A CLINICAL STUDY OF SPECTRUM OF ALCOHOLIC LIVER DISEASES WITH RESPECT TO PREDICTORS OF SEVERITY AND PROGNOSIS

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ABSTRACT

BACKGROUND

Chronic and excessive alcohol ingestion is one of the major causes of liver disease. The traditional disease specific prognostic model used for this purpose is the Maddrey Discriminant Function (DF). MELD score has been recently developed to predict mortality in patients with alcoholic hepatitis.

This study aims at correlating MELD score, serum sodium, MELD NA score, serum albumin and Maddrey discriminant function in determining short-term prognosis in patients with alcoholic liver disease and its complications.

MATERIALS AND METHODS

A total number of 100 patients of age >18 years with significant history of alcohol abuse who were admitted in ESIC, PGIMSR, Bengaluru, with alcoholic liver disease or related complications who met the inclusion and exclusion criteria were analysed. MELD, DF, MELD NA were calculated at admission and correlated with severity and mortality.

RESULTS

There were 16 deaths in the study attributable to alcoholic hepatitis or its complications. We found that DF largely correlates with MELD at lower values; at higher values, many patients have disproportionally higher MELD score compared to DF. Among these patients, deaths appear to track more closely with MELD rather than DF.

CONCLUSION

In summary, MELD and MELD NA are useful for predicting 30-day mortality in patients with alcoholic hepatitis and maintains some practical and statistical advantages over DF in predicting mortality rate in these patients. The MELD NA score performed better than MELD in predicting short-term mortality. Presence of ascites, hyponatraemia, hepatic encephalopathy, variceal bleeding and SBP were independent predictors of adverse prognosis in alcoholic hepatitis/cirrhosis.

KEYWORDS

ALD, MELD, DF, MELD NA, Hyponatraemia, ROC and AUROC.

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BACKGROUND

Alcohol intake remains the most important cause of cirrhosis in the world.[1] The causal association between alcohol intake and the development of alcoholic liver disease has been well demonstrated.[2,3] Nevertheless, it remains a conundrum that only a small proportion of heavy drinkers develop the most advanced form of the disease (liver cirrhosis).[3] Although, alcohol is considered a direct hepatotoxin, only between 10 and 20% of alcoholics will develop alcoholic hepatitis.[4] Possible factors that affect the development of liver injury are the dose, duration and type of alcohol consumption; drinking patterns, sex, ethnicity and other risk factors, cirrhosis is defined as a diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.[5] Alcohol is the world's third largest risk factor for disease burden. The harmful use of alcohol results in 2.5 million deaths each year. Most of the mortality attributed to alcohol is secondary to cirrhosis.[6] Major complications of cirrhosis include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, variceal bleeding and hepatorenal syndrome.[7]

Assessing severity of disease in patients with alcoholic hepatitis is useful for predicting mortality, guiding treatment decisions and stratifying patients for therapeutic trials. The traditional disease specific prognostic model used for this purpose is the Maddrey Discriminant Function (DF). MELD score has been recently developed to predict mortality in patients with alcoholic hepatitis. The Model for End-Stage Liver Disease (MELD) score is the method most widely used for organ allocation in liver transplantation. Low serum sodium was associated with an increased risk of death in all subpopulations of patients with cirrhosis and serum sodium and MELD were found to be independent predictors of survival.[8]

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This study aims at correlating MELD score, serum sodium, MELD Na score, serum albumin and Maddrey discriminant function in determining short-term prognosis in patients with alcoholic liver disease and its complications.

Aim and Objectives

1. To study the prevalence of different forms of alcoholic liver disease.
2. To determine the MELD score, serum sodium levels and serum albumin levels and Maddrey discriminant function in patients of alcoholic liver disease and its complications.
3. To establish a correlation with clinical profile and observed laboratory parameters and their significance in predicting short-term prognosis and mortality in patients.

MATERIALS AND METHODS

Source of the Data

The data gathered from inpatient records and case sheets of patients admitted at Employees State Insurance Corporation-Medical Collage-Postgraduate Institute of Medical Sciences and Research (ESIC-MC-PGIMSR) in a period of 18 months from November 2014 to June 2016.

Method of Collection of Data- Patients satisfying inclusion criteria are enrolled within 24 hours of admission after informed consent.

Patients categorised into respective form of alcoholic liver disease and involved complications and graded accordingly.

Baseline investigations include-

- Complete haemogram.
- Renal function test.
- Serum electrolytes.
- Chest x-ray.
- ECG.

