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PROGNOSTIC UTILITY OF LILLE SCORE IN ALCOHOLIC HEPATITIS

Dhananjay Mishra [1], Anupa Prasad [*2] and R. K. Jha [1]

Department of Medicine [1], Department of Biochemistry [2], Rajendra Institute of Medical Sciences (RIMS), Ranchi - 834009, Jharkhand, India.

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Alcoholic Hepatitis, Maddrey's Discriminant Function score, Lille Score, Corticosteroids

Correspondence to Author:
Dr. Anupa Prasad

Associate Professor, Department of Biochemistry, Rajendra Institute of Medical Sciences (RIMS), Ranchi - 834009, Jharkhand, India.

E-mail: anupaprasad651@gmail.com

ABSTRACT: Background: Alcoholic liver disease is a spectrum of alcohol induced injury that includes fatty liver, alcoholic hepatitis and alcoholic cirrhosis. Corticosteroids are used in cases of severe alcoholic hepatitis with Maddrey's Discriminant Function score > 32. However, many of the patients who are being managed by corticosteroids are non responders and mortality increases in such patients. Lille model is a prognostic model which helps in identification of steroid responders and non responders within 7 days of start of treatment. In the present study we identified the alcoholic hepatitis patients with Lille score < 0.45 and with > 0.45. Survival in the patients was compared with the Lille score. **Method:** Prospective study of 100 patients of alcoholic hepatitis aged 18 to 85 years was done for a period of six months. All of the patients were managed with similar treatment protocols including general supportive measures and treatment of associated complications. Oral or Intravenous corticosteroid therapy was given for 28 days and then tapered off over next two weeks in the subgroup of patients with Lille score < 0.45. Patients were followed up till the end of 6 months. **Result:** Lille score was significantly ($p < 0.005$) lower in survival group (mean 0.35 ± 0.17) compared to non survival group (mean 0.72 ± 0.15). Using Receiver Operating curve, we found that cut off points for Lille Score in our population is 0.47. These patients are not benefitted from steroid therapy and should be considered for alternative therapy like liver transplant. **Conclusion:** brief summary and potential implications: Lille score is a valuable marker for identifying the patients who could be benefitted by corticosteroids. This study indicates a need for developing a new cut off point for Lille Score.

INTRODUCTION: Alcoholic liver disease is a common entity worldwide. It includes a spectrum of liver disorders ranging from fatty liver to alcoholic hepatitis and finally alcoholic cirrhosis of the liver. There is high Mortality in alcoholic hepatitis as well as in cirrhosis patients; however, therapies may improve clinical outcome. Alcoholic hepatitis is a well documented precursor of cirrhosis increasing the risk by nine fold.

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The point prevalence of cirrhosis is 1% in persons drinking 30 to 60 gm of alcohol a day and upto 5.7% in those consuming 120 gm daily [1]. It is presumed that other factors such as sex, genetic characteristics and environmental factors play a role in the causation of alcoholic liver disease.

Alcohol is a direct hepatotoxin and only 10 to 20% of alcoholics develop hepatitis and cirrhosis. Different alcohol dehydrogenase isoenzymes having different alcohol elimination rates cause different alcohol metabolism amongst individuals [2]. In some of the Asian and Native American populations, there is genetic defect of mitochondrial aldehyde dehydrogenase enzyme [3]. Alcohol abstinence and correction of nutritional deficiencies have been the main treatment options[4].

Glucocorticoids and pentoxiphylline have been used to decrease the mortality in alcoholic hepatitis patients [5]. Inflammation is a major contributor in the pathogenesis of alcoholic hepatitis. Steriods have been found to be beneficial for short term survival in severe alcoholic hepatitis (AH) [6, 16]. Improvement in liver function may be seen from the first week of starting steroids. It reduces inflammatory processes by inhibiting the action of transcription factors such as activator protein 1 (AP-1) and NF κB. This effect is manifested by decreased level of inflammatory cytokines like Tumor necrosis factor (TNF) - α, intercellular adhesion molecule 1 (ICAM-1), Interleukin 6 (IL-6) and Interleukin 8 (IL-8) [7]. However, treatment of AH with prednisolone can increase susceptibility to infection. Level of circulating bacterial DNA before treatment may identify patients at high risk of infection [8].

