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Chronic intravascular coagulation in liver cirrhosis predicts a high hemorrhagic risk

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Abstract. – OBJECTIVE: In liver cirrhosis, a complex coagulopathy does exist. The aim was to investigate whether a possible chronic consumption coagulopathy is the underlying phenomenon of the disease.

PATIENTS AND METHODS: We measured endogenous thrombin generation with and without thrombomodulin (ETP ratio) along with D-Dimer in a group of consecutive 282 cirrhotic patients. Fibrinogen, Platelet count and the Hemorrhagic score were previously computed in the same patients. The ETP ratio represents the resistance to the anticoagulant activity of TM and should be considered as an index of a procoagulant imbalance.

RESULTS: ETP ratio and D-Dimer showed higher values in the cirrhotic patients when compared to controls thus showing a hypercoagulable state. When the patients were divided based on the Hemorrhagic score >7, we found that Fibrinogen, ETP ratio, D-Dimer and the platelet count were significantly different between the two groups. Again, when we considered ETP ratio >0.88, the median value of the cirrhotic patients, all parameters, were statistically different between the two groups. D-Dimer were higher while fibrinogen and platelet count were statistically lower in cirrhotic patients with higher ETP ratio values. Even when the same patients were divided based on their platelet count (</> 100 x 10^9/L) the results showed a similar behavior. ROC curves showed significant AUCs when the hemorrhagic score was challenged against Fibrinogen, D-Dimer, Platelet count and ETP ratio.

CONCLUSIONS: In liver cirrhosis hypercoagulable state is associated with an increase in D-Dimer levels along with a decrease in fibrinogen and platelet count thus indicating a low-grade intravascular coagulation which predicts a high hemorrhagic risk.

Key Words:
Liver cirrhosis, Endogenous thrombin generation, Fibrinogen, Platelet count, D-Dimer, Intravascular coagulation.

Introduction

In liver cirrhosis, a complex coagulopathy does exist[1-2]. A hypercoagulable state has been demonstrated by Tripodi et al[3] on one hand while a decrease in the velocity and acceleration of clot formation has been found on the other[4]. Paradoxically, even though a tendency to an increased risk for thrombosis has been found, this seems to be associated to an increased risk for bleeding in these patients as it has been recently reported[5]. An opposite behavior of the coagulopathy in liver cirrhosis seems therefore to be concomitantly present leading to an instable balance of the coagulative system as suggested by Tripodi et al[6]. This condition prompted us to investigate whether a hypercoagulable state, detected by the thrombin generation, may coexist along with a high hemorrhagic score, an increased D-Dimers levels, low fibrinogen levels and platelet count. For this purpose, we used both the clinical data and the plasma samples of a group of cirrhotic patients previously reported in two studies[4,5]. This study is therefore an extension of the previous reports. The aim was to obtain or not solid evidence for a possible consumption coagulopathy which may represent the final frame of the complex coagulopathy of liver cirrhosis.

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Patients and Methods

Plasma samples of 282 consecutive cirrhotic patients (207 males and 75 females, median age 62 years, range 36-88 years) referred both to the outpatient unit and to the clinical ward of the Gastroenterology Unit of our University Hospital were used for this further analysis. Diagnosis of cirrhosis was made based on clinical, laboratory, imaging and histological criteria. Characteristics of the patients studied have been previously reported[4,5]. Child-Pugh A, B and C categories were respectively present in 209, 51 and 22 patients. Bleeding risk, computed in the previous study[5], was assessed using a general hemorrhagic score proposed by the American College of Chest Physician[6]. A hemorrhagic score ≥7 indicated a high bleeding risk. A total of 64 healthy subjects (31 males and 33 females, median age 59 years, range 50-57 years) was also studied. Informed consent was obtained from all patients and controls. Approval of this study was obtained by the local Ethical Committee (Prot. PG/2021/153).

Blood samples was centrifuge at 2020 g for 20 minutes to room temperature.

Plasma samples for thrombin generation and D-Dimer were stored at -80°C after being kept in liquid nitrogen and were used for each patient and controls after thawing at 37°C.