Investigations needed for the study-

- Hepatitis B profile.
- Hepatitis C profile.
- Liver function test.
- PT, APTT, INR.
- Serum sodium levels, serum albumin levels, USG abdomen.

Sample Size- All the patients admitted with confirmed diagnosis of alcoholic liver disease in the study period. To increase the sensitivity and power of tests applied in analysis and in view of number of patients admitted with alcoholic liver disease, a minimal of 100 patients are enrolled.

Institutional Ethical Committee approved the study protocol.

Informed consent was obtained from the patients.

Study Design- Longitudinal prospective study.

Inclusion Criteria

1. Patients aged above 18 years admitted under medicine department (both gender included).
2. Patients diagnosed as alcoholic liver disease based on history, liver function tests (increased bilirubin and decreased albumin), ultrasound studies and clinical parameters.
3. Alcohol consumption within 2 months and exceeding 40 g/day for males and 20 g/day for females and AST/ALT ratio >1.5 with AST >45 U/L and total bilirubin >2 mg/dL.

Exclusion Criteria

1. Patient under age 18 years.
2. Patient with known hepatocellular carcinoma.
3. Patients with history of prior diuretic and anticoagulant intake.
4. Patients who have undergone TIPS.
5. Patients with known cause of hepatitis infections (A/B/C/D/E).
6. Patients with other causes of cirrhosis other than alcoholism.

Follow Up

Follow up was done on the outpatient basis once every week, every time detailed history was taken and clinical examination was done. The aim is to follow the patients for a period of at least 30 days. Few of the patients who couldn't attend the OPD on a regular basis were followed over the phone were in detailed history was taken.

RESULTS

A total number of 100 patients of age >18 years with significant history of alcohol abuse who were admitted in ESIC, PGIMSR, Bengaluru, with alcoholic liver disease and related complications were analysed.

Variable	Mean (SD)
Age	49.99 (10.5) years

Table 1. Demographic Characteristics

Gender	Number	Percentage
Male	89	89
Female	11	11
Total	**100**	**100**

Table 2. Gender Distribution

Variable	Mean (SD)
Hazardous drinking	13.2 (5.98) years

Table 3. Hazardous Drinking

Alcohol consumption more than two drinks (22-30 g) per day in women and three drinks (33-45 g) in men was considered significant.

Variable	Mean (SD)
MELD	22.5 (6.1)
MELD sodium	26.3 (5.7)
Maddrey DF	64.4 (44.8)

Table 4. Mean MELD, MDF and MELD Na Scores

All the three variables had mean value, which was higher than significant cut off.

Status	Number	Percentage
Alive	90	90
Death	10	10
Total	**100**	**100**

Table 5. Mortality at 7 Days

Status	Number	Percentage
Alive	84	84
Death	16	16
Total	**100**	**100**

Table 6. Mortality at 30 Days

Variable	Odds Ratio with 95% CI	P Value
MELD	1.51 (1.24-1.85)	<0.001
MELD sodium	2.01 (1.41-2.89)	<0.001
DF	1.1 (1.02-1.07)	<0.001
Ascites	1 (perfect prediction)	
Renal insufficiency (create ≥1.5)	6 (1.89-19.04)	0.002
Variceal bleed	5 (1.6-15.42)	0.005
Lower limb swelling	4.1 (0.87-19.2)	0.074
Hepatic encephalopathy	3.81 (1.14-12.79)	0.001
Creatinine	5.3 (1.4-19.7)	0.013
PT	1.2 (1.1-1.32)	<0.001
INR	8.69 (2.93-25.75)	<0.001
Bilirubin	1.89 (1.36-2.64)	<0.001
Sodium	0.58 (0.44-0.76)	<0.001

Table 7. Univariate Logistic Regression (Outcome-Mortality at 30 Days)

All variables except lower limb swelling are able to predict 30-day mortality in univariate analysis with significant 'p' value.

Parameter	MELD	MELD Sodium	P Value
AUC	0.94	0.96	0.04

Table 8. Both MELD and MELD Na had Good Sensitivity and Specificity in Predicting 30-Day Mortality

There is a statistically significant higher AUC when we use MELD sodium compared with MELD alone in predicting 30-day mortality (P value = 0.04).