Identification of alcoholic hepatitis with high risk for mortality is of paramount importance. Maddrey Discriminant Function (MDF) score is a prognostic index which identifies patients who may benefit from corticosteroid therapy [9]. MDF score > 32 is currently used as a threshold to start corticosteroids therapy [10, 11]. However, early identification of subgroup of patients with alcoholic hepatitis (MDF>32) not responding to corticosteroids is crucial [12, 13].

Lille model is a prognostic model for identification of patients of alcoholic hepatitis with poor prognosis. It combines six reproducible variables (age, renal insufficiency, albumin, prothrombin time, bilirubin and evolution of bilirubin at day seven). Lille score identifies alcoholic hepatitis patients who are steroid responders and non responders within seven days of start of therapy.

It is highly predictive of death at six months in patients with alcoholic hepatitis [14]. Lille score may be as accurate at day 4 as at day 7 in predicting response to corticosteroids as well as 90 day mortality [15]. Jharkhand is an eastern state of India where alcoholic liver disease is highly prevalent due to consumption of local alcohols brewed from products like rice and mahua (*Bassia Longifolia*) and is known as Hadia and Mahuwa respectively. This study will help us to plan the therapeutic strategy in cases of severe alcoholic hepatitis.

MATERIALS AND METHODS: Present study was a prospective cross sectional observational study, with an objective of study of utility of Lille Score in assessment of patients with alcoholic liver disease.

A total of 160 patients of alcoholic hepatitis with or without cirrhosis were taken from different wards of medicine department at Rajendra Institute of Medical Sciences, Ranchi from August 2015 to September 2016. An approval was obtained from institutional ethics committee, vide reference number 45 IAEC/IEC RIMS, Ranchi Dated 07/04/2016. Informed consent was taken from patients included in the study. Out of 160 patients, 2 patients had sepsis, 5 patients were found to be on hepatotoxic drugs, 7 had stroke, 2 was confirmed to be having meningitis, 1 was positive for Australia antigen, 1 had gastrointestinal (GI) bleeding and in 22 patients investigations could not be completed. So, finally 120 patients were included in our study.

Inclusion and Exclusion Criteria were as Follows: The patients were included in the study if they fulfilled the following criteria: (1) A history of heavy alcohol use (frequent drinking, early morning drinking, presence of dependence), (2) AST : ALT Ratio > 1.5, (3) Total Bilirubin > 1.5, (4) Adults patients with age ≥ 18 yrs. Exclusion criteria were unwillingness to participate in the study, pregnancy, history of intake of hepatotoxic drugs, patients with signs of meningitis on clinical examination as well as on CSF examination, patients with stroke as evidenced by history or by CT scan, patients with history of sudden onset of cognitive impairment, patients with uncontrolled infection or sepsis, recent GI bleeding (in last 15 days), patients with positive serology for HIV, HBs Ag or HCV infection, patients with acute pancreatitis, active tuberculosis, neoplasms and patients in whom investigations could not be completed.

Detailed history of patients was taken. Routine biochemical tests, diagnostic imaging tests (USG, CT Scan for abdomen and if required for brain) and Lumbar Puncture for CSF examination (if required) was done. The epidemiological data included age, gender, history of alcohol intake, duration of hospital stay and in hospital mortality.

Alcoholic hepatitis was defined as history of heavy alcohol intake and presence of jaundice along with AST/ALT Ratio > 1.5 and /or enlarged liver [16]. A histological diagnosis of alcoholic hepatitis was not obtained, because of coagulopathy which might cause bleeding during performance of percutaneous liver biopsy and facilities for transjugular liver biopsy is not available at our centre. Cirrhosis was defined by clinical stigmata associated with chronic liver disease, USG showing nodular or irregular surface and/or splenomegaly (> 12 cm maximum diameter) [17].

Presence of ascites, jaundice, oedema, abdominal wall collaterals, encephalopathy and variceal hemorrhage were recorded. Daily advice and progress of the patients was noted. Lille score and Modified Maddrey's discriminant function score were calculated based on lab values using an electronic scientific calculator.

Lille Score was defined as: 3.19 - 0.101 *(age in years) + 0.147* (albumin day 0 in g/L) + 0.0165 *(evolution in bilirubin level in µM) - 0.206 (renal insufficiency) - 0.0065*(bilirubin day 0 in µM) - 0.0096* (prothrombin time in seconds). Renal insufficiency was rated 0 if absent and 1 if present (below or above 115 µM [1.3 mg/dl]) [18]. The final Lille model score fluctuated from 0 to 1.