D-Dimer were determined on an ACL TOP 500 CTS (Werfen, Barcelona, Spain) using the reagents D-Dimer HS (Werfen, Barcelona, Spain).

Thrombin Generation (TG) was carried out by the Calibrated Automated Thrombogram (CAT) method (Diagnostica Stago, Asnières sur Seine France)[7]. Eighty µl of PPP were pipetted into a well of a microtiter plate together with 20 µl of PPP-Reagent +/- TM (with and without Thrombomodulin) (Thrombinoscope BV, Maastricht, The Netherlands). PPP-Reagent contains a mixture of Tissue Factor (5pM final concentration) and synthetic phospholipids (4 µM final concentration). The reaction was started with 20 µl of a mixture composed of the fluorogenic thrombin substrate [(Z-GlyGly-Arg-AMC, Thrombinoscope BV, 417 µM final concentration) and $CaCl_2$ (15 mM final concentrations)]. The substrate is then cleaved by the thrombin formed and liberates a fluorophore, which is converted to thrombin-equivalent concentrations (nM) using a reference curve[8]. Fluorescence was read in a Fluoroscan Ascent® reader (Thermo Fisher Scientific Corporation, Vantaa, Finland) and TG curves were calculated using the Thrombinoscope Software. TG curves were plotted and endogenous thrombin potential (ETP, area under the curve, nM*min) was recorded. This parameter was expressed as with/without thrombomodulin. The ratio was also computed. This ratio represents the resistance to the anticoagulant activity of TM and should be considered as an index of the procoagulant imbalance. The higher the ratio, the greater the procoagulant activity. The ETP is the area under de curve (AUC) that represents all the enzymatic activity of thrombin when is activated. Fibrinogen and the platelet count have been previously measured by an ACL TOP 500 CTS (QFA Thrombin, Hemosil, Werfen, Barcelona, Spain) and a cell counter (Beckman Coulter, Milan, Italy) respectively as reported in a previous study[5].

Statistical Analysis

Since the data were not normally distributed, they are expressed as median and ranges. Mann-Whitney test for independent data was used for the statistical comparison of the data. Receiver Operating Characteristic (ROC) analysis was carried out to determine the Area Under the Curve (AUC) to assess the role of the different variables in predicting a high hemorrhagic score. MedCalc software (Version 17.7.2, Ostend, Belgium) was used to perform the statistical analysis of the data.

Results

ETP ratio, was different between patients and controls showing increased values demonstrating a hypercoagulable state. D-Dimer showed increased values in cirrhotic when compared to the controls. When the patients were divided on the basis of the Hemorrhagic score ≥7, we found that Fibrinogen, ETP ratio, D-Dimer and the platelet count were significantly different between the two groups. When we divided the patients into two groups based on the ETP ratio ≥0.88, the median value of the cirrhotic patients, all parameters, were statistically different between the two groups. In particular, D-Dimer were higher while fibrinogen and platelet count were statistically lower in cirrhotic patients with higher ETP ratio values. When we divided the patients into two groups, based on the median values of ETP without TM ≥/<1.076.70 nM*min, only Fibrinogen was statistically different between the two groups. When we divided the patients into two groups based on the median value ETP with TM ≥/< 901.84 nM*min, all parameters were statis-

tically different between the two groups except the fibrinogen values. Finally, data referred to the same patients divided on the basis of their platelet count (</> 100 × 10^9/L) showed a significant difference between Fibrinogen, D-Dimer, ETP with TM and ETP ratio. All these results are presented in Table I. ROC curves showed significant AUCs when the hemorrhagic score was challenged

Table I. All parameters studied in healthy subjects and in cirrhotic patients also divided on the basis of the different parameters considered. Data are expressed as median and range.

