European Review for Medical and Pharmacological Sciences 2021; 25: 7616-7618

Letter to the Editor

Comment on: Chronic intravascular coagulation in liver cirrhosis predicts a high hemorrhagic risk

Dear Editor,

We read with great interest the article by Ruberto et al[1] on the role of intravascular coagulation in liver cirrhosis about the hemorrhagic risk.

This retrospective study demonstrated the existence of a state of hypercoagulability in patients with liver cirrhosis. The plasma of 282 cirrhotic patients was examined measuring the endogenous generation of thrombin (ETP) with and without thrombomodulin (TM) and the D-dimer. Hypercoagulability conditions were evidenced by higher ETP ratio and D-Dimer levels in cirrhotic patients compared to the control group. In accordance with the scores proposed by the American College of Chest Physician, considering patients with a Hemorrhagic score > 7, the ETP ratio, D-Dimer levels and platelet count were significantly different in patients compared to control. Noting the ETP ratio > 0.88, D-Dimer was higher while fibrinogen and platelet counts were statistically lower in cirrhotic patients, compared to healthy individuals. A similar trend occurred when the same patients were divided by platelet count (< / > 100 x 109 / L).

These results indicated a state of hypercoagulability, associated with an increase in D-Dimer levels and a decrease in fibrinogen levels and platelet count, resulting in a low-grade intravascular coagulation, a potential risk factor of bleeding (Figure 1).

Liver cirrhosis is a chronic and progressive disease, characterized by the widespread and irreversible alteration of the liver structure[2-4]. This condition is a consequence of damage of various kinds accumulated over a long period[5]: i) viral infections (hepatitis B, hepatitis C, hepatitis D and herpesviruses)[6-11]; ii) chronic alcohol abuse[12]; iii) non-alcoholic fatty liver disease[12]; iv) autoimmune diseases[13]; v) primary sclerosing cholangitis[14]; vi) hemochromatosis[15] and vii) Wilson's disease[16].

Liver cirrhosis involves hemostatic alteration, resulting in changes in primary hemostasis, coagulation and fibrinolysis[17,18]. The coagulation system of healthy individuals has evolved to maintain a safe balance of pro- and anti-hemostatic systems. This balance promotes rapid coagulation during vessel rupture and simultaneously preserves local thrombosis control during vascular remodeling. Most co-

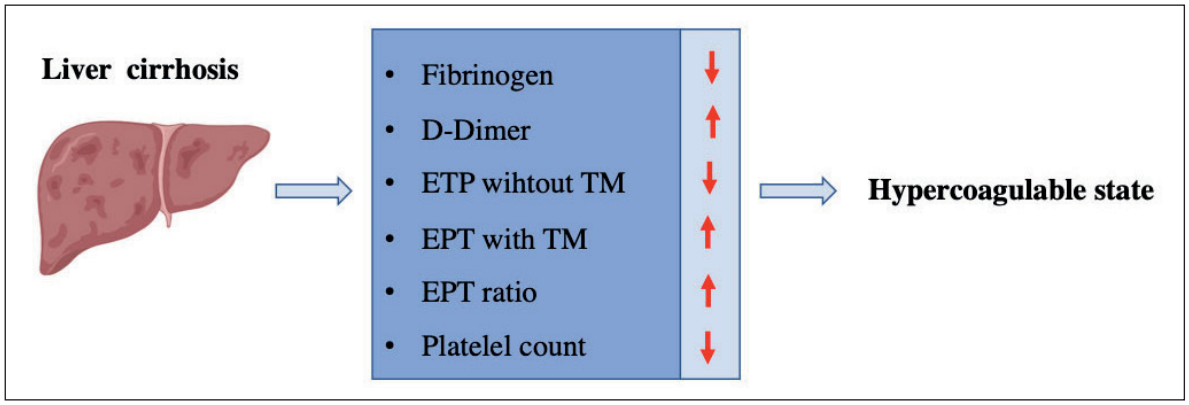

Figure 1. Coagulation imbalance in patients with liver cirrhosis.

