0%		
	thrombosis	Count	0	7	12	7.9	0.005
		% within sample	0.0%	23.3%	20.0%		
Total		Count	30	30	60		
		% within sample	100.0%	100.0%	100.0%		

Table (9): ascites in the studied groups.

Crosstab

			Group		Total		
			I	II			
Ascites	Marked	Count	**6**	**9**	**15**		
		% within sample	**20.0%**	**30.0%**	**25.0%**		
	Mild	Count	**10**	**9**	**19**		
		% within sample	**33.3%**	**30.0%**	**31.7%**		
	Mod	Count	**5**	**0**	**5**	**6.08**	**0.108**
		% within sample	**16.7%**	**0.0%**	**8.3%**		
	No	Count	**9**	**12**	**21**		
		% within sample	**30.0%**	**40.0%**	**35.0%**		
Total		Count	**30**	**30**	**60**		
		% within sample	**100.0%**	**100.0%**	**100.0%**		

Table (10): focal lesion in the studied groups.

Crosstab

			Group		Total
			I	II	
fl	**No**	Count	30	30	60
		% within sample	100.0%	100.0%	100.0%
Total		Count	30	30	60
		% within sample	100.0%	100.0%	100.0%

Table (6-10): describes U.S data in the studed groupes as regard to liver appearance, spleen size, ascits and abscence of focal lesion, demonstrate that no significant difference in both the group as regard to U.S data (P > 0.05). but as regard to portal vein thrombosis in the bleeder group there was significant difference in bleeder group.

Table (8 a): Conformation of PV Thrombonsis in the studied groups.

Crosstab

			Group		Total		
			I	II			
Dopller pv	NO	Count	**30**	**23**	**53**		
		% within sample	**100.0%**	**76.7%**	**88.3%**		
	thromb	Count	**0**	**7**	**7**	**7.92**	**0.005****
		% within sample	**0.0%**	**23.3%**	**11.7%**		
Total		Count	**30**	**30**	**60**		
		% within sample	**100.0%**	**100.0%**	**100.0%**		

Table (8 a): demonstrate significant association between PV thrombonsis in group II (P< 0.05)

Table (10 a): exclusion of FL by triphasic CT in the studied groups.

Crosstab

			Group		Total		
			I	II			
ct	NO	Count	**30**	**23**	**53**		
		% within sample	**100.0%**	**76.7%**	**88.3%**		
	Pvt \ nof.l	Count	**0**	**7**	**7**	**7.92**	**0.005***
		% within sample	**0.0%**	**23.3%**	**11.7%**		
Total		Count	**30**	**30**	**60**		
		% within sample	**100.0%**	**100.0%**	**100.0%**		

Table (10 a): demonstrates no significant differences among studied group as regard to abscence focal lesion.

Table (11): OV grads in group II (bleeder group).

			Total
			II
OV	**I**	Count	11
		% within sample	36.7%
	II	Count	19
		% within sample	63.3%
Total		Count	30
		% within sample	100.0%

Table (12): Labolatory data in the studed groups.

	group	N	Mean	Std. Deviation	t	P
Age	I	**30**	**50.7000**	**6.07510**	**1.791**	**0.078**
	II	**30**	**48.0667**	**5.28455**		
BIL	I	**30**	**2.5767**	**1.14972**	**0.643**	**0.523**
	II	**30**	**2.4067**	**.88198**		
ALB	I	**30**	**3.0577**	**.40431**	**1.781**	**0.080**
	II	**30**	**2.8987**	**.27509**		
ALT	I	**30**	**38.1000**	**12.16935**	**-1.435**	**0.157**
	II	**30**	**42.6000**	**12.11326**		
AST	I	**30**	**42.7333**	**11.71481**	**-1.194**	**0.237**
	II	**30**	**46.2667**	**11.20016**		
TLC	I	**30**	**4.6600**	**1.16814**	**-0.048**	**0.962**
	II	**30**	**4.6733**	**.99479**		
HB	I	**30**	**10.2867**	**1.18721**	**10.064**	**0.00****
	II	**30**	**7.4000**	**1.02889**		
Plat	I	**30**	**89.7000**	**46.02334**	**1.014**	**0.315**
	II	**30**	**80.0333**	**24.68070**		
Cr	I	**30**	**.74**	**.214**	**-2.220**	**0.030***
	II	**30**	**.85**	**.153**		
AFP	I	**30**	**23.9000**	**10.15178**	**-1.773**	**0.081**
	II	**30**	**31.6333**	**21.62770**		
PT	I	**30**	**18.1000**	**2.00603**	**-0.887**	**0.378**
	II	**30**	**18.5667**	**2.06670**		