Parameters	Cirrhotic patients n = 282	Healthy subjects n = 64	p
Fibrinogen (mg/dl)	244.50, 82.00-662.00	291.50, 182.00-423.00	< 0.0001
D-Dimer (ng/ml)	197.50, 8.00-9778.00	151.50, 34.00-334.00	0.0016
ETP without TM (nM*min)	1076.70, 450.39-2297.73	1373.19, 859.02-2020.65	< 0.0001
ETP with TM (nM*min)	901.84, 261.86-2065.33	831.38, 303.55-1527.13	0.2405
ETP ratio	0.88, 0.31-1.08	0.60, 0.33-1.04	< 0.0001
Parameters	**Cirrhotic patients with hemorrhagic score ≥ 7 n = 64**	**Cirrhotic patients with hemorrhagic score < 7 n = 218**	**p**
Fibrinogen (mg/dl)	219.50, 86.00-424.00	253.00, 82.00-662.00	0.0016
D-Dimer (ng/ml)	371.00, 69.00-2947.00	171.00, 8.00-9778.00	< 0.0001
ETP without TM (nM*min)	1083.35, 465.26-218.34	1075.63, 450.39-2297.73	0.8295
ETP with TM (nM*min)	941.93, 261.86-2065.33	889.34, 309.31-1667.04	0.0190
ETP ratio	0.94, 0.44-1.08	0.85, 0.31-1.07	< 0.0001
Platelet count (×10^9/L)	86.00, 22.00-252.00	139.00, 31.00-511.00	< 0.0001
Parameters	**Cirrhotic patients with ETP ratio ≥ 0.88 n = 141**	**Cirrhotic patients with ETP ratio < 0.88 n = 141**	**p**
Fibrinogen (mg/dl)	212.00, 86.00-552.00	278.00, 82.00-662.00	< 0.0001
D-Dimer (ng/ml)	245.00, 8.00-9778.00	159.00, 13.00-7535.00	< 0.0001
Platelet count (×10^9/L)	113.00, 22.00-352.00	146.00, 25.00-511.00	< 0.0001
Parameters	**Cirrhotic patients with ETP without TM ≥ 1076.70 (nM*min) n = 141**	**Cirrhotic patients with ETP without TM < 1076.70 (nM*min) n = 141**	**p**
Fibrinogen (mg/dl)	265.00, 104.00-662.00	226.00, 82.00-408.00	< 0.0001
D-Dimer (ng/ml)	199.00, 8.00-9778.00	185.00, 13.00-3360.00	0.2083
Platelet count (×10^9/L)	136.00, 30.00-352.00	130.00, 22.00-511.00	0.1712
Parameters	**Cirrhotic patients with ETP with TM ≥ 901.84 (nM*min) n = 141**	**Cirrhotic patients with ETP with TM < 901.84 (nM*min) n = 141**	**p**
Fibrinogen (mg/dl)	237.00, 86.00-662.00	248.00, 82.00-540.00	0.5925
D-Dimer (ng/ml)	220.00, 8.00-9778.00	173.00, 13.00-3038.00	0.0012
Platelet count (×10^9/L)	116.00, 22.00-352.00	143.00, 25.00-511.00	0.0029
Parameters	**Cirrhotic patients with platelet count > 100 × 10^9/L n = 1 91**	**Cirrhotic patients with platelet count < 100 × 10^9/L n = 91**	**p**
Fibrinogen (mg/dl)	283.00, 82.00-662.00	191.00, 104.00-424.00	< 0.0001
D-Dimer (ng/ml)	175.00, 8.00-9778.00	244.00, 30.00-3240.00	0.0165
ETP without TM (nM*min)	1076.22, 450.39-2297.73	1077.18, 645.50-1774.53	0.9160
ETP with TM (nM*min)	852.46, 261.86-2065.33	969.82, 426.13-1564.42	0.0016
ETP ratio	0.83, 0.31-1.08	0.92, 0.54-1.05	< 0.0001

Table II. Areas under the Curve (AUC) obtained for all parameters studied vs. the hemorrhagic score.

Parameters	Hemorrhagic Score AUC, 95% CI	p
Fibrinogen (mg/dl)	0.63, 0.57-0.69	0.0010
D-Dimer (ng/ml)	0.70, 0.65-0.76	< 0.0001
ETP without TM (nM*min)	0.51, 0.43-0.59	0.8312
ETP with TM (nM*min)	0.59, 0.52-0.67	0.0155
ETP ratio	0.68, 0.62-0.73	< 0.0001
Platelet count ($\times 10^9$/L)	0.71, 0.65-0.76	<0.0001

against Fibrinogen, D-Dimer, Platelet count, ETP ratio and ETP with TM (Table II). A significant difference was found between the ROC curves ETP ratio and ETP with TM (p=0.023) (Figure 1).