Corresponding Author: Massimiliano Galdiero, MD; e-mail: massimiliano.galdiero@unicampania.it

agulation proteins are produced by the liver, such as I (fibrinogen), II (thrombin), V, VII, IX, X and XI, as well as protein C, protein S, hepcidin and antithrombin[19]. Patients with liver cirrhosis present an altered hemostatic system, due to low platelet counts and increased levels of von Willebrand factor. Furthermore, a reduced synthesis of inhibitors, procoagulant factors and an impaired fibrinolysis occurs in cirrhotic patients. Previous evidence[20] reported that altered hemostatic system promoted bleeding, protecting against thrombosis. Later studies proved a "dynamic state" of the hemostatic system in cirrhotic patients, which could undertake a condition of hypercoagulability or hypocoagulability[17]. Consistent with the present study, Tripodi et el[21] reported that the plasma of cirrhotic patients was characterized by a pro-coagulant imbalance, induced by resistance to the anticoagulant action of thrombomodulin. This resistance was related to a condition typical of patients with liver cirrhosis, who present high plasma levels of factor VIII (procoagulant driver) and low levels of protein C (anticoagulant driver).

From a clinical point of view, portal vein thrombosis (PVT) is a common complication in liver cirrhosis, especially in advanced cirrhosis[22]. PVT can be of non-neoplastic and neoplastic origin, and the latter is common in patients with hepatocellular carcinoma (HCC)[23,24]. PVT in cirrhotic patients with HCC are estimated to have an annual incidence ranging from 7.4% to 24%[25]. HCC in patients with liver cirrhosis worsens the prognosis and may limit the indication for liver transplantation[26,27]. In addition, even in the absence of HCC, liver cirrhosis can lead to the onset of PVT, due to increased intrahepatic vascular resistance and reduced portal flow velocity[28].

