REVIEW ARTICLE

CONTENTS

Clinical classification of liver cirrhosis - a way to plan individual definitive treatment

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ABSTRACT

Aim: To develop clinical classification of liver cirrhosis, which can aid individualization and planning definitive treatment for this group of patients.

Materials and Methods: Computerized search of the literature was performed via PubMed using the following medical subject headings or keywords: "liver", "cirrhosis" and "classification"; or "liver", "cirrhosis" and "complications"; or "liver", "cirrhosis" and "treatment"; or "portal"", "hypertension" and "complications". Articles were independently evaluated by each author, the etiological, morphological and current clinical classifications of LC were analyzed, their advantages and disadvantages identified, and after discussion classification of LC was developed by consensus.

Conclusions: The developed clinical classification of liver cirrhosis will facilitate the planning of therapeutic tactics for each patient, allow to personalize the treatment of patients with this pathology.

KEY WORDS: liver cirrhosis, clinical classification, liver cirrhosis complications, portal hypertension

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INTRODUCTION

Liver cirrhosis (LC) is widely prevalent, rather common disease in the practice of both general practitioners and surgeons, and is the leading cause of death from liver diseases worldwide [1-5].

Different classification systems have been used for categorization of cirrhosis, focused on morphological and etiological features - small-nodular, large-nodular and mixed cirrhosis, and etiology - viral, alcoholic, toxic, autoimmune etc., amongst which Child-Pugh (CP) classification and the Model for End Stage Liver Disease (MELD) score are the most common [6,7]. While CP classification is widely used clinically and can give an indication of the severity of liver disease, the MELD score was developed and validated to predict mortality in patients with PH undergoing placement of transjugular intrahepatic portosystemic shunts (TIPS), but it is now more commonly used to predict survival in cirrhosis and for prioritization of patients for liver transplant. Undoubtedly, this is important information that a doctor needs to know. At the same time, it is important for a practitioner not only to establish the diagnosis of LC, but also to plan appropriate treatment.

Based on our many years of experience in treatment patients with LC, we have come to conclusion, that the formulation of a clinical diagnosis in this pathology should reflect the characteristics of the presence / absence of the main complications of the disease, with assessment of their severity.

AIM

The aim of our study was to develop clinical classification of LC, which can aid individualization and planning definitive treatment for this group of patients.

MATERIALS AND METHODS

Computerized search of the literature was performed via PubMed using the following medical subject headings or keywords: "liver", "cirrhosis" and "classification"; or "liver", "cirrhosis" and "complications"; or "liver", "cirrhosis" and "treatment"; or "portal"", "hypertension" and "complications". The following criteria were applied for study inclusion: publication in peer-reviewed journals, and publication since 1980. Articles were independently evaluated by each author, the etiological, morphological and current clinical classifications of LC were analyzed, their advantages and disadvantages identified, and after discussion classification of LC was developed by consensus.

REVIEW AND DISCUSSION

We emphasize that there is no LC without portal hypertension (PH), but the severity of its clinical manifestations are determined by the degree of morphological changes in the liver. Therefore, the diagnosis of cirrhosis should reflect this syndrome and its complications. Liver dysfunction is present at all stages of cirrhosis.

Based on the above, the clinical classification of LC can be presented as follows (with brief description of points):

1. Liver cirrhosis:
1.1. The stage of compensation
1.2. The stage of parenchymal decompensation.
1.3. The stage of vascular decompensation.
1.4. The stage of parenchymal-vascular decompensation.
1.5. The stage of hepatocerebral decompensation.
2. Portal hypertension ((mild or clinically significant portal hypertension (CSPH)):
2.1. Splenomegaly.
2.2. Gastroesophageal varices (GOV) (small, medium, large; type 1or 2); isolated gastric fundal varices (IGV) (type 1or 2).
2.3. Portal hypertensive gastropathy (PHG) (mild, severe).
2.4. Hypersplenism syndrome.
3. Complications of liver cirrhosis:
3.1 Ascites: uncomplicated (mild, moderate, large), refractory (diuretic resistant, diuretic intractable).
3.2. Gastrointestinal bleeding.
3.3 Jaundice.
3.4. Hepatic encephalopathy (HE).
3.5. Hepatorenal syndrome (HRS) (type 1 or 2).
3.6. Spontaneous bacterial peritonitis (SBP).
3.7. Hyponatremia (hypovolemic, hypervolemic).
3.8. Hepatic hydrothorax (HH).
3.9. Hepatopulmonary syndrome (HPS).
3.10. Portopulmonary hypertension (PPHTN).
3.11. Chronic liver failure (CLF) ((slowly progressive or acute exacerbative type (include acute-on-chronic liver failure (ACLF)).

