COMPARISON OF MODIFIED DISCRIMINANT FUNCTION AND GLASGOW ALCOHOLIC HEPATITIS SCORE IN PREDICTING ONE MONTH MORTALITY

G. Vasumathi¹, S. Geetha², G. Rengaraj³

¹Associate Professor, Department of Medicine, Government Stanley Medical College, Chennai.

²Assistant Professor, Department of Medicine, Government Stanley Medical College, Chennai.

³Senior Resident, Department of Medicine, Government Stanley Medical College, Chennai.

ABSTRACT

BACKGROUND

Alcoholic Liver Disease (ALD) includes a wide range of injury from reversible steatosis, steatohepatitis to irreversible cirrhosis. Alcoholic hepatitis is a very important entity, because severe alcoholic hepatitis is associated with a high short term mortality rate of 40-45%, which is unacceptable and has to be prevented. So far the severity of alcoholic hepatitis is identified by calculating 'Modified Discriminant Function' (mDF) score. This score includes only Prothrombin Time (PT) and bilirubin in calculating the severity of alcoholic hepatitis. MDF of greater than or equal to 32 is considered severe and treated with steroids and pentoxifylline. New scoring system 'Glasgow Alcoholic Hepatitis Score (GAHS)' which includes age, white cell count, urea, PT and serum bilirubin level is used in identifying the patients in need of drug therapy.

AIM OF THE STUDY

To compare GAHS score with mDF score to predict one month mortality in alcoholic hepatitis patients.

METHODS

Prospective observational study of 50 patients of Alcoholic Hepatitis patients in the Departments of General Medicine and Medical Gastroenterology of Stanley Medical College, Chennai, was done in the year March 2012 to August 2012.

RESULTS

The results show GAHS score is found to have higher sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy when compared to mDF score.

KEYWORDS

Alcoholic Hepatitis, mDF Score, GAHS Score.

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INTRODUCTION

Liver is the major organ of alcohol metabolism. Alcohol is metabolized by 3 major enzyme systems.

1. Alcohol Dehydrogenase-ADH (80% to 85%).
2. Cytochrome P450 isoenzyme namely Cytochrome P4502E1 (10% to 15%).
3. Catalase (less than 5%).

The above enzyme systems convert alcohol to acetaldehyde, which is a highly reactive and toxic compound. Acetaldehyde forms adducts with proteins, which induce host's immune system and results in autoimmune-like mechanisms. Oxidative stress-CYP2E1 leaks electrons to initiate Oxidative Stress in Hepatocytes. Alcohol increases intestinal permeability causing frequent endotoxemia, which in turn increases production of TNF alpha by Kupffer cells. TNF alpha activates chemokines (IL-8), which leads to

inflammation, fibrosis apoptosis and organ damage. Alcoholic hepatitis is a clinical syndrome of icterus and hepatic dysfunction that usually manifest following continuous excessive alcohol intake (an average of 100grams/day). The usual age at which the disease presents is 40 to 60 years, but can vary from 20 to 80 years. The cardinal sign is rapid onset of jaundice. Typically, the liver is enlarged and tender.¹ The importance of alcoholic hepatitis lies in its potential reversibility.

Histological Characteristics of Alcoholic Hepatitis

1. Ballooning of hepatocytes,
2. Mallory bodies - eosinophilic cytoplasmic inclusions,
3. Neutrophilic infiltration surrounding the degenerating hepatocyte.

Diagnosis of Alcohol Abuse

The diagnosis of alcohol abuse can be done by using AUDIT.² (Alcohol Use Disorders Identification Test) or CAGE.² questionnaire, of which we used AUDIT. It is a 10-item questionnaire designed by the WHO for screening of problem drinking. A total ≥ 8 for men up to age 60 or ≥ 7 for women, adolescents, or men over 60 is considered positive screening test. Any value greater than this is suggestive of alcohol abuse.

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Corresponding Author:

Dr. G. Vasumathi,

52, Madipakkam Main Road,

Madipakkam,

Chennai-91.

E-mail: vasumathivenkatesan@yahoo.co.in

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Diagnosis of Alcoholic Hepatitis

The disease is suspected when icterus and other symptoms and signs of decompensation like ascitis happens to an individual with excess ethanol intake.⁽³⁾ Clinical diagnosis has an accuracy of about 80% when compared with histology. However, along with history of chronic excess alcohol ingestion, AST>500 (or ALT<300). Serum bilirubin was set at a minimum level of >80µmol/L (4.67mg/dl), the accuracy becomes 99.2%. In this study too the inclusion criteria of serum bilirubin is >5mg/dl. To improve the diagnostic accuracy measurement of prothrombin time in patients has high prognostic value. An abnormal prothrombin time with confirmed PT >5 to 6 seconds above control often precedes by days the manifestations of liver failure. The degree of prolongation of PT is a prognostic factor for patients with alcoholic steatonecrosis. Progressive return of PT to normal accompanies other evidence of clinical improvement.