Parameter	Dead (n=16)	Alive (n=84)	P value
Age	44.5 (9.9)	51.0 (10.4)	0.03
Ascites	16 (100)	66 (78.6)	0.04
Hepatic encephalopathy	12 (75.0)	37 (44.1)	0.02
Variceal bleed	10 (62.5)	21 (25)	0.003
SBP	4 (25.0)	0 (0)	<0.001
Renal impairment	8 (50.0)	12 (14.3)	0.001
Bilirubin	13.6 (4.4)	6.9 (3.0)	<0.001
Albumin	2.2 (0.4)	2.6 (0.6)	0.001
INR	3.2 (1.5)	1.8 (0.5)	0.002
Creatinine	1.4 (0.3)	1.1 (0.4)	0.007
Sodium	121.2 (5.6)	130.8 (4.0)	<0.001
MELD score	31.1 (4.7)	20.9 (4.9)	<0.001
MELD sodium score	34.3 (2.9)	24.7 (4.8)	<0.001
DF score	119.9 (70.8)	53.8 (8.0)	0.002

Table 9. Comparison of Clinical and Biochemical/Laboratory Parameters of Those Who Survived 30 Days and Those who Did not

All variables studied and described above had significant 'p' value and important parameters in prognostication.

DISCUSSION

The Model for End-Stage Liver Disease (MELD) score is the method most widely used for organ allocation in liver transplantation. This model, which includes variables related to both liver and renal function was implemented in the USA in 2002 and is currently being used in many countries to classify patients with cirrhosis awaiting transplantation according to the severity of their liver disease.[9,10,11] In this regard, several recent studies have shown that serum sodium concentration is a good marker of prognosis in patients awaiting transplantation. According to the results of these studies, the use of serum sodium in the assessment of severity of cirrhosis has been recommended.[12-13] Low serum sodium was associated with an increased risk of death in all subpopulations of patients with cirrhosis categorised according to the major complication developed before listing.[8] The addition of serum sodium did not significantly improve the accuracy of the MELD score in the prediction of survival at 3 and 12 months and concluded that in patients with cirrhosis awaiting liver transplantation, serum sodium and MELD were found to be independent predictors of survival. Larger studies are needed to determine whether the addition of serum sodium to MELD can improve its prognostic accuracy.[8] A study done by Scott W. Biggins, W. Ray Kim, Norah A. Terrault et al on Evidence-Based Incorporation of serum sodium concentration into MELD showed that an evidence-based method to incorporate Na into MELD, which provides more accurate survival prediction than MELD alone.[14] The new score, MELD Na is calculated by the following formula-

MELD Na = MELD + 1.59 (135-Na) where the minimum value for serum Na is 120 mEq/L and the maximum 135 mEq/L.

In this study, the efficacy of MELD Na was tested in comparison with MELD alone.

The potential limitations of MELD have been appreciated even by many of its strongest proponents, who have acknowledged that addition of other variables might refine and improve the accuracy of these risk models.[15] A study done by Douglas Heuman and others to show persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death found that MELD score, persistent ascites and low serum sodium (<135 mEq/L) were independent predictors of early mortality. Ascites, hyponatraemia and other findings indicative of haemodynamic decompensation merit further prospective study as prognostic indicators in patients awaiting liver transplantation should be considered in setting minimal listing criteria.[15] Assessing severity of disease in patients with Alcoholic Hepatitis (AH) is useful for predicting mortality, guiding treatment decisions and stratifying patients for therapeutic trials no Indian study has been done exclusively to evaluate and compare MELD and MELD Na in alcoholic liver disease with its complications. In our study, 100 patients diagnosed to have alcoholic liver disease and its complications based on detailed history, clinical examinations and relevant investigations were analysed with performance of MELD, MELD Na and DF score in interpretation of severity and prognosis of alcoholic liver disease. Mean age of 100 patients studied was 49.99 years and it was also found to be significant 30-day mortality with significant 'p' value in univariate analysis. About 89% of patients were males and 11% females enrolled in the study. Sex of the patient did not affect any study parameter as all of them had significant history of hazardous alcohol consumption.

Mortality- There were 16 deaths in the study attributable to alcoholic hepatitis or its complications. In this study, there were 10 deaths within 7 days of admission and further 6 within 30 days of first visit. We compared the efficacy of DF, MELD score and MELD sodium as predictors of mortality in these patients and analysed with scatter plot and AUROC. We found that DF largely correlates with MELD at lower values. At higher values, many patients have disproportionally higher MELD score compared to DF. Among these patients, deaths appear to track more closely with MELD rather than DF. It was also noticed that MELD Na performed better with a larger ROC statistic compared to MELD alone.

