The Predictive Values Of The Meld And Child-Pugh Scores In Determining Mortality From Chronic Liver Disease Patients In Anambra State, Nigeria.

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Citation

Abstract
Background: Chronic liver disease (CLD) is a major cause of morbidity and mortality worldwide with differing aetiology in different geographic regions. The Child-Pugh's (C-P) and Model for end-stage liver disease (MELD) scores are important determinants of severity and prognosis in CLD. We aimed to compare the predictability values of these scores in determining short-term mortality in a cohort of CLD patients in Anambra state, South-east, Nigeria. Method: This was a prospective study in two hospitals in Anambra state, Nigeria. A total of 112 subjects with CLD were recruited from September 2007 to May 2008 and were followed-up for three months to determine outcome (death or survival) at the end of this period. The C-P as well as the MELD score of each patient was calculated on enrolment. Results: Of the 112 patients recruited into the study, 60(54%) had HCC, 46(41%) had liver cirrhosis and 6(5%) had chronic hepatitis. Only 106 patients completed the study while 6 were lost to follow-up. Of those who completed the study, 70(66%) died and 36(34%) survived. HCC and liver cirrhosis comprised 48(69%) and 22(31%) of the non-survivors and both were associated with mortality (p=0.000). In multivariate analysis, the MELD and C-P scores were both independent predictors of 3-month mortality (p<.001). The AUROC for the MELD score was 0.827 (95% CI 0.746-0.907). It was superior to that of C-P score which was 0.777 (95% CI 0.689-0.864). Conclusion: The C-P and MELD scores are valid predictors of short-term mortality from CLD irrespective of aetiology, however, the MELD performed better than the C-P score.

INTRODUCTION
Chronic liver disease (CLD) is a major world health problem with a high mortality rate\(^1\). The Centre for Disease Control (CDC) had in 1998, listed CLD as the tenth leading cause of death in the United States of America\(^2\). In England, liver cirrhosis (resulting from alcoholic and non-alcoholic chronic hepatitis) was reported to account for 51% of all deaths within one year of admission from 1979-1998\(^3\). In Nigeria, CLD is the third most common cause of death accounting for 12% of all deaths in the medical wards of the University College Hospital, Ibadan over a 14 year period\(^4\). It is second to the Human Immunodeficiency Virus (HIV) infection as a cause of death in the medical wards of the University of Jos Teaching Hospital\(^5\).

The Child and Turcotte classification, first described in 1964\(^6\) but later modified by Pugh in 1973\(^7\), was developed to assess risk in patients undergoing surgical porto-caval shunting for portal hypertension—a major complication of liver cirrhosis. Subsequently, this classification was used to predict the survival in cirrhotic patients in general, and more recently, to stratify patients on the waiting list for liver transplantation.

The Child-Pugh(C-P) classification consists of five discrete variables; two clinical and three biochemical measures and has been found to have a good ability to predict mortality in CLD.\(^8\)

The Model for End-stage Liver Disease (MELD) scoring system was developed in the year 2000 to overcome the observer subjectivity associated with assessing patients using the C-P score. The MELD score uses three objective biochemical parameters and has been demonstrated to be a strong marker of disease severity and mortality in persons with CLD.\(^9\) It has replaced the C-P score for prioritization of liver grafts for transplantation in several countries.\(^10,11\)

The burden of CLD in Nigeria is enormous because of the
high prevalence of chronic hepatitis B virus infection\textsuperscript{12}. Though transplant facilities are not yet available in our country, using these established models to determine disease severity and mortality in our patients will validate these models in our patients and aid early referral. Since indices for predicting mortality are relevant tools for assessing prognosis, data obtained from this study would be essential in formulating health care policies to prioritize health interventions to allocate resources accordingly.

**PATIENTS AND METHODS**

This was a prospective longitudinal study done at the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi and the General Hospital, Onitsha both in Anambra state, south-east, Nigeria.

Ethical clearance was obtained from the Nnamdi Azikiwe University Teaching Hospital, Nnewi Ethical Committee. It also served as clearance for the recruitment of subjects at the General Hospital Onitsha.

One hundred and twelve adult patients (18yrs and above) presenting consecutively at the MOPD or admitted into the medical wards of the NAUTH and the General Hospital, Onitsha were recruited into the study, after obtaining an informed consent, if they had symptoms and signs of, and/or positive HBsAg or anti-HCV serological test which has lasted for more than 6 months, and/or showed the characteristic hepatic ultrasonographic and histologic features of CLD. The study lasted from September 2007 to May 2008. Patients with co-morbid conditions like CCF, Hypertension, DM, HIV infection and those on treatment for chronic hepatitis were excluded from the study.