INR	I	**30**	**1.7700**	**.21679**	**0.194**	**0.847**
	II	**30**	**1.7600**	**.18132**		
PTT	I	**30**	**38.4667**	**2.55604**	**-1.500**	**0.139**
	II	**30**	**39.5000**	**2.77613**		
plet2	I	**30**	**89.7000**	**46.02334**	**1.014**	**0.315**
	II	**30**	**80.0333**	**24.68070**		
Fibrinogen	I	**30**	**1.2040**	**.53366**	**0.082**	**0.935**
	II	**30**	**1.1873**	**.98050**		
Child	I	**30**	**9.00**	**2.936**	**0.174**	**0.863**
	II	**30**	**8.87**	**3.003**		
DIC	I	**30**	**4.6333**	**2.26645**	**-0.803**	**0.425**
	II	**30**	**5.1000**	**2.23375**		

Table (12) : labotratory data in the studied groups demenostrates that no significant differences between groups except in haemoglobin (HB).

Table (13): Child class in the studied groups.

Crosstab

			Child class			Total		
			A	B	C		X^2	P
sample	I	Count	8	11	11	30		
		% within Childclass	50.0%	47.8%	52.4%	50.0%		
	II	Count	8	12	10	30	0.091	0.95
		% within Childclass	50.0%	52.2%	47.6%	50.0%		
Total		Count	16	23	21	60		
		% within Childclass	100.0%	100.0%	100.0%	100.0%		

Table (13): demonstrates there is no significant difference among studied groups.

Table (14): sex in relation to child class among the studied groups.

Crosstab

			Child class			Total		
			A	B	C		X^2	P
Sex	F	Count	**7**	**7**	**8**	**22**		
		% within Childclass	**43.8%**	**30.4%**	**38.1%**	**36.7%**		
	M	Count	**9**	**16**	**13**	**38**	**0.74**	**0.68**
		% within Childclass	**56.2%**	**69.6%**	**61.9%**	**63.3%**		
Total		Count	**16**	**23**	**21**	**60**		
		% within Childclass	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

Table (14): No significant difference.

DM * Childclass

Tabel (15): DM in relation to child class in the studied groups.

Crosstab

			Child class			Total		
			A	B	C		X^2	P
DM	NO	Count	**8**	**11**	**7**	**26**		
		% within Childclass	**50.0%**	**47.8%**	**33.3%**	**43.3%**		
	DM	Count	**8**	**12**	**14**	**34**	**1.33**	**0.51**
		% within Childclass	**50.0%**	**52.2%**	**66.7%**	**56.7%**		
Total		Count	**16**	**23**	**21**	**60**		
		% within Childclass	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

Table (15): No significant difference.

Table (16): hypertension in relation to child class in the studied groups.

Crosstab

			Child class			Total		
			A	B	C		X^2	P
HTN	NO	Count	**8**	**20**	**14**	**42**		
		% within Childclass	**50.0%**	**87.0%**	**66.7%**	**70.0%**		
	HTN	Count	**8**	**3**	**7**	**18**	**6.3**	**0.04***
		% within Childclass	**50.0%**	**13.0%**	**33.3%**	**30.0%**		
Total		Count	**16**	**23**	**21**	**60**		
		% within Childclass	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

Table (16) significant difference in the presence of hypertension in child A among the studed groups.

Table (17): etiology of chronic liver disease in relation to child class among the studied groups.

Crosstab

			Child class			Total		
			A	B	C		X^2	P
Virology	B	Count	**4**	**3**	**3**	**10**		
		% within Childclass	**25.0%**	**13.0%**	**14.3%**	**16.7%**		
	B\C	Count	**0**	**4**	**11**	**15**	**15.25**	**0.004***
		% within Childclass	**0.0%**	**17.4%**	**52.4%**	**25.0%**		
	C	Count	**12**	**16**	**7**	**35**		
		% within Childclass	**75.0%**	**69.6%**	**33.3%**	**58.3%**		
Total		Count	**16**	**23**	**21**	**60**		
		% within Childclass	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

Table (17): significant association of combined etiology of hepatitis B and C in relation to increasing child class.

