Hepatic microcirculatory thrombosis in acute-on-chronic hepatic failure

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Background
Acute-on-chronic hepatic failure is an increasing number of identified distinct disorders encompassing an acute deterioration of hepatic functions in patients with chronic liver disease
Aim
The aim was to evaluate the possibility of hepatic microcirculatory thrombosis in acute-on-chronic hepatic failure and the value of plasma fibrin monomer (FM) and D-dimer in the diagnosis.
Patients and methods
A total of 50 patients with chronic hepatitis C infection developing new-onset ascites, encephalopathy, and/or jaundice with raised international normalisation ratio (INR) (group 1); group 2 included 30 patients with compensated chronic hepatitis C virus infection who served as the control group. Ascetic fluid examination and culture were done for group 1, in addition to complete blood count, liver enzymes, INR, serum bilirubin and albumin, blood culture, α-fetoprotein, D-dimer, plasma FM, abdominal ultrasound, and Doppler for portal vein were done for all patients groups.
Results
Group 1was subdivided according to the level of FM into subgroups A and B. FM showed a significant difference between group 1A and other groups; group IB showed nonsignificant elevation of the level of FM and a significant increase in D-dimer compared with the control group. A marked reduction in portal flow mean velocity in group 1A was recorded with further deterioration of portal flow direction after 2 weeks from the admission time. Three months follow-up showed significant reduction of FM, improvement of portal flow mean velocity and direction in group 1A; FM was significantly positively correlated with portal flow mean velocity.
Conclusion
Hepatic microcirculatory thrombosis may occur in acute-on-chronic hepatic disease; determination of the FM and D-dimer level may be useful biomarkers predicting hepatic microcirculatory thrombosis.

Keywords:
acute-on-chronic hepatic failure, d-dimer, plasma fibrin monomer

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Introduction

The term acute-on-chronic hepatic failure (ACLF) was first utilized in 1995 to portray a condition in which two insults to the liver are working all the while, one of them being chronic and progressing whereas the other being acute [1]. Commonly two definitions are regularly utilized. The first was advanced by the Asia-Pacific Association for the Study of the Liver which provided the first consensus on ACLF, defined as 'an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy'; the 2014 definition was further expanded to include 'high 28-day mortality' [2,3].

The second definition is the operating definition of a studies consortium of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. They proposed: 'acute deterioration of current chronic hepatic disease', typically in reference to a triggering event combined with higher mortality rate at 3 months due to multisystem organ failure [4].

Chronic hepatic disease, till these days taken into consideration as a prototype of acquired coagulopathy leading to bleeding, have to be regarded as a circumstance associated with normal or accelerated thrombin generation and the bleeding that happened in those patients most probably associated with superimposed conditions that often occur on this circumstance [5,6].

In view of expanded factor VIII (procoagulant driver) joined with diminished protein C (anticoagulant driver), a procoagulant imbalance, described as a partial resistance to the in-vitro anticoagulant activity of thrombomodulin, can be proven in chronic hepatic disease [7]. This hypercoagulable state might be the reason for the discovered expanded danger of venous thromboembolism appeared by epidemiological studies, with additional confirmation of intrahepatic thrombosis in patients with acute-on-chronic hepatic disease [8–12].

It is far properly installed that the D-dimer test has poor specificity proving the occurrence of venous system thromboembolism, because of the degradation of extravascular fibrin into the D-dimer by the fibrinolytic system, which, as a result of their low molecular weight, effectively diffuses into the blood circulation [13]. This idea is confirmed by the regularly elevated D-dimer levels found in patients with cancer, infection, acute inflammatory diseases, ascites, recent surgery, trauma, and active bleeding [14].

In comparison, plasma fibrin monomer (FM) cannot originate from inflammatory sites, due to its high molecular weight; in this manner the existence of FM in plasma is a marker of initiation of intravascular coagulation [15,16]. Accompanying assurance of FM and D-dimer levels will turn out to be clinically valuable in the fast determination of thromboembolism. An additional favorable option is that FM levels can conceivably be utilized to screen the outcomes of subsequent anticoagulant therapy [17].

