Prognostic Indexes for Alcoholic Hepatitis

REVIEW

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Abstract

Alcohol abuse is the major source of liver disease. The prevalence of alcoholic hepatitis (AH) is unknown, but histologic studies demonstrated that AH may be present in approximately 10% to 35% of hospitalized patients with alcoholism. The assessment of severity permits the identification of patients that will improve without medical therapy and those that will have a high mortality if not treated. A variety of scoring systems has been used to quantify the severity of AH and guides its treatment. The scores more commonly used are: Maddrey's discriminant function (DF), Model for End-Stage Liver Disease (MELD), Glasgow Alcoholic Hepatitis Score (GAHS) and Age, serum Bilirubin, INR (International Normalized Ratio), and serum Creatinine (ABIC). Some others prognostic indexes assess the efficacy of treatment, like Lille score, and Early Change in Bilirubin Levels. Histologic findings are showed to predict additional findings like risk of infection and poor prognosis even in a subgroup considered of better prognosis. The authors strongly recommend liver biopsy to confirm the diagnosis of AH and to discriminate patients with risk of infection and death without medical therapy. In our point of view, this method has been showed to be the best prognostic markers for AH in nowadays. In conclusion, AH is a severe complication among heavy drinkers and frequently results in poor short term prognosis. Various clinical scores are useful to differentiate patients with high mortality if not treated and are similar in predicting the outcome. More recently, the liver biopsy and a histologic score including fibrosis, megamitochondria, neutrophil infiltration and bilirubinostasis showed promising results and should be recommended.

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Introduction

Global Disease Burden was evaluated in a recent study, showing that alcohol use was the third leading source of disease. Importantly, this study considered 67 risk factors at 21 regions of the world [1]. Mo-

reover, alcohol use is the major source of liver disease worldwide and is responsible for about 2.5 million deaths annually [2, 3]. A study showed that alcoholic liver cirrhosis was the cause of 493,300 deaths and 14,544,000 disability adjusted life years, indicating 0.9% of all global deaths, 47.9% of all liver cirrhosis deaths and 80,600 deaths of liver cancer (14,800 female deaths and 65,900 male deaths) in 2010 [4].

In a population-based study evaluating 16 countries of America the mortality of alcohol was also important. Liver disease was responsible for 63% of deaths following by mortality for neuropsychiatric disorders [5].

In Brazilian population, liver diseases were the eighth leading cause of death. Cirrhosis was the main etiology of death by liver disease in Brazil and alcohol was the second leading cause of cirrhosis [6].

Fatty liver develops in approximately 90% of individuals who drink more than 60 g/day of alcohol and continuous alcohol use (40 g/day) increased the risk of progression to fibrosis and cirrhosis in approximately 37% [7, 8]. Some patients with Alcoholic Liver Disease (ALD) will develop alcoholic hepatitis (AH), which is a clinical syndrome of liver injury that frequently occurs after decades of heavy alcohol use and has a significantly poor prognosis [9,10]. AH can range from mild to severe, life-threatening, and can present acutely or in a patient with chronic ALD [2, 10]. The true prevalence of AH is unknown, but histologic studies of patients with ALD demonstrated that AH may be present in approximately 10% to 35% of hospitalized patients with alcoholism [2, 11]. Clinically, the most frequent presentation of AH is a rapid onset of jaundice; other common signs and symptoms are fever, ascites and encephalopathy [10]. Moreover, some patients with cirrhosis can have an acute decompensation named acute-on-chronic liver failure (ACLF), a condition associated with multiple organ failure and higher mortality. Recently, a multicen-

ter European study, evaluating 1,343 hospitalized patients with cirrhosis and acute decompensation, showed a 28-day mortality of 33.9% among patients with ACLF and 1.9% among those who did not have this complication. In this study, the leading cause of ACLF were alcoholic cirrhosis [12].

Traditionally, corticosteroids are recommended as first line therapy for severe AH, although some studies presented contradictory results [2, 13, 14]. Three of five meta-analyses showed improvement in short-term survival in AH patients receiving corticosteroid treatment [15, 16, 17], whereas two meta-analyses showed no improvement [18].

Pentoxifylline has also been used in patients with severe AH. Three randomized clinical trials compared pentoxifylline in combination with corticosteroids and corticosteroids monotherapy in severe AH [19,20,21]. In these studies there was no additional survival for the combination of drugs compared with corticosteroids alone in a 6-month survival. The guidelines of AASLD recommend pentoxifylline in the patients with severe AH, especially if there are contraindications to the corticosteroids [2]. The EASL guidelines recommend using pentoxifylline instead of corticosteroids in patients with sepsis [14].