Patients with cirrhosis without any symptoms are termed to have compensated cirrhosis. Complications such as ascites, variceal bleeding, hepatic encephalopathy, or non-obstructive jaundice, which can develop with cirrhosis of any origin, herald the onset of decompensated cirrhosis [3]. In the stage of compensation, additionally to the typical liver abnormalities, esophageal /gastric/gastroesophageal varices may not be present yet, or low grade varices may be present. On esophagogastroduodenoscopy (EGDS), esophageal varices should be graded as small or large (>5 mm) with the latter classification encompassing medium-sized varices when 3 grades are used (small, medium, large). The presence or absence of red signs (red wale marks or red spots) on varices should be noted. It was recommended that the size classification be as simple as possible, i.e., in 2 grades (small and large), either by semiquantitative morphological assessment or by quantitative size with a suggested cut-off diameter of 5 mm, with large varices being those greater than 5 mm. When varices are classified in 3 sizes–small, medium, or large–as occurs in most centers by a semiquantitative morphological assessment (with small varices generally defined as minimally elevated veins above the esophageal mucosal surface, medium varices defined as tortuous veins occupying less than one-third of the esophageal lumen, and large varices defined as those occupying more than one-third of the esophageal lumen) [8].

According Sarin classification, especially useful in describing the distribution of varices in the distal esophagus and stomach, fundal varices are included in two groups: GOV 2, when the esophageal and fundal varices are present in continuity over the cardia, which might include IGV 1 that are usually isolated gastric fundal varices. GOV 1 are typically a continuation of esophageal varices into the lesser curvature varices. IGV 2 are gastric varices at ectopic sites in the stomach outside the cardiofundal region or the first part of the duodenum. [9,10].

However, there is splenomegaly already present, increase in the diameter of the portal and splenic veins with an abnormal blood flow in them due to existing PH.

The stage of parenchymal decompensation is determined when the patient has ascites and/or parenchymal jaundice along with clinical manifestations of the disease.

The International Ascites Club proposed to link the choice of treatment of uncomplicated ascites to a classification of ascites on the basis of a quantitative criterion [11]. Uncomplicated ascites is the ascites that is not infected and which is not associated with the development of the HRS. Ascites can be graded as follows:

grade 1 (mild) - ascites is only detectable by ultrasound examination; grade 2 (moderate) - ascites causing moderate symmetrical distension of the abdomen; grade 3 (large) - ascites causing marked abdominal distension.

Refractory ascites is the ascites that cannot be mobilized or early recurrence of which (that is, after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy. This includes two different

subgroups: diuretic resistant ascites - ascites that is refractory to dietary sodium restriction and intensive diuretic treatment (spironolactone 400 mg/day and frusemide 160 mg/day for at least one week, and a salt restricted diet of less than 90 mmol/day (5.2 g of salt/day); diuretic intractable ascites–ascites that is refractory to therapy due to the development of diuretic induced complications that preclude the use of an effective diuretic dosage [11].

The stage of vascular decompensation is diagnosed when there is acute variceal bleeding. However, the doctor should remember that the presence of rectal (hemorrhoid) bleeding or metrorrhagia in a patient can also be clinical manifestations of PH due to already formed LC.

The stage of parenchymal-vascular decompensation is determined when the patient has signs of a combination of bleeding and ascites. This is a rather severe group of patients that requires a special approach to treatment.