Table (18 -19): Conformation portal vein thrombosis by Doppler &CT in relation to child class

Tiph ct pvt * Child class

Crosstab

			Child class			Total		
			A	B	C		X^2	P
Tiph ct	No	Count	**16**	**23**	**14**	**53**		
		% within Childclass	**100.0%**	**100.0%**	**66.7%**	**88.3%**		
	PV no f.l	Count	**0**	**0**	**7**	**7**	**14.71**	**0.001****
		% within Childclass	**0.0%**	**0.0%**	**33.3%**	**11.7%**		
Total		Count	**16**	**23**	**21**	**60**		
		% within Childclass	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

Table (20): OV grades in relation to child class among the studied groups.

Crosstab

			Child class			Total		
			A	B	C		X^2	P
OV	No	Count	**8**	**11**	**11**	**30**		
		% within Childclass	**50.0%**	**47.8%**	**52.4%**	**50.0%**		
	I	Count	**2**	**9**	**0**	**11**	**13.99**	**0.007***
		% within Childclass	**12.5%**	**39.1%**	**0.0%**	**18.3%**		
	II OR MORE	Count	**6**	**3**	**10**	**19**		
		% within Childclass	**37.5%**	**13.0%**	**47.6%**	**31.7%**		
Total		Count	**16**	**23**	**21**	**60**		
		% within Childclass	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

Table (20): Significant association between OV grades and child class

Table (21): ANOVA

	Child	N	Mean	Std. Deviation	Minimum	Maximum	F	P
Age	A	**16**	**47.0000**	**4.99333**	**40.00**	**55.00**	**1.967**	**0.149**
	B	**23**	**49.9565**	**6.04136**	**40.00**	**59.00**		
	C	**21**	**50.5714**	**5.82728**	**40.00**	**59.00**		
BIL	A	**16**	**1.8437**	**.38982**	**1.40**	**2.90**	**88.842**	**0.00****
	B	**23**	**1.8478**	**.09941**	**1.60**	**2.00**		
	C	**21**	**3.6905***	**.78734**	**2.80**	**6.00**		
ALB	A	**16**	**3.3831**	**.26479**	**2.90**	**3.70**	**61.522**	**0.00****
	B	**23**	**3.0026**	**.22079**	**2.80**	**3.60**		
	C	**21**	**2.6429**	**.09783**	**2.50**	**2.80**		
ALT	A	**16**	**40.1875**	**7.35952**	**30.00**	**59.00**	**0.041**	**0.960**
	B	**23**	**40.9130**	**13.16991**	**22.00**	**60.00**		

	C	**21**	**39.8571**	**14.51305**	**19.00**	**70.00**		
AST	A	**16**	**45.6250**	**7.05100**	**35.00**	**60.00**	**0.496**	**.612**
	B	**23**	**42.6087**	**9.58094**	**30.00**	**66.00**		
	C	**21**	**45.7143**	**15.66251**	**20.00**	**69.00**		
TLC	A	**16**	**5.3188#**	**1.49631**	**2.00**	**8.00**	**6.799**	**0.002***
	B	**23**	**4.7130**	**.81704**	**3.90**	**7.00**		
	C	**21**	**4.1190#**	**.58534**	**3.00**	**5.00**		
HB	A	**16**	**9.8875#**	**1.79067**	**7.00**	**12.00**	**5.486**	**0.007***
	B	**23**	**8.8696**	**1.78133**	**6.00**	**11.00**		
	C	**21**	**8.0190#**	**1.53187**	**5.00**	**10.00**		
Plat	A	**16**	**134.7500**	**27.46270**	**90.00**	**180.00**	**96.769**	**0.00****
	B	**23**	**79.5217**	**9.70412**	**60.00**	**99.00**		
	C	**21**	**52.7143**	**15.69759**	**29.00**	**80.00**		
CR	A	**16**	**0.74**	**0.213**	**0**	**1**	**1.137**	**0.328**
	B	**23**	**0.83**	**0.194**	**0**	**1**		
	C	**21**	**0.80**	**0.172**	**1**	**1**		
AFP	A	**16**	**11.5000**	**3.55903**	**7.00**	**17.00**	**59.130**	**0.00****
	B	**23**	**22.5217**	**5.54215**	**12.00**	**39.00**		
	C	**21**	**45.9048**	**15.50776**	**25.00**	**77.00**		
PT	A	**16**	**15.5625***	**.89209**	**14.00**	**17.00**	**62.626**	**0.00****
	B	**23**	**19.3043**	**1.25896**	**18.00**	**22.00**		
	C	**21**	**19.3810**	**1.21352**	**18.00**	**22.00**		
INR	A	**16**	**1.4750***	**.10646**	**1.30**	**1.60**	**109.538**	**0.00****
	B	**23**	**1.8609**	**.07223**	**1.70**	**2.00**		
	C	**21**	**1.8810**	**.09843**	**1.71**	**2.00**		
PTT	A	**16**	**35.8750***	**1.66833**	**34.00**	**39.00**	**28.926**	**0.00****
	B	**23**	**39.7826**	**2.39235**	**38.00**	**49.00**		
	C	**21**	**40.4762**	**1.50396**	**38.00**	**43.00**		
PLET2	A	**16**	**134.7500**	**27.46270**	**90.00**	**180.00**	**96.769**	**0.00****
	B	**23**	**79.5217**	**9.70412**	**60.00**	**99.00**		
	C	**21**	**52.7143**	**15.69759**	**29.00**	**80.00**		
Fibrinogen	A	**16**	**2.0544***	**.83727**	**1.20**	**3.50**	**23.409**	**0.00****
	B	**23**	**.9496**	**.40911**	**.32**	**1.70**		
	C	**21**	**.8110**	**.53135**	**.31**	**2.27**		
Child	A	**16**	**5.69**	**.479**	**5**	**6**	**343.655**	**0.00****
	B	**23**	**7.87**	**.694**	**7**	**9**		
	C	**21**	**12.57**	**1.121**	**11**	**14**		
DIC	A	**16**	**1.6875**	**1.13835**	**.00**	**4.00**	**107.710**	**0.00****
	B	**23**	**5.4783**	**1.12288**	**4.00**	**7.00**		
	C	**21**	**6.6190**	**.86465**	**5.00**	**8.00**		