Complete Blood Count:

Mild anemia (usually macrocytic), platelets in the range of normal to decreased and elevated white cell count. PMN>5500 in the presence of mDF>32 indicates poor prognosis. Values of urea and creatinine rises. These elevations are found to have significant correlation with the severity of the disease Percutaneous liver biopsy cannot be performed in patients with ascitis and/or coagulopathy and transjugular biopsy needs expertise.

SCORING SYSTEM

Discriminant Function=(4.6xPT)+serum bilirubin(mg/dl) 1. mDF Modified Discriminant Function.

It is discovered by Maddrey and Boitnott. It is calculated as 4.6xPT prolongation [patient's-control value (seconds)]+serum bilirubin(mg/dl). The mDF is proved useful for delineating 28 days and 84 days mortality. Evidence has proven that patients with an mDF value of 32 or more experienced a worse prognosis with 28 days mortality rates of 35% to 45%.

In contrast patients with an mDF value less than 32 have short survival rates of 90% to 100%. MELD Score=3.78 [serum bilirubin (mg/dl)]+11.2 [INR]+9.57 [serum creatinine (mg/dl)]+6.43 includes the serum bilirubin level, INR along with creatinine level. Prognosis is poor if the score is ≥18.

The disadvantage in MELD score is that it needs calculators for calculation since it involves logarithms. It includes creatinine as a measure of renal function. Evaluation of creatinine is commonly done based on Jaffe reaction. In diseases associated with hyperbilirubinemia, creatinine will be underestimated. So the observed value based on Jaffe's method needs correction, which is cumbersome.

Glasgow alcoholic hepatitis score includes age, WBC count, urea level, serum bilirubin level, prothrombin time ratio; i.e., ratio of the patient's prothrombin time to the control value also have been shown to predict survival in patients with severe alcoholic hepatitis. Because both the MELD and Glasgow scores include measures of renal functions, they appear to be more accurate than the mDF in determining the prognosis of patients.

Score	1	2	3
Age	<50	>50	
WCC(10^9)	<15	>15	
Urea(mmol/L)	<5	>5	
PT ratio or INR	<1.5	1.5-2	>2
Bilirubin(µmol/l)	<125	125-250	>250

Table 1: Glasgow Alcoholic Hepatitis Score

GAHS is more easy to calculate and it uses urea as a measure of renal function. Prognosis is poor if the score is ≥9.

MATERIALS AND METHODS

Study Design : Observational study.

Study Place : Departments of General Medicine and Medical Gastroenterology, Government Stanley Medical Hospital, Chennai-1.

Study Period : 6 months (March 2012-August 2012).

Study

Population : Patients admitted with alcoholic hepatitis.

Sample Size : 50 patients.

Sampling : Simple Random Sampling.

How this Study was Conducted

Patients admitted with alcoholic hepatitis were included in the study after applying the inclusion and exclusion criteria. They were subjected to thorough history, clinical examination, biochemical investigations, ultrasonogram of the abdomen. They were followed up after one month of their present admission.

Assessment Panel Includes

History with specific focus on alcoholic intake-amount, type and duration and with AUDIT score ≥8 in males and ≥7 in females and elderly males' age.

Biochemical Investigations

White cell count, serum urea, serum albumin, PT and INR, SGOT and SGPT, ultrasonogram of abdomen done to exclude cirrhosis and malignancy. Results were duly collected and analysed. The patients were followed up for one month and the mortality is assessed. MDF and GAHS were calculated.

The patients with mDF≥32 or GAHS score ≥9 were given prednisolone for 4 weeks and then tapered over next 4 weeks. If the patient had contra indications to steroids, Pentoxifyllin is given. The patients were followed for one month and the mortality is observed. Sensitivity, specificity and accuracy of mDF and GAHS in calculating one mortality were calculated. The results were analysed. P-value of 0.05 is considered statistically significant.

