Pharmacologic Treatment of Alcoholic Hepatitis: Examining Outcomes Based on Disease Severity Stratification

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Objectives: **Maddrey discriminant function (MDF) score is a measure of disease prognosis in alcoholic hepatitis (AH) used to identify patients at highest risk of mortality and determine the need for initiation of pharmacologic treatment. The purpose of this study was to evaluate the effects of pharmacologic therapy for hospitalized AH patients as stratified by MDF score.** ***Methods:*** **A retrospective review of patients with an AH diagnosis admitted to a Methodist LeBonheur Healthcare adult hospital between 06/2009 and 06/2014 was conducted. Patients ≥18 years of age with an ICD-9 code for AH were evaluated.** ***Results:*** **Of the 493 patients screened, 234 met the inclusion criteria, comprised of 62 patients with an MDF ≥ 32 (treatment, *n* = 42 vs. no treatment, *n* = 20) and 172 patients with an MDF < 32 (treatment, *n* = 15 vs. no treatment, *n* = 157). For the patients with an MDF ≥ 32, there was no statistically significant difference between the treatment group vs. non-treatment group regarding 28-day mortality (31% vs. 11%, respectively; *P* = 0.18) and 6-month mortality (45% treatment vs. 38% non-treatment; *P* = 0.75). For the patients with an MDF <32, there was no statistically significant difference between the treatment group vs. non-treatment group regarding 28-day mortality (0% vs. 7%, respectively; *P* > 0.99) and 6-month mortality (11% treatment vs. 13% non-treatment; *P* > 0.99). There was no difference in incidence of acute kidney injury, hepatorenal syndrome, development of infection or hepatic encephalopathy between the treatment vs. non-treatment groups.** ***Conclusions:*** **Pharmacologic treatment showed no survival benefit, regardless of disease severity. Given the mortality risk seen in mild–moderate AH patients not receiving treatment and concern for a possible treatment ceiling effect in severe AH patients, more data are needed to adequately assess the utility of MDF in selecting appropriate candidates for AH treatment. (J Clin Exp Hepatol 2016;6:275–281)**

Alcoholic liver disease (ALD) is a form of liver injury resulting directly from alcohol consumption with injury manifesting as reversible fatty liver to alcoholic hepatitis (AH) or cirrhosis.[1] ALD is associated with increased healthcare costs resulting from multiple hospital readmissions, and has been identified as the second most leading indication for liver transplantation.[1] ALD encompasses AH that occurs as a result of prolonged alcohol consumption and ranges in severity from asymptomatic to liver failure.[2] AH is associated with a high mortality burden, up to 15% at 30 days, which is dependent on disease severity at presentation.[1] Per American Association for the Study of Liver Diseases (AASLD) guidelines, disease severity should be initially established upon presentation in all AH patients to aid in therapeutic management.[3] One measure of disease severity and prognosis specific to AH patients is the Maddrey discriminant function (MDF) score, which utilizes the patient's prothrombin time (PT) and total bilirubin to predict short-term mortality. An MDF score greater than or equal to 32 indicates severe disease with a 1-month mortality rate up to 30–50%.[3] Patients with severe disease and concurrent hepatic encephalopathy appear to be at the highest risk of death.[3] The MDF score can be utilized in clinical practice for early identification of patients at highest risk of mortality and initiation of pharmacological therapy to prevent further liver damage and development of complications.[3,4]

Corticosteroids have been most commonly studied in AH patients and are regarded as the treatment of choice. However, the results from small placebo-controlled trials have varied from reduction in short-term mortality to no effect.[3] The most recent meta-analysis data provide

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Abbreviations: AASLD: American Association for the Study of Liver Diseases; AH: alcoholic hepatitis; AKI: acute kidney injury; ALD: alcoholic liver disease; ARR: absolute risk reduction; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; HRS: hepatorenal syndrome; INR: international normalized ratio; MDF: Maddrey discriminant function; MELD: Model for End-Stage Liver Disease; PT: prothrombin time; SCr: serum creatinine; SD: standard deviation
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evidence that corticosteroid treatment is primarily beneficial in severe AH patients.[5,6] While a 28-day duration of prednisolone 40 mg daily is regarded as the gold standard of therapy, it may not be ideal in patients with an active gastrointestinal (GI) bleed or infection due to risk of further exacerbation of these conditions. One alternative to corticosteroid therapy that has been studied is an oral phosphodiesterase inhibitor, pentoxifylline. This therapy has been shown to reduce 28-day (absolute risk reduction (ARR): 21.6%) as well as 3-month mortality (ARR: 20.6%), with its beneficial effects mostly attributed to the reduction of hepatorenal syndrome (HRS).[7,8] Given the potential benefits of pentoxifylline, it was postulated that combination therapy with corticosteroids may lead to improvement in outcomes surpassing what is recognized with steroids alone. However, two small studies have concluded that combination therapy does not improve 4-week or 6-month survival.[9,10]