Discriminant function score was defined as: 4.6 X (patient's PT - control PT) + total bilirubin) mg/dl) [19, 20]. The diagnosis of alcoholic hepatitis with or without cirrhoiss, was confirmed with the help of clinical history, biochemical parameters and imaging tests. DF scores were calculated at admission and daily hepatic decompensation with ascitis, encephalopathy, and variceal hemorrhage were monitored. At the seventh day of admission, serum bilirubin was measured again and then Lille score was calculated. The patients whose Lille score was < 0.45, received 40mg methyl-prednisolone for 28 days and then it was tapered off over next 2 weeks. The patients who were unable to take oral medicines or unconscious patients who had hepatic encephalopathy, were treated with intravenous infusions of 32 mg of methylprednisolone once daily till the patients were able to take it orally [8]. All the patients were managed with similar treatment protocol including general supportive measures, treatment of associated complications such as infection and hepatic encephalopathy. They were followed up daily till the primary end point which was either discharge from the hospital or in hospital mortality. In case of discharge from the hospital, they were followed up by telephonic conversation and / or by outpatient department monthly till the end of 6 months.

Statistical analysis was performed using SPSS version 20.0 for windows. Continuous variables were tested for normal distribution and expressed as mean ± SD. Clinical and biological variables in survivors and non survivors were identified by univariate analysis using chi square and Student t test. A p value of less than 0.05 was considered significant. ROC curve for Lille score was plotted to find out the cutoff point with maximum sensitivity and specificity.

RESULTS: A total of 120 patients were recruited who met the inclusion criteria for the study and were followed up for 6 months. However, 20 patients were lost to follow up. Hence we had a total of 100 patients with complete follow up and available data for analysis. Out of them, 92 were males and 8 were females. Icterus was present in almost all the patients. We studied the presentation of different clinical features in the study group at the time of admission. 97% had icterus, 75% had pallor, 73% presented with ascitis, 56% had hepatic encephalopathy, 49% had oedema, 30% had hepatomegaly and only 2% patients presented with splenomegaly. **Fig. 1** shows the percentage of different clinical features in the study population.

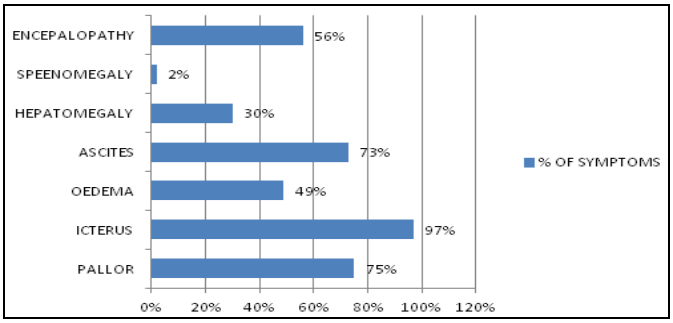

FIG. 1: SHOWS THE PERCENTAGE OF DIFFERENT CLINICAL FEATURES IN THE STUDY POPULATION

Biochemical parameters were studied in all the patients and MDF and Lille score were calculated in the study population. **Table 1** shows the descriptive statistics of the study population.

Age ranged from 28 to 58 years while the mean age of the study group was 39.76 ± 6.67 years. It was remarkable to see that 80% of the patients of ALD had serum creatinine more than 1.2 mg/dL. Mean MDF score at admission was 79.56 ± 29.82 whereas mean Lille score was 0.54 ± 0.24. After the follow up period of 6 months, the patients were categorized in two groups: Survivors and Non survivors.