RESULTS

This study included 50 patients diagnosed with alcoholic hepatitis admitted in Department of General Medicine and Medical Gastroenterology, Government Stanley Hospital. The one month mortality prediction by modified discriminant function and GAHS score is calculated and compared with observed one month mortality. The results were tabulated and analysed as follows:

AGE GROUP [Years]	Number	Percentage
21-30	7	14
31-40	18	36
41-50	16	32
Above 51	9	18

Table 2: Age Distribution

Fig. 1

Age Group (Years)	1 Month Mortality				Total		P-Value
	Survived		Died				
	N	%	N	%	N	%	
21 - 30	7	100.0	0	0.0	7	100.0	0.005
31 - 40	14	77.8	4	22.2	18	100.0	
41 - 50	11	68.8	5	31.3	16	100.0	
>51	3	33.3	6	66.7	9	100.0	
Total	35	70.0	15	30.0	50	100.0	
Table 3: Trend Chi-Square to Compare the Proportions							

Table 3: Trend Chi-Square to Compare the Proportions

This table shows that as age increases the mortality increases too.

Fig. 2

AGE

Variable	1 Month Mortality	N	Mean	Std. Deviation	P-Value
Age (Years)	Survived	35	38.23	7.99	0.002
	Died	15	46.80	9.33	

Table 4: Independent Samples T-Test to Compare Mean Values between Variables

This table shows that patients who survived had a mean age of 38.23, whereas patients who died at the end of 1 month had a mean age of 46.8. This difference is significant as suggested by a P-value of 0.002.

Fig. 3

Variable	1 Month Mortality	N	Mean	Std. Deviation	P-Value
WCC	Survived	35	8917.1	3324.5	<0.001
	Died	15	15913.3	4652.6	

Table 5: White Cell Count

Patients who died at the end of 1 month had significantly raised white cell count (mean of 15913) with a P-value of <0.001 indicating the importance of white cell count in indicating the prognosis of alcoholic hepatitis.

Variable	1 Month Mortality	N	Mean	Std. Deviation	P-Value
Urea	Survived	35	31.74	8.98	0.014
	Died	15	38.63	8.15	

Table 6: Serum Urea

Patients who died at the end of 1 month had significant rise in urea compared to those survived (p- 0.014), indicating renal involvement altering the prognosis of alcoholic hepatitis.

Fig. 4

Variable	1 Month Mortality	N	Mean	Std. Deviation	P-Value
Total Bilirubin	Survived	35	8.81	2.46	0.007
	Died	15	13.39	5.57	

Table 7: Serum Bilirubin

The average value of serum bilirubin in patients who died was 13.3, compared the value of 8.81 in those who survived (p- value = 0.007) indicating its value in assessing the prognosis.

Fig. 5

Variable	1 Month Mortality	N	Mean	Std. Deviation	P-Value
PT	Survived	35	17.17	2.07	0.073
	Died	15	18.33	2.02	

Table 8: Prothrombin Time

In our study, the prothrombin time among the patients who died was raised compared to those who survived, but this rise was not statistically significant (P-value-0.073).

Fig. 6

m DF and GAHS score	Died	
	N	%
m DF<32.0 & GAHS<9.0	1	6.7
m DF<32.0 & GAHS≥9.0	2	13.3
m DF≥32.0 & GAHS<9.0	0	0.0
m DF≥32.0 & GAHS≥9.0	12	80.0
Total	15	100.0

Table 9: Comparison of mDF and GAHS in patients who died at 1 month

Of the 15 patients who died, 12 were detected as having severe disease by both mDF and GAHS. But 2 patients who had mDF <32 and GAHS ≥9 died. These patients if identified as severe could have benefitted with steroids or pentoxifylline. One patient who had both mDF <32 and GAHS <9 died and both scores failed to identify the severity. GAHS identifies severity in all patients identified by mDF ≥32, apart from identifying severe disease in patients with mDF <32. The only patient where GAHS failed, mDF too failed to identify the severity.

Fig. 7

Kappa Statistics to measure the Agreement between the Two Scoring Procedures

		mDF Score		Total
		≥ 32.0	< 32.0	
GAHS Score	≥ 9	14	2	16
	< 9	9	25	34
Total		23	27	50

Table 10

Measure of Agreement	Value	P-Value
Kappa	0.547	<0.001

Table 11

Kappa value of 0.547 shows only moderate agreement between GAHS and mDF.

ROC Curve analysis to find out the best cut-off point for GAHS to predict the 1 month mortality.

Fig. 8

Area Under the Curve = 0.972

The ROC curve analysis suggests that GAHS value ≥9.0 is the best cut-off point to predict the 1 month mortality.

Sensitivity Specificity Analysis for mDF

		1 Month Mortality		Total
		Died	Survived	
mDF Score	≥ 32	13	12	25
	< 32	2	23	25
Total		15	35	50

Table 12

Parameter	Estimate (%)	Lower-Upper 95% CIs
Sensitivity	86.67	62.12, 96.26
Specificity	65.71	49.15, 79.17
Positive Predictive Value	52.00	33.50, 69.97
Negative Predictive Value	92.00	75.03, 97.78
Diagnostic Accuracy	72.00	58.33, 82.53

Table 13

Thus mDF has an accuracy of 72% in predicting 1 month mortality. Also, out of 25 patients who had discriminant function of >32, 13 patients died and 12 survived with a specificity of 65.7%. Out of 25 patients who had score <32, 2 patients died. Also, the positive predictive value is low (52%).