A recent large trial randomized 1103 patients with severe AH to one of four treatment groups: prednisolone and pentoxifylline, prednisolone and placebo, pentoxifylline and placebo, or double placebo. Prednisolone, but not pentoxifylline, was associated with a lower risk for 28-day mortality [22].

Newly, the addiction of metadoxine to standard treatment with corticosteroids in patients with severe AH was evaluated. Seventy patients with severe disease were randomized to receive prednisone or prednisone plus metadoxine. Patients treated with metadoxine had a higher survival at 30 days (74.3% vs. 45.7%) and at 90 days (68.6% vs. 20.0%). Additionally, patients treated with the combination of drugs had fewer encephalopathy and hepatorenal syndrome, severe complications of AH [23]. On the

other hand, further studies were necessary to confirm these results.

Mild AH often resolves with abstinence of alcohol while the severe form has worse prognosis; therefore, the assessment of severity permits the identification of patients that will improve without medical therapy and those that will have a high mortality if not treated [24].

A variety of scoring systems has been used to quantify the severity of AH and guides its treatment. The scores more commonly used are: Maddrey's discriminant function (DF), Model for End-Stage Liver Disease (MELD), Glasgow Alcoholic Hepatitis Score (GAHS) and Age, serum Bilirubin, INR (International Normalized Ratio), and serum Creatinine (ABIC) [25-32]. Some others prognostic indexes assess the efficacy of treatment, like Lille score, and Early Change in Bilirubin Levels [33-34].

Classic Prognostic Scores

The first and the most frequent score used to identify patients with poor prognosis in AH is Maddrey's DF. This score was first describing in a placebo-controlled study aimed to assess the efficacy of corticosteroid therapy in 55 patients with AH. The original formula considered the absolute value of prothrombin time (PT) [35]. Further, the authors presented a modification in the original score (DF) using prolongation of PT in seconds (over control) instead of the absolute value, as follows: $4.6 \times (\text{PT} - \text{control time}) + \text{serum bilirubin (mg/dL)}$, in a randomized multicenter trial with methylprednisolone therapy in patients with severe AH. In this trial, patients with a score ≥ 32 in a placebo group had a mortality of 35% in 28 days [25]. Subsequently to this study, DF is the prognostic marker of AH more frequently used.

The MELD score, traditionally used for the prediction of mortality from end-stage liver disease, has also been used as a prognostic marker in alcoholic hepatitis [26-29]. Sheth *et al* [27] studied 34 patients with severe AH and demonstrated that

a MELD score higher than 11 or the presence of ascites and bilirubin over than 8 mg/dl was an indicative of poor prognosis. In the same manner, a retrospective study of 73 patients with AH demonstrated that MELD was the only independent predictor of mortality; MELD score of 21 had a sensitivity of 75% and a specificity of 75% in predicting mortality in 90 days [28]. The accuracy of MELD score in different moments was also evaluated in 202 patients with AH. In this study, MELD score at admission, MELD score at first week, and first week increase in MELD score were independently associated with in-hospital mortality. Furthermore, when MELD score at first week was equal or higher than 20, the sensitivity (91%) and specificity (85%) to predict mortality was superior than MELD score at admission or first week change in MELD score [29].

The inclusion of sodium in MELD score has also been evaluated. A prospective study from Mayo Clinic showed that MELD score of 27 and a MELD Na score of 28 had sensitivity of 76.5% and 87.5% and specificity of 64.9% and 52.5%, to predict mortality in AH respectively. Furthermore, in patients with AH and ascites, MELDNa was a better predictor of mortality in 180 days than MELD [36].

Other score that is traditionally used for the assessment of AH prognosis is the GAHS. Forrest *et al* [30] analyzed the variables related to poor prognosis of AH in 241 patients. The variables identified (age, white blood cell count, urea, PT and bilirubin) were included in GAHS score and validated in a distinct cohort of 195 patients. Patients with AH and GAHS greater than 9 had a poor prognosis. Moreover, in this study, GAHS was more accurate than DF in predicting outcome at 28 and 84 days after admission [30]. Further, the same authors evaluated the efficacy of GAHS to identify patients who would benefit from corticosteroids. They select 225 patients with an DF greater than or equal to 32 in a multicenter study; of these, 144 patients also had a GAHS greater than or equal to 9. When GAHS

was less than 9, there was no difference in survival between patients untreated or treated with corticosteroids. On the other hand, when patients with a GAHS greater than or equal to 9 were evaluated, it was demonstrated that those treated had a higher survival in 28 days comparing with untreated (78% and 52% respectively). Moreover, they showed that even in patients with DF greater than or equal to 32, when GAHS was less than 9 and, there was no significant benefit from treatment with corticosteroids [31].