In conclusion, the current study provided novel evidence on cirrhotic coagulopathy, revolutionizing the therapeutic interventions and prophylactic procedures implemented on patients with cirrhosis. Furthermore, this evidence suggests coagulation factors as prognostic indicators in liver cirrhosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Ruberto MF, Piras MS, Sorbello O, Civolani A, Usai P, Fanni D, Orrù G, Faa G, Marongiu F, Barcellona D. Chronic intravascular coagulation in liver cirrhosis predicts a high hemorrhagic risk. Eur Rev Med Pharmacol Sci 2021; 25: 5518-5524.
2) Rosato V, Ascione A, Nevola R, Fracanzani AL, Piai G, Messina V, Claar E, Coppola C, Fontanella L, Lombardi R, Staiano L, Valente G, Fascione MC, Giorgione C, Mazzocca A, Galiero R, Perillo P, Marrone A, Sasso FC, Adinolfi LE, Rinaldi L. Factors affecting long-term changes of liver stiffness in direct-acting anti-hepatitis C virus therapy: a multicenter prospective study. J Viral Hepat 2021. doi: 10.1111/jvh.13617. Online ahead of print.
3) Rinaldi L, Folliero V, Palomba L, Zannella C, Isticato R, Di Francia R, Berretta M, Sio I de, Adinolfi LE, Morelli G, Lastoria S, Altucci L, Pedone C, Galdiero M, Franci G. Sonoporation by microbubbles as gene therapy approach against liver cancer. Oncotarget 2018; 9: 32182-32190.
4) Chianese A, Santella B, Ambrosino A, Stelitano D, Rinaldi L, Galdiero M, Zannella C, Franci G. Oncolytic Viruses in Combination Therapeutic Approaches with Epigenetic Modulators: Past, Present, and Future Perspectives. Cancers (Basel) 2021; 13: 2761.
5) Esposito V, Verdina A, Manente L, Spugnini EP, Viglietti R, Parrella R, Pagliano P, Parrella G, Galati R, De Luca A, Baldi A, Montesarchio V, Chirianni A. Amprenavir inhibits the migration in human hepatocarcinoma cell and the growth of xenografts. J Cell Physiol 2013; 228: 640-645.
6) Rinaldi L, Nevola R, Franci G, Perrella A, Corvino G, Marrone A, Berretta M, Morone MV, Galdiero M, Giordano M, Adinolfi LE, Sasso FC. Risk of Hepatocellular Carcinoma after HCV Clearance by Direct-Acting Antivirals Treatment Predictive Factors and Role of Epigenetics. Cancers (Basel) 2020; 12: E1351.
7) Rinaldi L, Perrella A, Guarino M, De Luca M, Piai G, Coppola N, Pafundi PC, Ciardiello F, Fasano M, Martinelli E, Valente G, Nevola R, Monari C, Miglioresi L, Guerrera B, Berretta M, Sasso FC, Morisco F, Izzi A, Adinolfi LE. Incidence and risk factors of early HCC occurrence in HCV patients treated with direct acting antivirals: a prospective multicentre study. J Transl Med 2019; 17: 292.
8) Wang J-N, Ling F. Zika Virus Infection and Microcephaly: Evidence for a Causal Link. Int J Environ Res Public Health 2016; 13: E1031.
9) Marrone A, Franci G, Perrella A, Nevola R, Chianese A, Adinolfi LE, Sasso FC, Rinaldi L. Editorial - HCC in HCV patients and the direct acting antivirals: is there really a link? Eur Rev Med Pharmacol Sci 2020; 24: 983-987.
10) Montella M, D'Arena G, Crispo A, Capunzo M, Nocerino F, Grimaldi M, Barbieri A, D'Ursi AM, Tecce MF, Amore A, Galdiero M, Ciliberto G, Giudice A. Role of Sex Hormones in the Development and Progression of Hepatitis B Virus-Associated Hepatocellular Carcinoma. Int J Endocrinol 2015; 2015: 854530.
11) Giudice A, D'Arena G, Crispo A, Tecce MF, Nocerino F, Grimaldi M, Rotondo E, D'Ursi AM, Scrima M, Galdiero M, Ciliberto G, Capunzo M, Franci G, Barbieri A, Bimonte S, Montella M. Role of Viral miRNAs and Epigenetic Modifications in Epstein-Barr Virus-Associated Gastric Carcinogenesis. Oxid Med Cell Longev 2016; 2016: 6021934.