Symptoms- All the symptoms analysed in this study were clinically significant. Most patients presented with jaundice, pain abdomen and abdominal distension as chief complaint. Presence of any comorbidity did not alter the study significantly. The mean values for all the parameters calculated including symptoms, investigations and complications and analysed for significance.

All symptoms had significant 'p' value expect lower limb swelling.

Biochemical parameters including serum creatinine, PT, INR and serum sodium all had significance in the study and matched with MELD score observed. All test values had significant 'p' value and correlated well with the severity of disease and mortality.

Complications

The complications studied were ascites, SBP, hepatic encephalopathy and variceal bleeding. All of them had significant prediction of prognosis and correlated well with MELD and MELD Na score.

Sensitivity and Specificity

Both MELD and MELD Na were used in analysis with ascites, hepatic encephalopathy, variceal bleeding and SBP. All values correlated with Youden index and ROC and analysed for sensitivity and specificity. All had significant values and no much significance was noted between MELD and MELD Na. Variceal bleeding and SBP were found to have high sensitivity and specificity compared to ascites and hepatic encephalopathy.

1. The maximum sensitivity and specificity for MELD in correlation to ascites was at MELD >21 with sensitivity of 66% and specificity of 78%.
2. The maximum sensitivity and specificity for MELD in correlation to variceal bleeding was at MELD >28 with sensitivity of 35% and specificity of 87%.
3. The maximum sensitivity and specificity for MELD in correlation to SBP was at MELD >29 with sensitivity of 100% and specificity of 85%.
4. The maximum sensitivity and specificity for MELD in correlation to hepatic encephalopathy was at MELD >17 with sensitivity of 87% and specificity of 20%.
5. The maximum sensitivity and specificity for MELD Na in correlation to ascites was at MELD Na >25 with sensitivity of 70% and specificity of 67%.
6. The maximum sensitivity and specificity for MELD Na in correlation to variceal bleeding was at MELD Na >29, with sensitivity of 52% and specificity of 75%.
7. The maximum sensitivity and specificity for MELD Na in correlation to SBP was at MELD Na >33 with sensitivity was 100% and specificity was 86%.
8. The maximum sensitivity and specificity for MELD Na in correlation to hepatic encephalopathy was at MELD Na >34 with sensitivity was 14% and specificity was 54%.

All C statistic value were >0.9 indicating high level of significances.

In multivariate logistic regression, both backward elimination and forward selection procedures selected MELD and MELD Na as the independent predictor of 30-day mortality rate and no additional variables increased its accuracy. It shows that when the six remaining variables

were added to MELD one at a time using forward selection, all six variables lost significance and the combined (c) statistics did not significantly improve compared with MELD or MELD Na alone. A series published by Sheth et al[16] recently provided initial evidence that MELD may be useful in estimating 30-day prognosis in patients with AH; a more recent analysis of MELD conducted by Said et al across a broad spectrum of liver disease, which included a cohort of patients with AH, also supports this concept. The current study establishes the ability of MELD to rank patients with AH by risk of death and provides evidence that MELD accurately predicts mortality up to 30 days.

Serum Sodium- In our study, it was found that serum sodium was an independent predictor of mortality and severity of alcoholic liver disease. Further prospective studies are needed to determine the clinical significance of hyponatraemia and to identify its correlation with the incidence of possible complications.

MELD 2016- In January 2016, OPTN policy 9.1 (MELD score) was updated to include serum sodium as a factor in the calculation of the MELD score. This policy was approved by the OPTN/UNOS Board of Directors in June 2014. Sodium was added to it and new formula given was based on article "A model to predict survival in patients with end-stage liver disease."[9]

MELD (2016) = MELD (i) + 1.32 x (137-Na)-(0.033 x MELD (i) x (137-Na)).

As seen in our study, which was done much before this update, the inclusion of sodium into MELD and subsequent increase in performance of MELD sodium score was proved beyond doubt and now internationally accepted.

CONCLUSION

In summary, MELD and MELD Na are useful for predicting 30-day mortality in patients with alcoholic hepatitis and maintains some practical and statistical advantages over DF in predicting mortality rate in these patients. The MELD Na score performed better than MELD in predicting short-term mortality. Presence of ascites, hyponatraemia, hepatic encephalopathy, variceal bleeding and SBP were independent predictors of adverse prognosis in alcoholic hepatitis/cirrhosis.

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