* Significant difference

** high significant difference

By LSD

* group cause the significance

sig is only between these group

Table (21): Significant association between DIC, increasing INR, prolonged PT, decrease PL, decrease fibrinogen and increasing D. Dimer in relation to increasing child class among the studied groups.

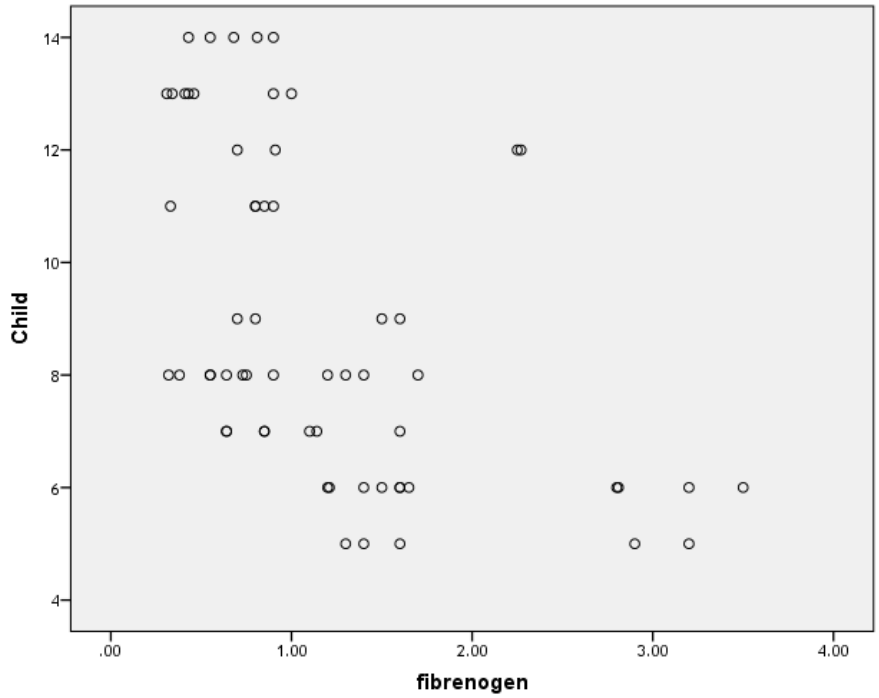

Fig 1 fibrinogen in relation to child class

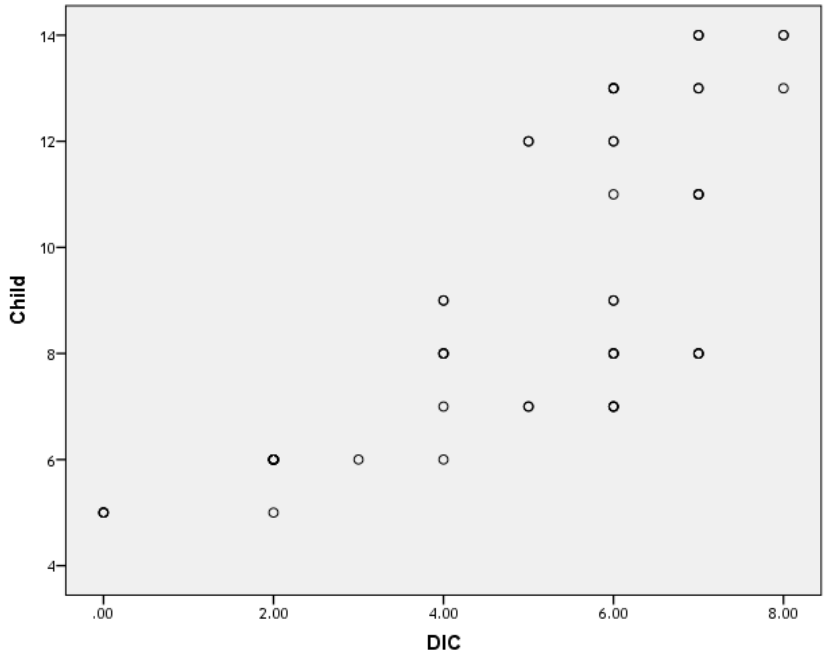

Fig 2 DIC in relation to child class

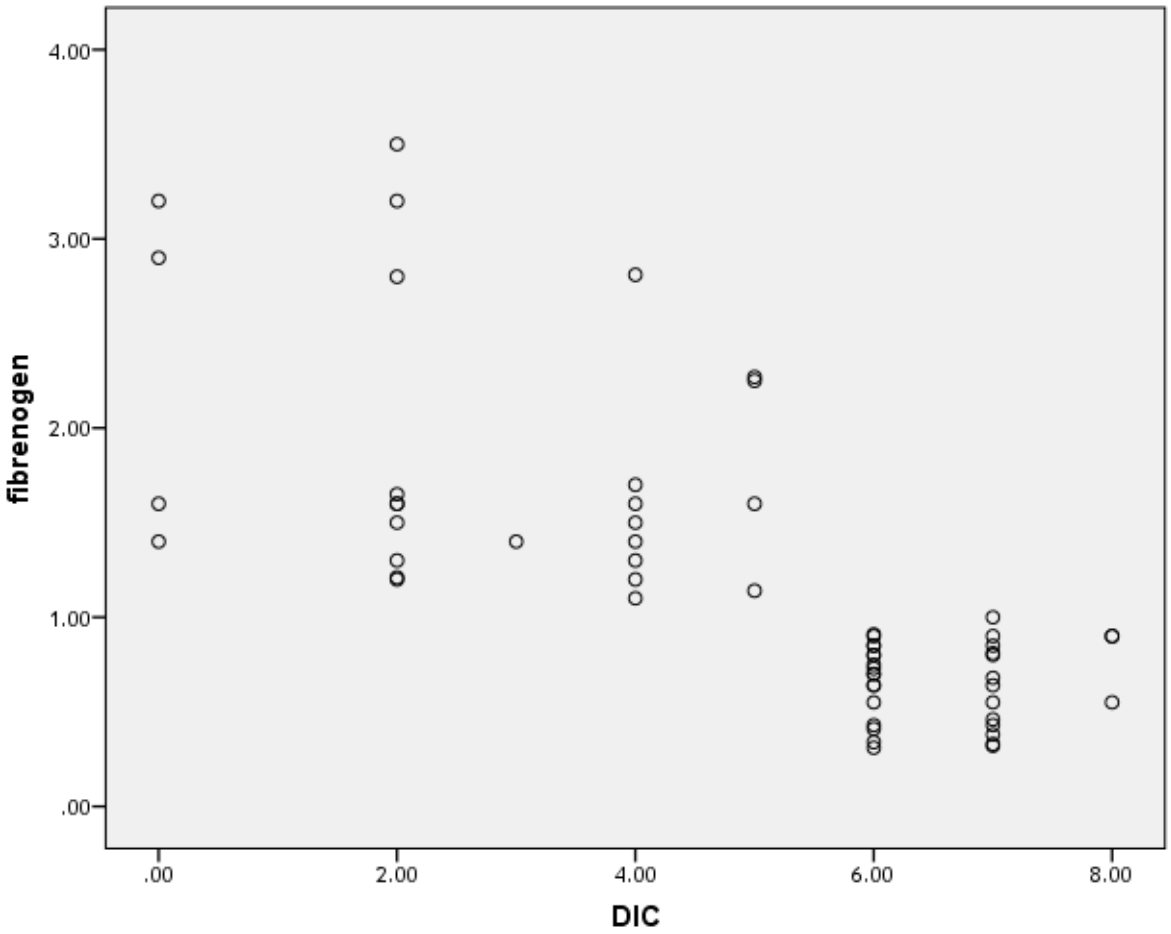

Fig 3 DIC in relation to fibrinogen

Discussion:

The liver has many haemostatic functions, including the synthesis of most coagulation factors and inhibitors as well as fibrinolytic factors .The balance between procoagulant and anticoagulant factors is essential to prevent excessive blood loss from injured vessels and to prevent spontaneous thrombosis **(13).** Thus, the global effect of liver disease with regard to hemostasis is complex, so that patients with advanced liver disease can experience severe bleeding or even thrombotic complications. **(14).**Haemostatic abnormalities in liver disease include decrease in clotting factors syntheses, excessive fibrinolysis, thrombocytopenia**,** platelet function defect, DIC and thrombosis **(6).** Analysis of the results of our study revealed that significant association between prolongation of prothrombin time and advanced child class from (A to C), that was found in many previous studies such as described in **Deitcher,(2002)(15) ,Kerr,(2003)(16) ,Hollestelle et al., (2004)(17) &Tacke et al.,(2006)**(5). As the liver is the primary source for most of the coagulation factors, circulating levels of these factors can be significantly reduced in patients with chronic liver disease who have extensive hepatocellular damage **(5).**