Discussion

The results of this study show that a hypercoagulable state does exist in liver cirrhosis confirming the findings of Tripodi et al[9] who demonstrated that the ratio between the thrombin generation with and without TM was able to indicate a condition which represents a resistance to the natural anticoagulant activity of TM. This is an endothelial receptor for thrombin dedicated to the conversion of Protein C to its activated form[10]. Some mechanisms are involved in the pathogenesis of the hypercoagulable state in liver cirrhosis such as an increased level of von Willebrand factor, a decreased level of natural anticoagulants and elevated levels of intravascular tissue factor[11]. Again, the concomitant and opposite behavior of

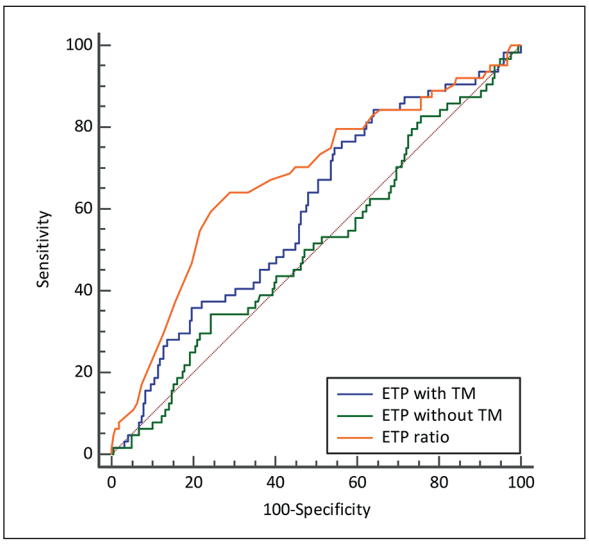

Figure 1. ROC curves related to ETP ratio and ETP with/without TM.

Protein C (decreased), and factor VIII (increased) can further explain why cirrhotic patients present such a complex hemostatic abnormalities[12]. All these biochemical pathological conditions can lead to a higher risk for venous thromboembolism[13]. However, it has been found that the clot formation of patients with liver cirrhosis is weak when measured by means of the Clot Waveform Analysis (CWA) which showed hidden parameters of both PT ratio and aPTT ratio, i.e., the 1st and 2nd derivatives[4]. A significant association between the PT ratio and the clot waveform analysis with both the hemorrhagic score and the history positive for bleeding in the cirrhotic patients has been also described[5]. Those findings challenged the concept which states the PT is not a reliable test for assessing the hemorrhagic diathesis in liver cirrhosis. In that study we also showed that bleeding events, although not clinically relevant, were significantly more frequent than the thrombotic episodes. Liver cirrhosis is therefore characterized by two opposite mechanisms underlying its complex coagulopathy. In this study we wished to expand further our previous findings by detecting the thrombin generation's parameters, expressed as the ratio obtained with and without TM, in the same series of consecutive patients with liver cirrhosis which has been the subject of our previous report[5]. We added to this study the measurement D-Dimer, to those of Fibrinogen and the platelet count, reported in our previous studies. Our results show that patients with high values of ETP ratio, the best expression of the thrombin generation, have a significant increase of D-Dimer supporting the concept that an increased fibrin formation is followed by a fibrinolysis activation. Interestingly, patients with high thrombin generation, i.e., high ETP ratio, also showed a significant decrease in Fibrinogen levels thus supporting the hypothesis that a consumption coagulopathy is present in liver cirrhosis. Even when we divided the patients on the basis of their platelet count, those with platelet less than 100 x 10^9/L showed both higher

values of thrombin generation and D-Dimer when compared to those with a platelet count >100 x 10^9/L. These findings confirmed the involvement of platelets in the pathophysiology of a consumption coagulopathy. A drawing illustrating the pathophysiology of chronic DIC in liver cirrhosis is presented in Figure 2.