Sensitivity Specificity Analysis for GAHS

		1 Month Mortality		Total
		Died	Survived	
GAHS Score	≥ 9	14	2	16
	< 9	1	33	34
Total		15	35	50

Table 14

Parameter	Estimate (%)	Lower-Upper 95% CIs
Sensitivity	93.33	70.18, 98.81
Specificity	94.29	81.39, 98.42
Positive Predictive Value	87.50	63.98, 96.50
Negative Predictive Value	97.06	85.08, 99.48
Diagnostic Accuracy	94.00	83.78, 97.94

Table 15

Thus GAHS has higher sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy when compared to mDF. Among these the specificity, positive predictive value and accuracy of GAHS is significantly higher compared to mDF. Hence, GAHS identifies the severity of alcoholic hepatitis accurately compared to mDF and this should be used in deciding upon treatment with steroids or pentoxifylline.

Parameter	mDF	GAHS
Sensitivity	86.67	93.33
Specificity	65.71	94.29
Positive Predictive Value	52.00	87.50
Negative Predictive Value	92.00	97.06
Diagnostic Accuracy	72.00	94.00

Table 16

Fig. 9

DISCUSSION

Alcoholic hepatitis when severe, the short term mortality is very high. This high mortality is mainly due to inflammatory processes occurring in acute alcoholic hepatitis. Identification of patients with severe disease is of key significance, because these patients can be treated with steroids or pentoxifylline and these patients need to be monitored for the development of complications like hepatic encephalopathy and renal failure.

Also these patients need to be followed up periodically because alcoholic hepatitis in the long run is associated with nine times increased risk of development of cirrhosis. The severity of disease is identified by mDF score ≥32. But the problem with this score is that it involves only serum bilirubin and prothrombin time.

It does not include any markers for inflammation or renal involvement. The MELD score is cumbersome to calculate and it too does not involve any marker for inflammation. The GAHS is easy to calculate, involves markers for renal involvement and inflammation and is much more accurate than mDF. Our study which was an observational study involved 50 patients with alcoholic hepatitis and comparison of actual prognosis with prognosis and severity calculated by mDF and GAHS. The observed mortality was 30%.

The severity predicted by GAHS had an accuracy of 94% compared to that calculated by mDF, which had 72% accuracy. Thus it is obvious that GAHS has much better severity prediction compared to mDF and this is helpful in treating patients. Also patients with GAHS <9 survived irrespective of their mDF, even if mDF ≥32. This shows that if GAHS <9, these patients need not be treated with steroids or pentoxifylline. There are many studies reported in literature, comparing the various prognostic scoring systems.

4	Population (Number)	Results
EH Forrest. ⁽⁴⁾	241	GAHS more accurate than mDF in predicting 28 and 84 day mortality
Altamirano-Gomez	120	GAHS superior to mDF in predicting in-hospital mortality
Sandahl. ⁽⁵⁾	274	GAHS, MELD and ABIC scores are equal in accuracy
H Lafferty	182	Improvement in outcome if patients are treated with GAHS grading for severity.
AJ Morris	225	At GAHS <9, no significant benefits with corticosteroids. ≥ 9 has poor prognosis if not treated
N Palaniappan. ⁽⁶⁾	44	mDF, MELD, GAHS and ABIC are equal in accuracy. CP score is poor in accuracy.
S. Ali	82	mDF, CP, GAHS are equal in accuracy.
Table 17		

These studies show the accuracy of GAHS in comparison with other prognostic scoring systems.

CONCLUSIONS

- 1) The GAHS score (94%) accurately predicted 1 month mortality when compared with mDF (72%).
- 2) The specificity and positive predictive value of GAHS (94.3% and 87.5%) were far more superior compared to mDF (65.7% and 52%).

- 3) Out of the 25 patients with mDF <32, three patients died. Of these three patients, two had GAHS ≥ 9 indicating that had GAHS been used to identify the severity. These patients could have benefitted with treatment of corticosteroids or pentoxifylline.
- 4) One patient who died had both GAHS <9 and mDF <32. In this case, both scores failed to identify the severity.
- 5) Each factor included in GAHS – Age, bilirubin, urea and white cell count with exception of prothrombin time had statistically significant rise in those patients who died compared to the survivors indicating that each factor itself gives a clue to the prognosis of the disease.

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