TABLE 1: DESCRIPTIVE STATISTICS OF THE PATIENTS IN THE STUDY POPULATION

Variables (n = 100)	Range	Mean ± SD
Age (years)	28-58	39.76 ± 6.67
Duration of Alcohol intake (years)	10-25	14.72 ± 4.09
Hb%	6.0-14.5	9.18 ± 1.79
Serum Bilirubin at admission (mg/dL)	3.4-34.7	15.23 ± 7.53
Serum Bilirubin on day 7 (mg/dL)	4.7- 35.5	16.26 ± 7.36
AST (IU/L)	25-463	206.73 ± 106.58
ALT (IU/L)	15-234	80.45 ± 37.13
AST /ALT Ratio		2.52 ± 0.70
Alkaline Phosphatase (IU/L)	140-561	324.41 ± 91.42
Gamma Glutamyl Transpeptidase (IU/L)	17-967	215.53 ± 192.50
Serum Na^+ (mmol/L)	110-146	132.14 ± 5.81
Serum K^+ (mmol/L)	2.40-7.50	3.8 ± 2 ± 0.70
Prothrombin Time (Seconds)	17-44	26.86 ± 6.88
Random Blood Sugar (mg/dL)	42-200	96.75 ± 28.65
Serum Albumin (g/dL)	1.0-3.2	2.15 ± 0.47
Serum Creatinine (mg/dL)	0.50-24.0	3.24 ± 2.24
DF Score	35-155	79.56 ± 29.82
Lille Score	0.04-0.97	0.54 ± 0.24

Mean MDF score for survivors was 78.51 ± 29.84 and for non survivors, it was 80.50 ± 30.07. The mean value of Lille score in survivors group was 0.35 ± 0.17 while in non survivors, it was 0.72 ± 0.15 (P value 0.000). **Table 2** shows the comparison of different variables and scores in survivors and non survivors groups. 76 patients had Lille score > 0.45. 52 patients died during follow up. Hence there were 68.4 % death in the subgroup of patients with Lille score > 0.45 whereas there were no deaths in the subgroup with Lille score < 0.45.

TABLE 2: COMPARISON OF DIFFERENT VARIABLES AND SCORES IN SURVIVORS AND NON SURVIVORS GROUPS

Variables	Total patients Mean ± SD	Survivors Mean ± SD	Non survivors Mean ± SD	P Value
Hb%	9.18 ± 1.72	9.66 ± 1.97	8.74 ± 1.48	0.009
Serum Bilirubin at Admission (mg/dL)	15.23 ± 7.53	13.62 ± 7.5	16.71 ± 7.3	0.039
Serum Bilirubin on day 7 (mg/dL)	16.26 ± 7.36	13.38 ± 6.69	18.91 ± 7.01	0.000
Serum albumin (g/dL)	2.15 ± 0.47	2.24 ± 0.54	2.06 ± 0.38	0.055
PT (Prothombin Time) (seconds)	26.86 ± 6.88	26.95 + 6.83	26.77 ± 6.99	0.894
Serum creatinine (mg/dL)	3.24 ± 2.24	2.98 ± 1.88	3.47 ± 2.52	0.457
DF SCORE	79.56 ± 29.82	78.51 ± 29.84	80.50 ± 30.07	0.743
Lille SCORE	0.54 ± 0.24	0.35 ± 0.17	0.72 ± 0.15	0.000

Fig. 2 shows the percentage of deaths in the two subgroups of Lille score. By taking a cutoff point of 0.45, the sensitivity of Lille score for death outcome is 100% but specificity is only 50%. Hence, to find out a new cut off of Lille score which had a better specificity, we opted to draw a Receiver Operator Curve (ROC). The cutoff point of 0.47 was found which had a sensitivity of 98.1% and a specificity of 68.7% respectively. The area under receiver operating characteristic (AUROC) for survival at 6 months of the derived score probability was 0.960 (95 % CI: 0.927-0.992). **Fig. 3** shows the ROC for cut off of Lille score.