The stage of hepatocerebral decompensation is determined when manifestations of HE are present. HE is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma [12, 13]. According West Haven criteria (WHC) used for grading HE, in grade I, patients show trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction, altered sleep rhythm. Despite oriented in time and space the patient appears to have some cognitive/behavioural decay with respect to his/her standard on clinical examination, or to the caregivers. In grade II, lethargy or apathy, disorientation for time (at least three of the followings are wrong: day of the month, day of the week, month, season or year), obvious personality change, inappropriate behavior, dyspraxia, asterixis are present. In grade III, patients may have somnolence to semi-stupor, they are responsive to stimuli, confused, gross disorientation is present, bizarre behavior may be demonstrated. Patients are also disoriented for space (at least three of the following wrongly reported: country, state (or region), city or place). In grade IV, patients are in coma and does not respond even to pain stimuli. When it became obvious that patients without clinical signs of HE may show alterations of brain function in neuropsychological or neurophysiological measures, a fifth grade was added to this system: the so-called subclinical or minimal HE (MHE). In this grade, psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change are present. Some experts have recommended that MHE and grade I HE be combined and classified as "covert HE" that contrasts to "overt" HE with clinical grades 2–4 [12].

PH is defined as an increase of portal pressure (PP) > 5 mmHg. The gold standard to measure portal venous pressure is the evaluation of hepatic venous pressure gradient (HVPG). Based on PP, patients with LC can be divided into those with mild PH (HVPG > 5 but < 10 mm Hg) and those with CSPH, defined by an HVPG ≥10 mm Hg, which is associated with an increased risk of complications like gastrointestinal varices, ascitic decompensation, gastrointestinal hemorrhage from portal hypertensive collaterals and HE [14,15].

PHG is diagnosed by characteristic endoscopic findings of small polygonal areas of variable erythema surrounded by a pale, reticular border in a mosaic pattern in the gastric fundus/body in a patient with cirrhotic or non-cirrhotic PH. The Baveno scoring system uses point calculations to define PHG as mild (≤ 3 points) vs severe (≥ 4 points) and also adds gastric antral vascular ectasia into the classification [16].

A serious complication of LC is secondary hypersplenism syndrome, which is defined by a combination of splenomegaly and peripheral blood pancytopenia. Its characterization allows assessing the severity of the patient's condition.

HRS is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure [17]. Type 1 HRS is a rapidly progressive acute renal failure that frequently develops in temporal relationship with a precipitating factor for a deterioration of liver function together with deterioration of other organ function. Type 2 HRS occurs in patients with refractory ascites and there is a steady but moderate degree of functional renal failure, often with avid sodium retention. Patients with type 2 HRS may eventually develop type 1 HRS either spontaneously or following a precipitating event such as SBP [17].

SBP is a very common bacterial infection in patients with cirrhosis and ascites. The diagnosis of SBP is based on diagnostic paracentesis. Patients with SBP may have one of the following: local symptoms and/or signs of peritonitis (abdominal pain, abdominal tenderness, vomiting, diarrhea, ileus); signs of systemic inflammation (hyper or hypothermia, chills, altered white blood cell count, tachycardia, and/or tachypnea); worsening of liver function; HE; shock; renal failure; and gastrointestinal bleeding. However, it is important to point out that SBP may be asymp-

tomatic, particularly in outpatients [11].

In patients with LC hyponatremia is defined when serum sodium concentration decreases below 130 mmol/L, but reductions below 135 mmol/L should also be considered as hyponatremia, according to recent guidelines on hyponatremia in the general patient population [18]. Hypervolemic hyponatremia is the most common and is characterized by low serum sodium levels with expansion of the extracellular fluid volume, with ascites and edema. By contrast, hypovolemic hyponatremia is less common and is characterized by low serum sodium levels and absence of ascites and edema, and is most frequently secondary to excessive diuretic therapy.

HH is defined as a pleural effusion, typically more than 500 mL, in patients with LC without coexisting underlying cardiac or pulmonary disease [19,20].

HPS is defined as the triad of liver dysfunction, intrapulmonary vasodilation and arterial oxygenation defect, which prevalence varies from 10% to 17% in the cirrhotic population and is associated with increased mortality [21].

PPHTN is a well-recognized complication of cirrhosis, defined as pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg) in a patient with coexisting portal hypertension and no other alternative cause of pulmonary hypertension [21].