Dominguez *et al* [32] analyzing 103 patients with AH, demonstrated that age, serum bilirubin, INR and serum creatinine were independently associated with mortality in 90 days of admission for AH. According to these results, the authors created the Age, serum Bilirubin, INR, and serum Creatinine (ABIC) score: $(\text{age} \times 0.1) + (\text{serum bilirubin} \times 0.08) + (\text{serum creatinine} \times 0.3) + (\text{INR} \times 0.8)$. Patients with low, intermediate, and high risk of death at 90 days (100%, 70%, and 25% of survival rate, respectively) were identified [32].

Some scores aimed to evaluating the response of corticosteroid therapy. Lille Score is a dynamic model that estimate the response to this therapy in the day seven of therapy; six months survival was 25% in patients with Lille score > 0.45 and 85% in those with Lille score < 0.45 [33]. In the same manner, studies demonstrated that any fall in serum bilirubin level after 1 week of corticosteroid therapy (Early Change in Bilirubin Levels) or more specifically a 25% fall can be simple indicators of corticosteroid response [34, 37].

Recently, because of the heterogeneity of previous studies, some authors attempted to compare the classic scores. In this setting, Sandahl *et al* [38] evaluated and compare GAHS, MELD, MELDNa, Lille model and ABIC in 274 patients demonstrating similar results between the scores in predicting mortality in AH at day 28, 84 and 180 [38].

Similarly, Palaniyappan *et al* [39] compared five scoring systems: Child Pugh, MELD, DF, GAHS and

ABIC score in 44 patients with AH confirmed by histology. This study showed that with exception of Child Pugh, that presented worse results, the other scores have a good comparable accuracy in predicting survival at 30 days, 90 days, 6 months, and 1 year. Nevertheless, they are equally poor in predicting survival in 6 months and 1 year (ROC curve not exceeding 0.74% and 0.66% respectively) [39].

Another prospective study analyzed the ability of GAHS, DF, MELD and ABIC in predicting mortality in AH and didn't find any difference between the scores in 182 patients at 28 and 90 days [40].

More recently, Papastergiou *et al* [41] aimed to validate the following nine score systems: DF; GAHS; MELD; ABIC; MELDNa; Early Change in Bilirubin Levels (ECBL); United Kingdom End-stage Liver Disease (UKELD); a 25% fall in bilirubin during the treatment and Lille score. In this study, the authors evaluated 71 patients with AH (confirmed by biopsy) and compared the prognostic models with respect to mortality in 30 and 90 days [41]. The results revealed similar areas under the receiver operating characteristics curve (AUROCs) for all scores. Additionally, the models showed very good negative predictive values (86–100%), signifying that these scores are best to recognize patients with low risk of mortality.

To validate the prognosis of AH in a US population, Cuthbert *et al* [42] studied 148 patients and analyzed a revised DF (using INR instead of PT) and peak values of MELD. The authors showed that the most significant predictor of short-term mortality was peak values of MELD, followed by revised DF [42].

Prognostic model of Asian patient cohort (MAGIC) were also lately presented and includes the following parameters: bilirubin, prothrombin time, creatinine, potassium at admission, and a spontaneous change in bilirubin levels from day 0 to day 7. MAGIC was able to accurately predict mortality in Asian patients with severe AH [43].

Liver Histology as Prognostic Factor

Alcoholic steatohepatitis is histologically characterized by steatosis, ballooning degeneration of hepatocytes, and lobular infiltration by inflammatory cells, particularly polymorphonuclear cells [44]. Additional findings include the presence of megamitochondria and Mallory bodies. Periportal ductular proliferation, ductular bilirubinostasis, and intraparenchymal cholestasis may also be observed. Fibrous tissue classically localizes in central zone (zone 3), in the terminal hepatic vein and in perisinusoidal and pericellular areas, frequently resulting in the typical “chicken-wire fibrosis” [45, 46].

Liver biopsy can be necessary to confirm AH and it's recommended in American Association for the Study of Liver Diseases (AASLD) guidelines however it's not mandatory [2]. The last guideline of European Association for the Study of Liver (EASL) also recommends liver biopsy, but only in patients with a high risk of dying without pharmacotherapy [14]. On the other hand, some of these patients have a contraindication to percutaneous liver biopsy, frequently they patients have ascites and clotting abnormalities; transjugular biopsy is recommended in these cases [24].