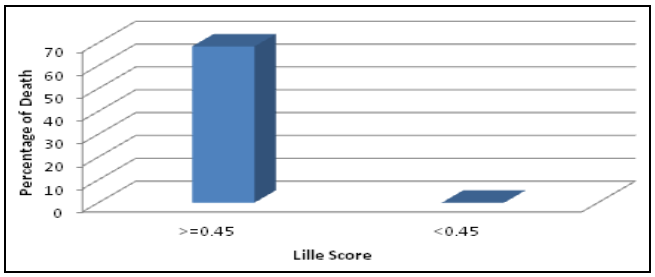

FIG. 2: PERCENTAGE OF DEATHS IN THE TWO SUBGROUPS OF LILLE SCORE

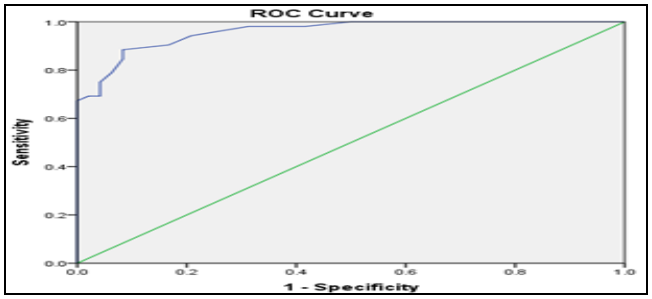

FIG. 3: ROC FOR CUT OFF OF LILLE SCORE

DISCUSSION: In our study, Lille model scored over MDF in predicting short term mortality in patients with alcoholic hepatitis. Most of the patients in our study belonged to the age group between 40 - 52 years and 92% of them were males. The male to female ratio was 11.5:1. We found that alcoholic liver disease develops in patients who are chronically abusing alcohols. Increasing age imposes negative influence over the prognosis of alcoholic liver diseases as it impairs body's rejuvenating capacity.

In the management of alcoholic liver disease, abstinence from alcohol is the key factor in preventing the disease progression. It helps in improvement of liver histology and reduction in the risk of portal hypertensive bleed. Despite having given medical advice, 86% of our patients were still taking alcohol and it was revealed on repeated questioning. Out of 100 patients who were included in our study, 52% died during the follow up of 6 months. This figure is high as compared to the study from a cohort of alcoholic hepatitis patients from Queens Medical Centre, Nottingham University Hospitals where six months cumulative mortality was found to be 21.4% [21].

This difference in mortality might be due to two reasons. One that in our case, most of the patients continued to consume alcohol despite being advised against it and the other reason might be due to consumption of locally brewed alcohol with higher hepatotoxic effects. Out of the 92%, 68% of the male patients took only locally brewed alcohol Hadia and Mahua whereas out of 8%, 6% of the female patients took local alcohols. 21% males and 2% females took mixed alcohols (local as well as whisky, wine and beer) and 3% males took only beer. The pattern of intake in 84% of the patients was daily drinking whereas 16% of the patients took twice or thrice a week. Average duration of alcohol intake in the patients of alcoholic liver disease was 14.72 years. This data suggests that locally brewed alcohol consumption is quite common in the eastern state of India.

Out of 100 patients 97% of the admitted patients had jaundice accounting for major causes of hospital admission as they presented with the complaint of yellowish discoloration of eye and urine. Presence of jaundice is a bad prognostic marker of alcoholic liver disease. This was followed by 75% of the patients complaining of pallor. Pallor is very common in patients of alcoholic liver disease as there is increased risk of GI losses due to variceal formation, poor absorption of nutrients from gut and less nutritious diet. 73% of the patients presented with the complaint of abdominal distension. Abdominal distension was due to ascites. Ascites in alcoholic liver disease occurs due to low serum albumin and increased hydrostatic pressure. Low oncotic pressure due to decreased formation of albumin by the liver results in accumulation of fluid in the peritoneal cavity. Presence of ascites is associated with poor prognosis.

Death outcome was reported in 65.8% of patients with ascites whereas it was seen only in 14.8% patients who do not have ascites. The presence of ascites is associated with increased morbidity and high risk of mortality. There is increased respiratory embarrassment, low cardiac output, syncopal attack and decreased bowel movement.

At the time of admission, 56% of the patients had encephalopathy, 49% had bilateral pedal edema, 30% had hepatomegaly, 24% of the patients complained of anorexia, 16% of patients complained of constipation and 11% of patients complained of decreased urine output. The basic cause of encephalopathy in hepatic disorders is due to failure of the process of detoxification in the liver. The toxins escape into the general blood circulation and get accumulated in the central nervous system causing altered brain function and development of hepatic encephalopathy. Impaired renal function was seen in 80% of our patients whereas 20% of the patients had normal renal function. 60% of deaths were reported in those patients who presented with serum creatinine level > 1.2 mg/dl whereas only 20% of deaths were

reported in those patients who had normal renal function. Renal dysfunction can be a part of hepatorenal syndrome or due to shock as there is fluid collection in the peritoneal cavity compressing the blood vessels causing hypo-perfusion of kidneys leading to high serum creatinine. Impaired renal function in patient of alcoholic liver disease is associated with poor prognosis and is also a cause of increased mortality.

Poor prognosis associated with poor response to the corticosteroids is reflected by little or no change in serum bilirubin levels and / or absence of clinical improvement of alcoholic hepatitis patients. The patients who respond to the corticosteroids and show decrease in the serum bilirubin and overall improvement of clinical picture are labeled as true responders whereas those who do not respond to the given dose of corticosteroids and are labeled as non responders. Early recognition of these subgroup of patients is very important in the management of alcoholic hepatitis. Continuing corticosteroid therapy in non-responders is of no use, rather it may lead to infections and other complications. The recognition of true responders has been extended to those patients whose Lille score is more than 0.45 at seventh day of admission. The non-responders are at increased risk of mortality within 3 months compared to the steroid responders.