In patients with cirrhosis, the annual incidence of HCC is about 3%-5%, which require special treatment, such as local liver resection, liver transplantation, ablation therapy and chemotherapy [21].

Patients with decompensated cirrhosis, because of complications or other factors, may experience either acute deterioration of liver function or slowly progressive disease. Acute deterioration of liver function is defined as the total bilirubin ≥ 171 μmol/L and prothrombin activity ≥ 40%. Accordingly, CLF can be divided into two types: slowly progressive, equivalent to the current slow progression of decompensated LC in patients with HE, and acute exacerbative type, equivalent to deterioration that occurs in decompensated LC, might include the ACLF proposed by EASL, which is more serious yet [22]. ACLF is defined as a syndrome characterized by acute decompensated cirrhosis, associated with the failure of various organs and a high short-term mortality rate (mortality at 28 days ≥15%) [23,24]. The Sequential Organ Failure Assessment (SOFA) score, was adapted to the characteristics of patients with cirrhosis and was called CLIF-SOFA, or its simplified version, CLIF-C Organ Failure score (CLIF-C OF). The presence of ACLF is identified according to the number and type of organ failure, while its severity is classed into 3 stages No ACLF is defined as no organ failure or 1 single organ failure, not including kidney failure, with serum creatinine <1.5mg/dL present and no hepatic encephalopathy. ACLF grade 1 is assumed if there is only one single kidney failure or 1 single organ failure linked to kidney failure (creatinine between 1.5 and 1.9mg/dL) or level 1–2 hepatic encephalopathy present. ACLF grade 2 is characterized by 2 organ failures, ACLF grade 3 – when ≥3 organ failures are present [24, 25].

According the classification we proposed above, the clinical diagnosis of LC patient is formulated with the stage of the disease, the presence/absence of CSPH and PH related complications (complication, its type/degree), complications of LC (complication, its type/degree).

For example, patient with LC in stage of compensation, PH (non CSPH) and splenomegaly require lowering portal pressure and prevention of complications by administration of non-selective β-blockers, EGDS repetition in 1 to 3 years, patient education (nutrition, physical exercises, safety of alcohol and medications, immunizations), screening for routine cancers and associated comorbidities.

Patient with LC in stage of parenchymal decompensation, CSPH, splenomegaly, uncomplicated moderate ascites requires symptomatic relief via a low-sodium diet and diuretics.

For patient with LC in stage of parenchymal decompensation, CSPH, splenomegaly, refractory diuretic resistant large ascites, HH control of ascites through large-volume paracentesis with albumin replacement, symptomatic relief by thoracentesis will be indicated. TIPS also could be considered, because it may be beneficial as for refractory diuretic resistant ascites, so for HH.

Patient with LC in stage of parenchymal-vascular decompensation, CSPH, splenomegaly, refractory diuretic resistant large ascites, medium-large GOV type 2, complicated by gastroesophageal bleeding, SBP require cautious transfusion in stable patients after volume resuscitation, hemostatic treatments (vasoactive and endoscopic), large-volume paracentesis with albumin replacement, intravenous antibiotics selected on the basis of local experience and risk of multidrugresistant bacteria.

CONCLUSIONS

In our opinion, the proposed above clinical classification of LC, will facilitate the planning of therapeutic tactics for each patient, which will allow to personalize the definitive treatment of patients with this pathology.