In our results there was reduction in fibrinogen level with increasing child class from (A to C) this was described in **Tacke et al., (2006)(5)** but other studies revealed that Plasma fibrinogen levels generally remain normal or elevated in patients with chronic liver disease although the presence of severe fibrosis (Child-Pugh grade C) may be associated with decreased levels as described in **Rodrıguez-Inigo et al, (2001)(18).**

In our results there was significant association between increasing D-dimer level and elevation of child score from (A toC) due to hyperfibrinolysis, results from an imbalance between activators and inhibitors of fibrinolysis. The levels of tissue plasminogen activator (tPA) are elevated because of reduced hepatic clearance, whereas the levels of plasminogen activator inhibitor-1 (PAI-1) do not respond appropriately to the changes in tPA level, change the balance between tPA and PAI-1 activity levels towards excessive tPA activity in patients with severe cirrhosis. Also, activity levels of the anti-fibrinolytic proteins, a2-antiplasmin and thrombin activatable fibrinolysis inhibitor, are reduced as a result of substantial liver damage, causing a further shift towards increased fibrinolysis, As described in **Hu K-Q et al.,(2001) (19), Agarwal et al., (2000)(20)&Colucci et al., (2003)(6)**.

In our results there was significant association between low platelet count and increasing child score from (A to C) that was described in many previous studies as **Peck-Radosavljevic, (2000)(21) , Iga et al., (2005) (22)&Tacke et al., (2006)** (5). Abnormalities in both platelet number and platelet function are common in chronic liver disease due to reduction in thrombopoietin level, hypersplenism related to portal hypertension or bone marrow suppression by hepatitis C virus or interferon antiviral treatment, and increased platelet destruction mediated by immune mechanisms involving anti-platelet auto antibodies and platelet-associated immune complexes (**Doi et al., 2002)**(23) .

Thrombocytopenia is associated with other coagulation abnormalities (including decreased fibrinogen level, decreased activity of coagulation factors, and increased fibrinolytic activity), and together, these abnormalities may synergistically increase the risk of bleeding in patients with cirrhotic liver disease **(5).**

As regard DIC score in our study which calculated according to (ISTH) depending on (PT , fibrinogen level, platelet count&D dimer) it was found that Significant association between DIC, prolongation PT decrease platelet count , decrease fibrinogen level and increasing child class among the studied groups that was also described by **Levi et al (2009)(24), Wada et al (2010)(25),Di -Nisio et al (2012)(26)&Wada et al (2013)(27).**

But **Ben-Ari et al (1999)**(28) was found that DIC and decompensated cirrhosis share similar haemostatic abnormalities, (i.e., elevated prothrombin, decreased fibrinogen, increased D-dimers, elevated fibrin degradation products, and thrombocytopenia), so the diagnosis of DIC is difficult, and there is some debate about whether DIC is a coagulation disorder in cirrhosis.