On the other hand, coagulation and secondary fibrinolysis is a physiologic system[14] devoted to maintaining vascular patency in that even very small amounts of fibrin goes toward dissolution thus avoiding vascular clots. The overexpression of the fibrinolytic activity following disseminated intravascular coagulation[15] is an extreme pathological example of this phenomenon. In liver cirrhosis, the same mechanism seems to be present although to a much less extent. An excess of fibrinolysis may explain why fibrinogen is further reduced in our patients with high ETP ratio. Our findings may also explain why a tendency to a hypercoagulable state has been described minimizing the role of PT in estimating the bleeding risk. This study and our previous findings clearly indicate that it is true that a hypercoagulable state is present in liver cirrhosis, but the final result is a weakness of clot formation which in turn is associated to a hemorrhagic diathesis. The fact that an increased thrombin generation is associated to a high hemorrhagic score further support our final frame of the hemostasis in liver cirrhosis. Our results also show that the ETP ratio is the best way for detecting a hypercoagulable state. In fact, in the ROC curves analysis the ETP ratio was found to show the best result in comparison with those of both ETP with and without TM. The behavior of the other parameters considered, i.e., fibrinogen, platelet count and D-Dimer, is coherent with a consumption coagulopathy, only using the ETP ratio. It should be considered that ETP ratio is an integral measure of a procoagulant imbalance due to the abnormal behavior of the Factor VIII-Protein C axis. In fact, Thrombomodulin forms a complex with thrombin to activate Protein C, the anticoagulant driver, usually decreased in liver cirrhosis, since it inhibits factor VIII. However, the ETP ratio is also driven by factor VIII, usually high in the disease[16]. This concept has been challenged by Potze et al[17]. They do not accept the expression of ETP by a ratio because, in their opinion, it only provides information on the capacity of thrombomodulin to down regulate thrombin generation. They believe that ETP with TM is the best way to express the amount of thrombin produced[18]. However, our findings demonstrate that the ETP ratio clearly show an imbalance of the coagulative system in liver cirrhosis due to a hypercoagulable state on one hand along with an increased