Spahr *et al* [47] assessed the liver biopsy of 163 patients with AH and demonstrated that intraparenchymal cholestasis was more prevalent in non survivors compared to survivors (70% vs 25%) at multivariate analysis. Moreover, serum bilirubin was higher in patients with severe intraparenchymal cholestasis [47].

Recently, Altamirano *et al* [48] identified four histological findings (fibrosis, neutrophil infiltration, type of bilirubinostasis, and presence of megamitochondria) associated with mortality at day 90 in AH [48]. This histologic features were further graded and classified as Alcoholic Hepatitis Histological Score (AHHS) and presented as low (0-3 points), moderate (4-5 points), or high (6-9 points) according to the risk of mortality in 90 days: 3%, 19% and 51%, respectively. In addition, in patients treated

with corticosteroids, the three months survival was 85% when AHHS score less than 5 and only 51% when the score was equal or higher than 5. Interesting, when analyzing patients with a MELD score less than 21, a score that traditionally is associated with a better outcome [28], the AHHS was also able to discriminate two different rates of survival, 94% in patients with AHHS less than 5 vs 72% in those with score equal or higher than 5. Then, the application of the AHHS in patients with MELD less than 21 may further differentiate the patients who might benefit from treatment. Moreover, in this study, bilirubinostasis predicted (in nearly half of the patients) the development of bacterial infections, a severe complication associated to AH. Clinicians must be aware to rule out infections in this subgroup of patients since sepsis is one of the main cause of death in severe AH and its presence can contraindicate corticosteroids.

As presented, we strongly recommend liver biopsy to confirm the diagnosis of AH and to discriminate patients with risk of infection and death without medical therapy. In our point of view, this method has been showed to be the best prognostic markers for AH in nowadays.

Others Prognostic Factors

Kasztelan *et al* [49] studying 116 patients demonstrated that alkaline phosphatase level higher than 1.5 times the upper limit of normal was an independent predictor of mortality of AH in 90 days. Moreover, this study demonstrated that two clinical parameters also had a significant prognostic value: all patients who died had ascites and 55% of them had also hepatic encephalopathy. Furthermore, the lack of ascites and encephalopathy was associated with 100% survival in 90 days [49].

The prognostic value of hepatic venous pressure gradient (HVPG) in patients with acute AH was also evaluated. Rincon *et al* [50] studied 60 patients with severe AH and demonstrated that a HVPG of more than 22mmHg in patients with DF of greater

than 32 was an independent predictor of in-hospital mortality [50]. On the other hand, a study done by Palaniyappan *et al* [39], was unable to demonstrate association between portal hypertension (HVPG $\geq$ 10 mmHg) with short or long survival in this group of patients [39].

The prognostic value of renal failure was assessed by Altamirano *et al* [51] in a study with 103 patients with AH. Twenty-nine patients (28%) developed acute kidney injury (AKI) during hospitalization. AKI was defined as an abrupt reduction (within 48 h) in kidney function that resulted in an absolute increase of at least 0.3 mg/dL (or a 50% increase) in serum levels of creatinine from baseline (the AKI network [AKIN] criteria). In this study, the 90-day mortality was significantly higher among patients with AKI than those without (65% vs 7%). The most accurate predictors of AKI in this study were the presence of systemic inflammatory response syndrome, levels of bilirubin, and value of INR at admission. Furthermore, the AKIN criteria were more accurate than classical criteria for renal failure (serum creatinine >1.5 mg/dl) in predicting 90-day mortality [51].

In a recent study, serum levels of 25-hydroxyvitamin D were determined in 324 patients with ALD. Severe deficiency was significantly associated with more severe steatosis, fibrosis and AH [52].

Conclusion

AH is a severe complication among heavy drinkers and frequently results in poor short term prognosis. Various clinical scores are useful to differentiate patients with high mortality if not treated, these scores (DF, MELD, MELD Na, GAHS, ABIC) are similar in predicting the outcome. More recently, a histologic score including fibrosis, megamitochondria, neutrophil infiltration and bilirubinostasis showed promising results and can be recommend in a subset of patients submitted to liver biopsy.

Author contributions

Gabriela P Coral and Angelo A Mattos conceptualized the manuscript; Gabriela P Coral, Mariana A Pranke and Cristiane V Tovo reviewed the literature and wrote the manuscript; Angelo A Mattos and Cristiane V Tovo reviewed it critically for important intellectual content and all authors approved the final version to be published.

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