Blood flow in the portal vein is forward flow (toward the liver) during the entire cardiac cycle. The mean velocity is 15–18 cm/s and varies with the cardiac cycle. In portal hypertension, velocity fluctuations disappear, resulting in a continuous flow. With a further increase in portal venous pressure, the blood flow direction becomes bidirectional (biphasic), and finally, the direction is nonforward (hepatofugal) [18].

Our study aims to evaluate the possibility of developing hepatic microcirculatory thrombosis in ACLF and the value of plasma FM and D-dimer assay in the diagnosisof such condition in chronic hepatitis C virus patients.

Patients and methods

This cross-sectional study was carried out in Zagazig University Hospital Internal Medicine Department from June 2015 to April 2016. A total of 50 patients with chronic hepatitis C infection who developed new-onset jaundice, encephalopathy, and/or ascites with elevated international normalisation ratio (INR) within few days before enrolling in the study group 1. All had regular follow-up in the Hepatology Clinic in Zagazig University Hospital with compensated clinical course in the past 3 months. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Group 2 included 30 patients with compensated chronic hepatitis C virus infection which served as the control group.

Patients in group 1 were 33 men and 17 women; their ages ranged from 43 to 65 years old.

Patients with hepatocellular carcinoma, portal vein thrombosis, deep venous thrombosis, recent esophageal variceal bleeding or injected varices and patients previously treated by anticoagulants or patients with evidence of disseminated intravascular coagulation (DIC) were excluded from this study.

Patients in group 1 were admitted and managed according to each condition. All patients and control groups were subjected to full medical history, thorough physical examination, and laboratory tests including INR, serum albumin, complete blood count, serum bilirubin, alanine transaminase (ALT), aspartate transaminase, ascetic fluid examination and culture, blood culture, α-fetoprotein, HBsAg, HBcAb, HAVIgM d D-dimer and FM, abdominal ultrasound (US), Doppler US for portal vein, and computed tomography of the abdomen for patients in group 1.

DIC scoring system was regularly checked using platelet count, D-dimer, INR, and FM.

Aliquots of plasma were prepared and frozen until the determination of FM.

D-dimer and FM were measured by immuno-turbidimetric assays. All analyses were performed by using STA-R evolution coagulation instrument (Diagnostica Stago, Asnieres, France).

Patients in group 1 were subjected to laboratory, US, and Doppler study and clinical assessment regarding (degree of ascites, jaundice, grade of encephalopathy, and hemodynamic stability) with follow-up every 2 weeks

for 3 months duration recording the peak of deterioration after 2 weeks and improvement after 2 months.

Statistical analysis

The results were presented as mean±SD. Statistical comparisons of individual groups were based on unpaired Student's *t*-test and one-way analysis of variance.

Receiver operating characteristic (ROC) curve analysis was performed to compare the diagnostic performance. According to the cut-off point of FM from the ROC curve, sensitivity, specificity was calculated.

Correlation between variables was done using correlation coefficient '*r*'. *P* value is considered significant at less than or equal to 0.05 levels, highly significant at less than or equal to 0.01, and nonsignificant at greater than 0.05.

Results

Patients in group 1 were further subdivided according to the level of FM (above and below the cut-off point) into group 1A including 29 patients with a raised level of FM and group 1B including 21 patients non-elevated FM. Upper gastrointestinal hemorrhage in three patients in group 1A and eight patients in group 1B, renal dysfunction in two patients in group 1A and five patients in group 1B, and bacterial infections in three patients in group 1A and six patients in group 1B. A total of 15 patients exhibited more than two complications and no detectable causes of acute hepatic decompensation in the other patients.