Although limited and conflicting evidence is available in this patient population, current AASLD practice guidelines recommend pharmacologic therapy in AH patients with an MDF score $\geq$32 with prednisolone or utilizing pentoxifylline as an alternative agent to improve survival. In contrast, pharmacologic therapy is not recommended for less severe patients (MDF <32), specifically those without hepatic encephalopathy, as these patients are unlikely to benefit from treatment.[3] Therefore, the purpose of this study was to evaluate the effects of pharmacologic therapy in hospitalized AH patients, examining outcomes in both mild-to-moderate and severe AH patients as determined via MDF score.

METHODS

A retrospective review of patients admitted to adult hospitals within the Methodist LeBonheur Healthcare System between June 2009 and June 2014 with a diagnosis of AH was conducted. Patients were identified through the corporate patient financial services database using ICD-9-CM code 571.1 for AH. Patients were included if they were at least 18 years of age and had a diagnosis of AH. The diagnosis was further confirmed by chart review for physician documentation of AH. Exclusion criteria consisted of other potential liver injury etiologies, reported current use of steroid or pentoxifylline prior to hospitalization (verified through home medication reconciliation), lack of complete data to calculate an MDF score (lack of total bilirubin or PT labs), history of liver transplantation, received N-acetylcysteine for AH, or experienced death within 24 h of hospital admission.

Patient demographics, as well as pertinent baseline laboratory findings were collected upon admission. Laboratory data included serum albumin, serum creatinine (SCr), estimated glomerular filtration rate (eGFR) via MDRD equation, international normalized ratio (INR), PT, and total bilirubin. Utilizing these data, an MDF score and a Model for End-Stage Liver Disease (MELD) score were calculated to assess disease severity. MDF score was calculated using the following equation: 4.6 (patient's prothrombin time – control prothrombin time) + total bilirubin, with a control prothrombin time of 14.5 based on the upper limit of normal for the lab assay utilized. Patients with a score $\geq$32 were defined as severe AH, while those with a score <32 were classified as mild-to-moderate disease. Clinical data including date of initiation and duration of inpatient AH treatment, preexisting or in-hospital development of AH complications, and mortality were also collected. AH treatment was defined as pharmacological treatment with prednisolone, prednisone, and/or pentoxifylline for more than 24 h as documented in the medication administration record. AH complications evaluated in this study included HRS or acute kidney injury (AKI), infection, GI bleed, and hepatic encephalopathy, which were all based on physician documentation of occurrence in the patient's medical record during index hospitalization 24 h after treatment was initiated. Mortality data were determined by subsequent readmissions and/or death within our hospital system or by follow-up visits in our outpatient hepatology clinic.

Patients were initially divided via MDF score into those with an MDF score <32 and those with an MDF score $\geq$32 to assess outcomes based on disease severity. These groups were further divided into treatment or non-treatment groups. The primary outcome of this study was to describe the 28-day and 6-month mortalities in patients who received AH treatment vs. no treatment based on disease severity, as stratified by their MDF score. Secondary outcomes included assessment of overall mortality and the incidence of AH complication development in the treatment vs. non-treatment groups, along with mortality outcomes in patients who received monotherapy with corticosteroid vs. combination therapy (corticosteroid plus pentoxifylline).

Categorical patient characteristics were compared using a chi-square test or Fisher's exact test. Continuous data were analyzed using a Student *t* test and are expressed as the mean $\pm$ standard deviation (SD). Incidence of 28-day and 6-month mortalities, as well as AH complication development were all identified and compared between the treatment and non-treatment groups utilizing a chi-square test. Data were analyzed using SPSS Statistics for Windows, version 21 (IBM Corporation, Armonk, NY). *P* values less than 0.05 was considered statistically significant. The study was approved by the University of Tennessee Health Science Center Institutional Review Board and in accord with the Helsinki Declaration of 1975. The study did not receive any financial grants or support from outside sources.

RESULTS

Overall, 493 admissions were screened with 234 meeting inclusion criteria. Of these 234 admissions, 62 patients had