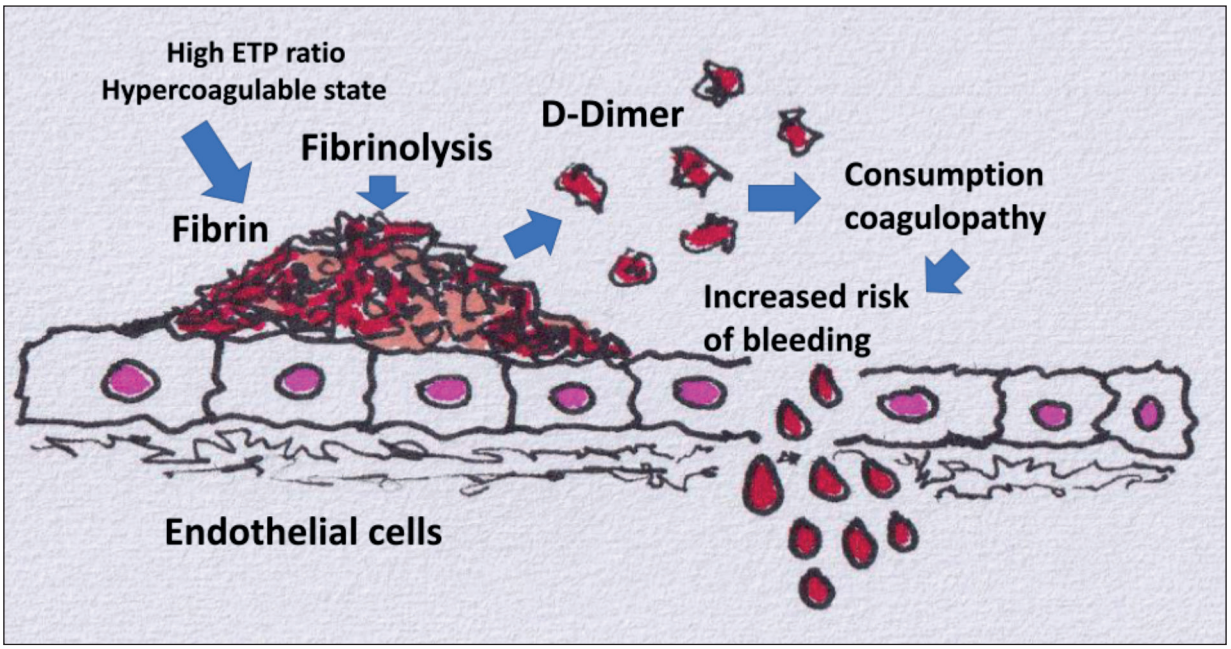

Figure 2. The consumption coagulopathy in liver cirrhosis is depicted here. The hypercoagulable state demonstrated a high ETP ratio inducing an intravascular fibrin deposition along with the involvement of fibrinogen and platelets which result to be lower in this condition. The final outcome is an increased risk of bleeding.

fibrinolytic activity on the other. Low levels of both fibrinogen and platelets are concomitantly present in this condition further confirming the presence of a consumption coagulopathy. Since a long time ago, the pathophysiology of this condition is thought to be explained by the release of tissue factor, the trigger of blood coagulation, coming from the necrotic hepatocytes. Platelets are thus induced to aggregate by an enhanced thrombin activity. Fibrinolysis is then activated as a secondary phenomenon. The slow flow of the blood in the increased collateral circulation and the congested spleen can further enhance this phenomenon[19]. It is difficult to deal with this complex coagulative abnormality since, from a practical point of view, a prolonged PT may be considered as an unbalance in the hemostatic system on one hand but of a hypercoagulable state on the other. The latter could be estimated by using the Padua Prediction Score as we did in a previous experience thus identifying those patients who may deserve an antithrombotic prophylaxis[20]. The ROC curves determined in this study further show that ETP ratio, when challenged against the hemorrhagic score, shows a significant value of the AUC indicating that a hypercoagulable state is the driver of a coagulative condition which can lead to a hemorrhagic diathesis, paradoxically. Recently, the possible condition of "accelerated intravascular coagulation and fibrinolysis" (AICF) coined by Joist in 1999[21], has been reviewed by the Faculty of the 7th conference on Haemostasis and Thrombosis in liver disease[22]. A final hypothesis was that hyperfibrinolysis may be the result of an unbalanced and precarious coagulative system as we now demonstrated in this study. On the other hand, many years ago Bakker et al found increased levels of Thrombin-Antithrombin complexes (TAT), soluble fibrin and D-Dimer interpreted as the result of a DIC in liver cirrhosis. They recalled what other authors published on this topic some years before about DIC that disease. Vestraete et al [23] along with wit Bloom[24] and ourselves[25,26] suggested that in liver disease a chronic DIC was present in that an increased thrombin activity with a concomitant secondary fibrinolysis were typical features of this condition. Some limitations of this study deserve attention. First, we did not measure other parameters linked to fibrinolysis such as tissue-plasminogen activator and its inhibitor, thus missing potential useful information on the pathophysiology of fibrinolysis impairment in liver cirrhosis. Second, this study is retrospective. Third, a relatively small sample size has been included in this study so that it was difficult to divide the patients into different categories.

Conclusions

This study showed that in liver cirrhosis an increased thrombin activity is associated with both increased D-Dimer levels on one hand and a decreased platelet count on the other. All these abnormalities should be carefully considered in the approach to a patient with liver cirrhosis. From a practical point of view if it is difficult to carry out the thrombin generation assay in a general laboratory but platelet count and d-Dimer are easy to perform. Following our experience in this study, a platelet count less than 86 x 10^9/L concomitantly with a D-dimer level greater than 374 ng/ml could be considered the first signs of DIC in liver cirrhosis. In fact, values respectively below and above that median cut-off showed a clear association with an increased thrombin generation. Moreover, these two parameters were significantly correlated with a high hemorrhagic score which, at least in our opinion, should be computed in the single patient during the daily clinical practice.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authorship

MFR MSP OS AC FM and DB: substantial contributions to the conception or design of the work, the acquisition, analysis, collection of the data and recording the clinical events and the interpretation of data for the work. FM and MFR: drafting the work or revising it critically for important intellectual content. PU, DF, GO, GF and DB: critical revising and final approval of the version to be published. All authors: agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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