FM was significantly higher with nonsignificant difference of D-dimer between groups A and B in group 1 (Table 1), reduced portal flow mean velocity with increased number of patients with nonforward portal flow in group 1A compared with other groups (Table 1).

Follow-up for 3 months determining 2 weeks as the peak of deterioration and 2 months for improvement, significant differences in FM, ALT, total bilirubin, INR and portal flow mean velocity, and direction with nonsignificant difference in platelet count in group 1A were observed (Table 2).

There were no significant changes in portal hemodynamic, FM level, platelet count, and ALT

Table 1 Clinical characteristics of the enrolled participants

	Group 1A (*N*=29)	Group 1B (*N*=21)	Group 2 (*N*=30)	*F*	*P*
Female/male	10/19	7/14	11/19	0.8	0.6
Age (years)	54.4±8.8	52.43±7.7	54.4±6.5	0.6	0.4
D-dime (μg/ml)	2982±362	1940±442	337.6±97	11.21	0.006
FM (μg/ml)	1071±149	228±63	179.9±33	14.4	0.001
ALT (mg/dl)	87.2±16.1	88.2±17.1	37.9±9.3	5.3	0.004
Total bilirubin (mg/dl)	4.7±0.7	3.8±0.9	1.5±0.2	16.7	0.001
INR	2.1±0.7	2.1±0.2	1.4±0.2	12.4	0.001
Platelet	89786±7413	101563±4811	105363±6871	0.73	0.3
Forward portal flow	2 (7)	14 (67)	20 (66)	39.3	0.001
Nonforward portal flow	20 (69)	2 (10)	1 (4)	21.1	0.002
Bidirectional flow	7 (24)	5 (23)	9 (30)	4.1	0.03
Portal flow(cm/s)	10.7±0.6	12.3±0.4	12.7±0.5	19.5	0.001

Data are represented as mean±SD and number (percentage). ALT, alanine transaminase; FM, fibrin monomer; INR, international normalisation ratio.

Table 2 Portal flow study and laboratory results at admission and during follow-up in patients of group 1A

	At admission (*N*=29)	After 2 weeks (peak of deterioration) (*N*=29)	After 2 months (*N*=29)	*F*	*P*
D-dime (μg/ml)	2982±362	3476±474	762±81	29.4.4	0.0001
FM (μg/ml)	1071±149	1290±178	797±478	16.4	0.0001
ALT (mg/dl)	87.2±16.1	146.5±65.5	90.5±30.5	5.3	0.007
Total bilirubin (mg/dl)	4.7±0.7	5.7±0.9	2.8±1.6	36.7	0.001
INR	2.1±0.7	2.7±0.8	2±0.9		0.001
Platelet	89786±7413	85443±14121	8443±14021	0.83	0.4
Forward portal flow	2 (7)	0 (0)	4 (14)	18.4	0.02
Nonforward portal flow	20 (69)	24 (83)	13 (45)	3.2	0.04
Bidirectional flow	7 (24)	5 (17)	12 (41)	21.3	0.001
Portal flow (cm/s)	10.4±0.6	9.4±0.7	10.9±1.3	6.9	0.002

Data are represented as mean±SD and number (percentage). ALT, alanine transaminase; FM, fibrin monomer; INR, international normalisation ratio.

Table 3 Portal flow study and laboratory results at admission and during follow-up in patients of group 1B

	At admission (*N*=21)	After 2 weeks (peak of deterioration) (*N*=21)	After 2 months (*N*=21)	*F*	*P*
D-dimer (μg/ml)	1940±442	1946±407	900±358	13.1	0.001
FM (μg/ml)	228±63	248±77	229±83	0.2	0.77
INR	2.1±0.2	2.7±0.8	1.9±0.5	3.1	0.06
Platelet	101563±4811	94543±4365	91543±4365	2.1	0.13
ALT (mg/dl)	88.2±17.1	106.3±38.2	87.3±18.2	1.8	0.18
Total bilirubin (mg/dl)	3.8±0.9	4.8±0.7	3.2±1.1	14.1	0.0001
	14 (67)	13 (62)	13 (62)	0.6	0.979
Nonforward portal flow	2 (10)	4 (19)	3 (14)	0.5	0.967
Bidirectional flow	5 (23)	4 (19)	5 (24)	0.4	0.873
Portal flow (cm/s)	12.1±0.7	11.9±0.4	11.9±0.7	0.7	0.34