REFERENCES

1. Roth GA, Abate D, Abate KH et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392(10159): 1736-1788. doi: 10.1016/S0140-6736(18)32203-7. DOI
2. Gu W, Hortlik H, Erasmus H-P et al. Trends and the course of liver cirrhosis and its complications in Germany: Nationwide population-based study (2005 to 2018). The Lancet Regional Health – Europe. 2022;12: 100240. doi: 10.1016/j.lanepe.2021.100240. DOI
3. Ginès P, Krag A, Abraldes JG et al. Liver cirrhosis Lancet. 2021;398(10308):1359-1376.doi: 10.1016/S0140-6736(21)01374-X. DOI
4. Shetty A, Jun Yum J, Saab S. The Gastroenterologist's Guide to Preventive Management of Compensated Cirrhosis. Gastroenterol Hepatol (N Y). 2019;15(8):423-430.
5. Heron M. Deaths: Leading Causes for 2016. Natl Vital Stat Rep. 2018;67(6):1-77.
6. El-Khateeb E, Darwich AS, Achour B et al. Review article: time to revisit Child-Pugh score as the basis for predicting drug clearance in hepatic impairment Alimentary Pharmacology & Therapeutics. 2021; 54(4): 388-401. doi: 10.1111/apt.16489. DOI
7. Tsoris A, Marlar CA. Use of the child pugh score in liver disease. [Updated 2021 Mar 22]. In: StatPearls. Treasure Island, FL: StatPearls Publishing. 202. https://www.ncbi.nlm.nih.gov/books/NBK542308/. [date access 15.05.2023]
8. Garcia-Tsao G, Sanyal AJ, Grace ND et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46(3): 922-938. doi: 10.1002/hep.21907. DOI
9. Al-Osaimi AMS, Caldwell SH. Medical and Endoscopic Management of Gastric Varices Semin Intervent Radiol. 2011; 28(3): 273–282. doi: 10.1055/s-0031-1284453. DOI
10. Sarin SK, Kumar A. Gastric varices: profile, classification, and management. Am J Gastroenterol. 1989;84(10):1244–1249.
11. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397-417. doi:10.1016/j.jhep.2010.05.004. DOI
12. Weissenborn K. Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles Drugs. 2019; 79(1): 5–9. doi:10.1007/s40265-018-1018-z. DOI
13. Biggins SW, Angeli P, Garcia-Tsao G et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;74(2):1014-1048. doi: 10.1002/hep.31884. DOI
14. de Franchis R, Bosch J, Garcia-Tsao G et al. Baveno VII – renewing consensus in portal hypertension. J Hepatol. 2022;76(4):959–74. doi: 10.1016/j.jhep.2021.12.022. DOI
15. Brol MJ, Gödiker J, Uschner FE et al. Non-invasive Assessment of Clinically Significant Portal Hypertension. Curr Hepatology Rep. 2023;22:206–215. doi: 10.1007/s11901-023-00609-4. DOI
16. Gjeorgjievski M, Cappell MS. Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history and therapy. World J Hepatol. 2016;8(4):231-62. doi: 10.4254/wjh.v8.i4.231. DOI
17. Salerno F, Gerbes A, Ginès P et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56(9):1310–1318. doi:10.1136/gut.2006.107789. DOI
18. Verbalis JG, Goldsmith SR, Greenberg A et al. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med. 2007;120(11):1-21. doi: 10.1016/j.amjmed.2007.09.001. DOI
19. Yong L, Guohong H, Daiming F. Hepatic Hydrothorax. Ann Hepatol. 2018;17(1):33-46. doi: 10.5604/01.3001.0010.7533. DOI
20. Machicao VI, Balakrishnan M, Fallon MB. Pulmonary complications in chronic liver disease. Hepatology. 2014; 59(4): 1627-1637. doi: 10.1002/hep.26745. DOI
21. Nusrat S, Khan MS, Fazili J et al. Cirrhosis and its complications: evidence based treatment. World J Gastroenterol. 2014;20(18):5442-60. doi:10.3748/wjg.v20.i18.5442. DOI
22. Xing TJ. Clinical Classification of Liver Failure: Consensus, Contradictions and New Recommendations. J Clin Gastroenterol Hepatol. 2017, 1(2). doi: 10.21767/2575-7733.1000016. DOI
23. Arroyo V, Moreau R, Jalan R. Acute-on-Chronic Liver Failure. N.Engl. J. Med. 2020;382(22):2137-2145. doi:10.1056/NEJMra1914900.
24. Solé C, Solà E. Update on acute-on-chronic liver failureActualización en la insuficiencia hepática aguda sobre crónica. 2018;41(1):43–53. doi: 10.1016/j.gastre.2017.05.011. DOI
25. Kumar R, Mehta G, Jalan R. Acute-on-chronic liver failure. Clin Med (Lond). 2020;20(5):501-504. doi: 10.7861/clinmed.2020-0631. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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