With the recent availability of assays that allow quantitative determination of proteolytic cleavage products of coagulation reactions (including fibrinopeptide A, prothrombin fragment, thrombin-antithrombin and plasmin-a2-antiplasmin complexes, soluble fibrin, and D-dimer), accelerated intravascular coagulation and fibrinolysis (AICF) can now be detected in patients with liver cirrhosis. The term DIC is used predominantly for decompensated AICF. Studies have detected AICF in less than 30% of patients with cirrhosis, and the extent of AICF appears to correlate

with the severity of cirrhosis (Child-Pugh grade). However, AICF does not appear to be common in patients with stable, uncomplicated, non-advanced liver cirrhosis (8).

Portal vein thrombosis (PVT) is an important complication of liver cirrhosis. Its reported incidence in compensated disease is between 0.6% and 5%, but becomes much higher (up to 25%) in advanced disease as described by **Garcia et al.,(2008)(29).** That matched with our results in which PVT represent 33.3% in advanced cirrhosis .

Hepatocellular carcinoma is the most frequent cause of PVT in cirrhosis, being present in up to 44% of cases, and always it has to be searched when a new diagnosis of PVT is made as described by **Huseyin et al., (2011)**(30) In our results 7 patients from the bleeder group 23.3% had PVTwithout underlying HCC or sepsis ,so we recommend further assessment to exlud other causes as protein C,protein S levels.

Chronic PVT can be nearly asymptomatic and incidentally detected following a routine imaging procedure. Patients with chronic PVT present with portal hypertension related complications like oesphageal varices, splenomegaly, anaemia and thrombocytopenia as described by **Hoekstra and Janssen , (2009)(31).** that could explain PVT among bleeder group which founded in our results.

Variceal bleeding is one of the most common bleeding events experienced by patients with advanced liver disease. Patients with cirrhosis will experience the development of varices at a rate of about 8% per year after the onset of cirrhosis. **(Groszmann et al., 2005)(32)** Once formed, risk factors for bleeding are predominantly related to hemodynamic and mechanical parameters such as hepatic vein– portal pressure gradient, varix size, their appearance (red marks and purple color), and the severity of the underlying liver disease Aside from the relationship to severity, there have been few data to support that coagulopathy is directly related to variceal bleeding risk, although increased markers of fibrinolysis were predictive of eventual variceal bleeding. However, this relationship may reflect worsening portal pressure rather than the direct effect of fibrinolysis. In addition the existence of the platelet plug (nipple sign) as a high-risk marker for variceal bleeding indicates at least some transient role of primary hemostasis in acute bleeding as discribed by **Garcia et al., (2007)**(33) which may support our results in which significant association between OV bleeding and advanced child score but no data can explain or support the association between OV grade and advanced cirrhosis .

In conclusion, **DIC** correlated with advanced cirrhosis with increasing Child's–Pugh score from A to C increasing in DIC in both group

.

References:

[1] Henri H. Versteeg, Johan W. M. Heemskerk, Marcel Levi, et al. New Fundamentals in Hemostasis; Physiol Rev 2013; 93: 327–358.

[2] Dale C. Baker and Jacqueline Brassard; Review of Continuing Education Course on Hemostasis; Toxicologic Pathology 2011; 39: 281-288

[3] Peck-Radosavljevic M. Review article: coagulation disorders in chronic liver disease. Aliment Pharmacol Ther 2007; 26:21-28.

[4] Kujovich JL. Hemostatic defects in end stage liver disease Crit Care Clin 2005; 21:563–587.

[5] Tacke F, Fiedler K, von Depka M, et al. Clinical and prognostic role of plasma coagulation factor XIII activity for bleeding disorders and 6-year survival in patients with chronic liver disease. Liver Int 2006; 26: 173–81.

[6] Colucci M, Binetti BM, Branca MG, et al. Deficiency of thrombin activatable fibrinolysis inhibitor in cirrhosis is associated with increased plasma fibrinolysis. Hepatology 2003; 38: 230–237.

[7] Jackson SP, Nesbitt WS, Kulkarni S, et al. Signaling events underlying thrombus formation. J Thromb Haemost 2003; 1: 1602–12.