Data are represented as mean±SD and number (percentage). ALT, alanine transaminase; FM, fibrin monomer INR, international normalisation ratio.

Table 4 Laboratory results and portal flow in group 1A showing clinical improvement

	After 2 weeks (peak of deterioration) (*N*=13)	After 2 months (*N*=13)	*P*
D-dimer (μg/ml)	3570±434	660±162	0.967
FM (μg/ml)	1257±494	434±49	0.0001
Platelet	87423±12123	88413±13113	0.5
ALT (mg/dl)	136.5±37.5	54.2±12.1	0.0001
Total bilirubin (mg/dl)	5.2±0.9	1.5±0.4	0.0001
INR	2.6±0.5	1.6±0.3	0.0001
Forward portal flow	0 (0)	4 (31)	0.0001
Nonforward portal flow	10 (77)	1 (8)	0.0001
Bidirectional flow	3 (23)	8 (61)	0.0001
Portal flow (cm/s)	9.5±0.4	11.9±0.6	0.0001

Data are represented as mean±SD and number (percentage). ALT, alanine transaminase; FM, fibrin monomer; INR, international normalisation ratio.

with significant difference of INR, bilirubin, and D-dimer with the same period of follow-up in group 1B (Table 3).

Clinical and laboratory improvements were recorded in 13 patients with persistent clinical state in 14 patients and two patients have expired in group 1A.

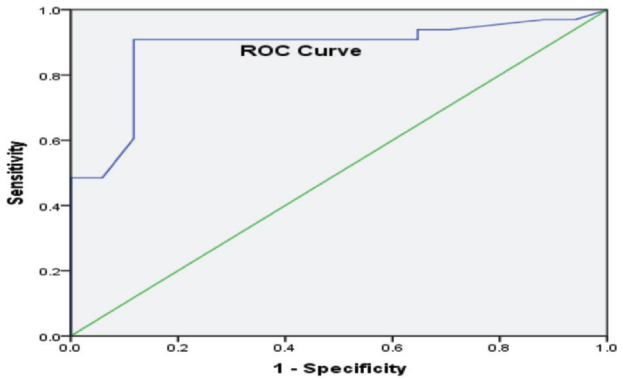
In group 1B three patients expired, with clinical and laboratory improvement in 10 patients and persistent clinical state in eight patients with a follow-up period of 3 months.

Patients with clinical improvement in group 1A showed significant reduction of D-dimer, FM, ALT, and INR with significant improvements of portal flow mean velocity and direction (Table 4).

On ROC curve analyses, the diagnostic performance of FM in groups 1A and 1B (Fig. 1; *P*=0.596), the values with the largest area under the curve were set as the cutoffs for FM (430 μg/ml). Below this cut-off, FM has high sensitivity and specificity.

Significant negative correlation between FM and portal means velocity (r=–0.842**; *P*=0.003; Fig. 2).

Figure 1

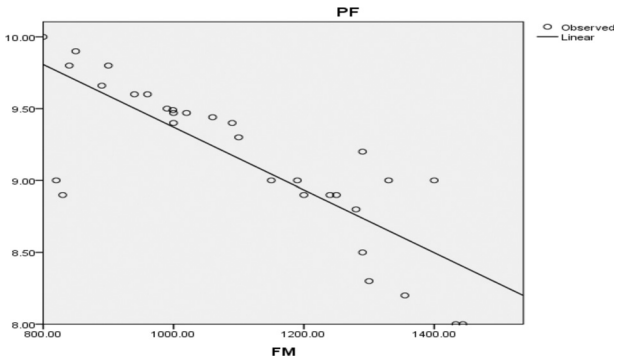


Receiver operating characteristic curve analyses, the diagnostic performance of fibrin monomer in group 1A and B.