12) Galiero R, Caturano A, Vetrano E, Cesaro A, Rinaldi L, Salvatore T, Marfella R, Sardu C, Moscarella E, Gragnano F, Calabrò P, Sasso FC. Pathophysiological mechanisms and clinical evidence of relationship between Nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease. Rev Cardiovasc Med 2021; 22: 755.
13) Chris-Olaiya A, Kapoor A, Ricci KS, Lindenmeyer CC. Therapeutic plasma exchange in liver failure. World J Hepatol 2021; 13: 904-915.
14) Berretta M, Cavaliere C, Alessandrini L, Stanzione B, Facchini G, Balestreri L, Perin T, Canzonieri V. Serum and tissue markers in hepatocellular carcinoma and cholangiocarcinoma: clinical and prognostic implications. Oncotarget 2017; 8: 14192-14220.
15) Wu L, Zhang W, Li Y, Zhou D, Zhang B, Xu A, Wu Z, Wu L, Li S, Wang X, Zhao X, Wang Q, Li M, Wang Y, You H, Huang J, Ou X, Jia J. Correlation of genotype and phenotype in 32 patients with hereditary hemochromatosis in China. Orphanet J Rare Dis 2021; 16: 398.
16) Omeish H, Hajjaj N, Abdulelah M, Bader H. You Only Find What You Are Looking for: Concurrent Alcoholic Liver Cirrhosis and Undiagnosed Wilson's Disease. Cureus 2021; 13: e17117.
17) Zermatten MG, Fraga M, Moradpour D, Bertaggia Calderara D, Aliotta A, Stirnimann G, De Gottardi A, Alberio L. Hemostatic Alterations in Patients with Cirrhosis: From Primary Hemostasis to Fibrinolysis. Hepatology 2020; 71: 2135-2148.
18) Pagliano P, Boccia G, De Caro F, Esposito S. Bacterial meningitis complicating the course of liver cirrhosis. Infection 2017; 45: 795-800.
19) Rinaldi L, Pafundi PC, Galiero R, Caturano A, Morone MV, Silvestri C, Giordano M, Salvatore T, Sasso FC. Mechanisms of Non-Alcoholic Fatty Liver Disease in the Metabolic Syndrome. A Narrative Review. Antioxidants (Basel) 2021; 10: 270.
20) Lenti MV, Pasina L, Cococcia S, Cortesi L, Miceli E, Caccia Dominioni C, Pisati M, Mengoli C, Perticone F, Nobili A, Di Sabatino A, Corazza GR, REPOSI Investigators. Mortality rate and risk factors for gastrointestinal bleeding in elderly patients. Eur J Intern Med 2019; 61: 54-61.
21) Lisman T, Hernandez-Gea V, Magnusson M, Roberts L, Stanworth S, Thachil J, Tripodi A. The concept of rebalanced hemostasis in patients with liver disease: Communication from the ISTH SSC working group on hemostatic management of patients with liver disease. J Thromb Haemost 2021; 19: 1116-1122.
22) Rinaldi L, Valente G, Piai G. Serial Liver Stiffness Measurements and Monitoring of Liver-Transplanted Patients in a Real-Life Clinical Practice. Hepat Mon 2016; 16: e41162.
23) Ascione A, Fontanella L, Imparato M, Rinaldi L, De Luca M. Mortality from cirrhosis and hepatocellular carcinoma in Western Europe over the last 40 years. Liver Int 2017; 37: 1193-1201.
24) Jayakrishnan TT, Bakalov V, Finley G, Monga D, Wegner RE. Influence of social determinants of health on timeliness to treatment for metastatic HCC and the impact of affordable care act. WCRJ 2021; 8: e2073.
25) Abdel-Razik A, Mousa N, Elhelaly R, Tawfik A. De-novo portal vein thrombosis in liver cirrhosis: risk factors and correlation with the Model for End-stage Liver Disease scoring system. Eur J Gastroenterol Hepatol 2015; 27: 585-592.
26) Valente G, Rinaldi L, Sgambato M, Piai G. Conversion from twice-daily to once-daily tacrolimus in stable liver transplant patients: effectiveness in a real-world setting. Transplant Proc 2013; 45: 1273-1275.
27) Biondi A, Malaguarnera G, Vacante M, Berretta M, D'Agata V, Malaguarnera M, Basile F, Drago F, Bertino G. Elevated serum levels of Chromogranin A in hepatocellular carcinoma. BMC Surg 2012; 12: S7.
28) Di Benedetto F, Tarantino G, Ercolani G, Baccarani U, Montalti R, De Ruvo N, Berretta M, Adani GL, Zanello M, Tavio M, Cautero N, Tirelli U, Pinna AD, Gerunda GE, Guaraldi G. Multicenter italian experience in liver transplantation for hepatocellular carcinoma in HIV-infected patients. Oncologist 2013; 18: 592-599.

F. Dell'Annunziata[1], V. Folliero[1], C. Zannella[1], M. Giordano[2], R. Galiero[2], M. Galdiero[1]

[1]Department of Experimental Medicine, Section of Microbiology, University of Campania Luigi Vanvitelli, Naples, Italy
[2]Department of Advanced Medical and Surgical Science, University of Campania Luigi Vanvitelli, Naples, Italy