[8] Amitrano L, Guardascione MA, Brancaccio V, et al. Coagulation disorders in liver disease. Semin Liver Dis 2002; 22:83–96.

[9] Venugopal A. Disseminated intravascular coagulation; Indian Journal of Anaesthesia 2014; 58. 603-308.

[10] McCormick PA and Murphy KM. Splenomegaly, hypersplenism and coagulation abnormalities in liver disease. Baillie`re's Clin Gastroenterol 2000; 14: 1009–31.

[11] Taylor FB, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001; 86:1327–1330.

[12] Toh, C.H. & Hoots, W.K. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. Journal of Thrombosis and Haemostasis 2007; 5, 604–606.

[13] Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology 2005;41(3):553-558.

[14] Lisman T, Leebeek FW and de Groot PG et al. Haemostatic abnormalities in patients with liver disease. J Hepatol 2002;37(2):280-287.

[15] Deitcher SR. Interpretation of the international normalised ratio in patients with liver disease. Lancet 2002; 359: 47–55.

[16] Kerr R. New insights into haemostasis in liver failure. Blood Coagul Fibrinolysis 2003; 14(Suppl. 1): S43–5.

[17] Hollestelle MJ, Geertzen HG, Straatsburg IH, et al. Factor VIII expression in liver disease. Thromb Haemost 2004; 91: 267–75.

[18] Rodrı´guez-In˜ igo E, Bartolome´ J, Quiroga JA, et al. Expression of factor VII in the liver of patients with liver disease: correlations with the disease severity and impairment in the hemostasis. Blood Coagul Fibrinolysis 2001; 12: 193–9.

[19] Hu K-Q, Yu AS, Tiyyagura L, et al. Hyperfibrinolytic activity in hospitalized cirrhotic patients in a referral liver unit. Am J Gastroenterol 2001; 96: 1581–6.

[20] Agarwal S, Joyner KA Jr, Swaim MW, et al. Ascites fluid as a possible origin for hyperfibrinolysis in advanced liver disease. Am J Gastroenterol 2000; 95: 3218–24.

[21] Peck-Radosavljevic M. (2000): Thrombocytopenia in liver disease. Can J Gastroenterol; 14(Suppl. D): 60D–6D.

[22] Iga D, Tomimatsu M, Endo H, Ohkawa S-I, Yamada O. (2005): Improvement of thrombocytopenia with disappearance of HCV RNA in patients treated by interferon-a therapy: possible etiology of HCV-associated immune thrombocytopenia. Eur J Haematol; 75: 417–23.

[23] Doi T, Homma H, Mezawa S, et al. (2002): Mechanisms for increment of platelet associated IgG and platelet surface IgG and their implications in immune thrombocytopenia associated with chronic viral liver disease. Hepatol Res; 24: 23–33

[24] Levi M, Toh CH, Thachil J, et al., (2009): Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol, 145:24–33

[25] Wada H, Asakura H, Okamoto K, et al, (2010): Japanese Society of Thrombosis Hemostasis/DIC subcommittee: Expert consensus for the treatment of disseminated intravascular coagulation in Japan. Thromb Res, 125:6–11.

[26] Di Nisio M, Baudo F, Cosmi B, et al., (2012): Italian Society for Thrombosis and Haemostasis: Diagnosis and treatment of disseminated intravascular coagulation: guidelines of the Italian society for haemostasis and thrombosis (SISET). Thromb Res, 129:e177–e184.

[27] Wada H, Thachil J, Di Nisio M, et al, (2013): The Scientific Standardization Committee on DIC of the International Society on Thrombosis Haemostasis: Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. J Thromb Haemost, 11:761–767.

[28] Ben-Ari Z, Osman E, Hutton RA, et al. (1999): Disseminated intravascular coagulation in liver cirrhosis: fact or fiction? Am J Gastroenterol; 94: 2977–82.

[29] Garcia JC, Hernandez M, Bosch J et al., Extrahepatic portal vein thrombosis. Semin Liver Dis 2008;28:282–92 .

[30] Huseyin A, Selime A, Nurgul Set al ., Hemostatic Abnormalities in Cirrhosis and Tumor-Related Portal Vein Thrombosis. CLIN APPL THROMB HEMOST . DOI:2011; 10.1177/1196..

[31] Hoekstra J and Janssen H Vascular liver disorders (II): portal vein thrombosis. Neth J Med 2009; 67: 46-53

[32] Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005;353:2254–2261.

[33] Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46:922–938.