Discussion

ACLF is an overwhelming disorder which describes a subgroup of patients with chronic hepatic illness who promote organ failure with increasing mortality, disturbed reaction of the patients to triggering injury assumes a crucial pathophysiological role in acute-on-chronic hepatic injury. However, there are zones of vulnerability in characterizing ACLF, such as heterogeneity of the disease, vagueness in qualifying

Figure 2



Linear curve estimation between fibrin monomer and portal mean velocity.

the underlying hepatic illness or evidence of infection as a promoting event [1].

The patients' immune status and the degree of organ failure decide the result of this syndrome [2]. At admission time, our study showed significant difference between group 1 and control groups regarding D-dimer and plasma FM, INR, ALT, and total bilirubin. Plasma FM and D-dimer were raised in 29 patients in group 1A, whereas in group 1B FM it was not elevated with significant elevation of D-dimer in 21 patients, high levels of both plasma FM and D-dimer are referring to the development of venous thrombosis. This result is agreement with Mirshahi *et al*. [17] who reported that assessment of plasma FM combined with D-dimer presents a conceivably helpful tool for the early detection of venous thromboembolism, provided that the patients have not been receiving anticoagulants.

Our data show elevated levels of ALT, INR, total, and direct bilirubin with DIC score in successive reading is less than five suggesting that the liver is the target organ affected in this insult. These results confirm the results of Edoardo *et al.* [19] who reported that hepatic illness is usually reflected by biochemical variations of one of the two distinctive hepatic systems or of liver function. In spite of the fact, the tests that measure the level of serum liver enzymes are usually eluded as liver function tests, reflecting cholestasis or integrity of hepatocytes more than hepatic function. The change in prothrombin time or serum albumin level is usually associated with a reduction in hepatic functioning mass, confirmed by the raised level of INR. Moreover, there were significant reduction in portal flow mean velocity and significant increase in the number of patients with nonforward flow of portal vein in group 1A compared with the other groups.

After 2 weeks of follow-up, we recorded a significant increase in FM, ALT, total bilirubin, and INR with significant deterioration of the portal flow mean velocity and direction in group 1A. This means that there is progressive increase in portal pressure; these results are in agreement with Khan [18] who reported that when the liver parenchyma is markedly affected, there will be reduction in portal venous blood flow, in which this reduction is roughly correlated to the severity of liver parenchymal affection.

In contrast, group 1B showed neither significant change in portal hemodynamic nor FM level in spite of progressive deterioration of liver functions.

Interestingly by 3 months of follow-up patients in group 1A showed clinical and laboratory improvements, recorded in 13 patients detected clearly after 2 months with persistent clinical state in 14 patients; during the rest of the follow-up period these were associated with improved portal flow velocity and directions, but by 3 months follow-up two patients showed progressive deterioration and have expired, besides three patients from group 1B.

The reduction of portal flow mean velocity and predominance of the nonforward portal flow in patients of group 1A at the time of admission worsened to reach its peak after 2 weeks, then resuming improvement in both flow direction and mean portal flow velocity associated with clinical and laboratory improvements after 2 months, all together with no similar changes in group 1B regarding portal hemodynamics and the FM level is most probably due to portal tributaries microthrombosis with absence of portal vein thrombosis excluded by Doppler US. This means that the thrombosis is localized in the hepatic microcirculation as microthrombotic lesions. This suggestion may explain the rapid deterioration of liver function tests. Anstee *et al*. [20] supposed that minute infarcts resulting from thrombi in the small branches of the hepatic vein and portal vein at areas of inflammation caused ischemia and cellular death with subsequent collapse of the hepatic parenchyma, forming characteristic parenchymal extinction lesions, subsequently replaced by fibrous tissue progressing to cirrhosis; also microthrombotic lesions were supposed to factor in progression of stable cirrhosis to decompensated hepatic form. The combination of thrombotic risk factors and advancement of fibrosis stage enforced the hypothesis of small vessel occlusion with the histological progression of chronic viral hepatitis, in which almost invariably hepatic microcirculatory obstruction was observed [21]. The reduction of procoagulant factors in patients with cirrhosis is compensated by the reduction of