The MDF score based on the serum bilirubin and prothrombin time as prognostic indicator is used most often to predict short term mortality. MDF score greater than 32 is shown to be associated with greater than 50% mortality and is currently used as a threshold to start corticosteroid therapy in most centres. Outcome risk of AH patients is widely stratified using Discriminant Function. The patients with an MDF score of ≥ 32 are considered to have severe AH. However, it has inadequate specificity of < 40% to 62 % and a sensitivity of 67 % to 100 % for short term mortality [17]. Higher cut off values have been proposed such as cut off of 33, 37, 41, 42 and 44 to increase the specificity. In a prospective study, Kumar *et al*., observed that MDF score was 45.44 ± 9.38 in survivor group whereas it was 99.92 ± 23.09 in non survivors group [18]. In contrast, in our study, MDF score was found to be 78.51 ± 30.07 and 80.50 ± 30.07 respectively in survivors and non survivors. The small difference in the mean of survivors and non survivors in our study suggests that it is not a good score factor for identifying the outcome risk in patients of AH.

F. Higuera de La Tijera *et al*., in their study compared five different scoring systems (Lille, ABIC, MELD, DF and GAHS scores) to assess the prognosis in AH. They demonstrated that the response to treatment evaluated through Lille score was the best predictor of early mortality in AH patients [19]. We observed that the mean value of Lille score in survivors group of our study was 0.35 ± 0.17 while in non survivors, it was 0.72 ± 0.15 (P value 0.000).

Louvet *et al*., had observed marked decrease in 6 months survival in the patients having Lille score ≥ 0.45. Mortality was 25 ± 3.8 % in the subgroup of patients having Lille score < 0.45 versus 85 ± 2.5% in the subgroup with Lille score ≥ 0.45 (P value < 0.0001) [14]. We found that there were 68.4% death in subgroup of patients with Lille score ≥ 0.45 whereas there were no death at all in the subgroup with Lille score < 0.45. We also observed that 76% of the patients in our study group had a Lille score > 0.45 whereas only 24% had a score of < 0.45. This was in contrast to the original study by Louvet *et al*., where only 38% of AH patients had a Lille score of ≥ 0.45. This again points towards the higher likelihood of getting more severe toxicity with locally brewed alcohol.

Lille score cut off of 0.45 for identifying the AH patients who have high risk of mortality at 6 months was suggested by Louvet *et al*., The term non responder (to steroid therapy) is extended to the patients whose Lille score is ≥ 0.45 [14]. The subgroup of non responders should be considered for alternative therapy like Liver transplantation. In the original study, Lille score cut off of 0.45 had sensitivity and specificity of 81% and 76% respectively in the validation cohort and 76% and 85% respectively in overall patients. However, we observed that by taking a cutoff point of 0.45, the sensitivity of Lille score for death outcome is 100% but specificity is only 50%.

Hence, we opted to draw a Receiver Operator Curve (ROC) to find out a new cut off of Lille

score which had a better specificity. We found the cutoff point of 0.47 which was a little higher than that suggested by Louvet *et al*., The sensitivity and specificity of this cut off point were 98.1% and 68.7% respectively. The area under the receiver operating characteristic (AUROC) for survival at 6 months of the derived score probability was 0.960 (95% CI: 0.927 - 0.992). Hence in our study, Lille score cut off appears to be 0.47. We suggest that larger studies are needed to establish a new cut off of Lille score for better risk stratification of AH patients.

CONCLUSION: In the present study Lille model scored over MDF in predicting short term mortality in patients with AH. Our study emphasizes on usefulness of Lille Model which has high accuracy for early identification of patients at high risk of death at six months. It predicts poor survival in subjects with alcoholic hepatitis. There is no benefit of continuing corticosteroid therapy after seven days if the Lille score is > 0.45. However, if Lille score is < 0.45, then it may be beneficial to continue corticosteroids beyond 7 days till 28 days after which it should be tapered off over next two weeks. From our research work it appears that the cutoff point of Lille score for steroid non responders is 0.47.

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CONFLICT OF INTEREST: Nil

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