anticoagulant factors, thus leaving the coagulation balance unaltered. The balance between the procoagulant and the anticoagulant drives is essential to ensure unwanted thrombin generation in physiological conditions [22]. Recently, evidence was provided that plasma from patients with cirrhosis could generate similar, or even greater, amounts of thrombin than plasmas from healthy participants, provided thrombin generation is measured in the presence of thrombomodulin [23]. Therefore composition change of the blood toward a hypercoagulable state in combination with endothelium change of hepatic microcirculation and/or in intrahepatic blood flow usually develops in chronic hepatic disease with cirrhosis, which certainly favors the development of intrahepatic microthrombosis. Thus, one could hypothesize that patients with chronic hepatic disorder who carry certain genetic disorder can easily acquire thrombotic risk factors and have a more rapid progression to more advanced staging of chronic hepatitis [24].Improvement of both clinical and laboratory results already with increase of portal vein mean velocity and improved direction recorded in 13 patients in group 1A predict the hypothesis of spontaneous resolution of microcirculatory thrombosis in these patients. This result is in agreement with Girleanu *et al*. [25] who concluded that more than half of cirrhotic patients with portal tract thrombosis had a stable or improved thrombus evolution without anticoagulant therapy and Luca *et al*. [26] who reported that nonmalignant portal tract thrombosis improved spontaneously in 45% of patients with cirrhosis, and the progression of portal tract thrombosis was not associated with clinical outcome, which appeared to be dependent on the severity of cirrhosis.

Our results show significant negative correlation between FM and portal flow mean velocity in group 1A. This correlation is clearer and more significant in patients after 2 weeks more than at the start of admission, suggesting continuing and dynamic process of thrombosis associated with continuing deterioration in liver functions and portal hemodynamics.

From the previous results we can conclude that the development of ACLF may result from precipitating factors like gastrointestinal tract bleeding, infection or renal impairment in group 1B with no evidence of vascular thrombosis and may occur with undetectable cause in most cases in group 1A, in which hepatic microthrombosis may be the triggering factor; moreover, it could complicate the clinical course in situations with presence of a precipitating cause.

Proofing and acceptance of the hypothesis of hepatic microcirculatory thrombosis and its role in the deterioration of liver function and progression of cirrhosis, an emerging query is whether this microthrombosis is a sequel with presence of a precipitating factor or a cause of developing acute deterioration in the absence of precipitating reason and may give us the value of using different therapeutic options like low molecular weight heparin or antithrombin 3 and studying its effect on protecting the liver from the hypercoagulable state in patients with acute-on-chronic and chronic hepatic disease.

Conclusion

Hepatic microcirculatory thrombosis may occur in acute-on-chronic hepatic disease as a cause or a complication of precipitating events. Evaluation of the level of plasma FM and D-dimer may be useful biomarkers to predict hepatic microcirculatory thrombosis. Further studies are needed to insure the occurrence of such condition and the suitable methods of treatment.

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Ehab Fawzy Mostafa designed the research and collected the materials and clinical data; Ayman Marei supervised the laboratory methods; Amr El Hawary performed the statistical analysis; and Waleed A. Ismael wrote the paper. All authors provided a critical revision of the article and approved the final version.

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Conflicts of interest

There are no conflicts of interest.

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