A structured questionnaire on demographic data, presence of past / present symptoms of liver disease, and exposure to risk factors of CLD was administered to each patient. A detailed physical examination to check for hepatic encephalopathy, which was graded from I – IV, splenomegaly and ascites using either shifting dullness or abdominal fluid thrill was carried out. Stigmata of CLD was sought for and documented. Ten milliliters of venous blood was collected from each patient with observance of universal precautionary measures. Six milliliters (mls) of blood was put in a plain bottle for chemical analysis (liver function tests, serum albumin, serum creatinine), two mls in a citrated bottle for prothrombin time and the remaining two mls in another plain bottle for assay of HBsAg, and anti-HCV. The tests were done at the Nnamdi Azikiwe University Teaching Hospital Chemical pathology and Haematology Laboratories. Initial clinical and laboratory data obtained on admission were used to calculate the C-P and MELD scores. The C-P score was calculated based on ascites (none = 1, mild = 2, moderate-severe = 3) encephalopathy (none = 1, grade 1-2 = 2, grade 3-4 =3), serum albumin (>35mg/dl =1, 28-35mg/dl = 2, <28mg/dl =3), total serum bilirubin (<2mg/dl = 1, 2-3mg/dl = 2, >3mg/dl = 3) and prolongation of prothrombin time in seconds (<4s = 1, 4-6s = 2, >6s = 3). The total points were converted into three classes (A = 5-6points, B = 7-9points, C = 10-15points). The MELD score was calculated by the formula 9.6 x log e (creatinine mg/dl) + 3.7 x log e (bilirubin mg/dl) + 11.2 x log e (international normalized ratio) + 0.64) downloaded at http://www.unos.org. The total points were grouped into four categories at interval of 10 points. MELD 1= ≤ 10 points, MELD 2 = 11-20 points, MELD 3= 21-30 points, MELD 4 = ≥ 31 points. Patients were followed-up for three months. The date of death was recorded and those who were alive at the end of three months were noted. All analyses were performed using SPSS version 11.5.1 (Chicago, IL) Continuous variables were tested for normal distribution and expressed as mean ± Standard deviation or median (range) as appropriate. Categorical variables were compared by Pearson chi-square test and continuous variables were compared by Students t-test. The cumulative survival at different categories of MELD score and C-P class was performed by Kaplan – Meier analysis and compared by the log rank test. The AUROC was used to measure the performance of MELD and C-P scores for short term mortality. A p-value of less than 0.05 was considered statistically significant.

**RESULTS**

Two thousand and ninety-one patients were seen at the Medical clinics and wards of the Tertiary and General hospitals during the study period out of which one hundred and twelve patients met the inclusion criteria. CLD thus, accounted for 5.3% of the total diagnoses during the study period. One hundred and six were followed up for three months and six were lost to follow up.

Of the 112 patients recruited into the study, 74 were males and 38 were females giving a m:f ratio of 2:1. Their ages ranged from 19-86years with a mean age of 50.67±17years. The mean age of males was 49.78±17.32years and the mean age of females was 52.39±16.65years. The highest frequency of the disease was found among those aged
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50-59 years. (Table 1).

**Figure 1**
Table 1: AGE AND SEX DISTRIBUTION OF STUDY POPULATION.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Male (n)</th>
<th>Female (n)</th>
<th>Total (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2.7</td>
</tr>
<tr>
<td>20-29</td>
<td>11</td>
<td>2</td>
<td>13</td>
<td>15.6</td>
</tr>
<tr>
<td>30-39</td>
<td>16</td>
<td>0</td>
<td>17</td>
<td>15.2</td>
</tr>
<tr>
<td>40-49</td>
<td>10</td>
<td>3</td>
<td>13</td>
<td>13.4</td>
</tr>
<tr>
<td>50-59</td>
<td>9</td>
<td>4</td>
<td>13</td>
<td>13.6</td>
</tr>
<tr>
<td>60 and above</td>
<td>12</td>
<td>8</td>
<td>20</td>
<td>13.7</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>28</td>
<td>112</td>
<td>100</td>
</tr>
</tbody>
</table>

One hundred and six patients completed the study while 6 were lost to follow-up. Of those who completed the study, 70 (66%) died and 36 (34%) survived. Of the 70 non-survivors, 48 (69%) had HCC and 22 (31%) had liver cirrhosis. Mortality was not recorded in the category of subjects with chronic hepatitis within the duration of follow-up. There was a statistically significant association between diagnosis (HCC and liver cirrhosis) and mortality (p< 0.01). This could not be calculated for chronic hepatitis as no mortality was recorded in that category within the duration of follow-up (Table 2).

**Figure 2**
Table 2: RELATIONSHIP BETWEEN DIAGNOSIS AND OUTCOME

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Outcome (after 3 months)</th>
<th>Unknown(%)</th>
<th>Alive(%)</th>
<th>Dead(%)</th>
<th>Chi sq.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular Carcinoma (n=69)</td>
<td>4 (6.7)</td>
<td>8 (12.2)</td>
<td>58 (88)</td>
<td>27.595</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis (n=46)</td>
<td>2 (4.3)</td>
<td>22 (47.8)</td>
<td>22 (47.8)</td>
<td>4.061</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis(n=0)</td>
<td>-</td>
<td>6 (100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total (n=112)</td>
<td>6 (5.4)</td>
<td>36 (32.1)</td>
<td>70 (62.5)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

The mean C-P score at admission for the survivors was 8.42 and their mean MELD score was 13.33. For the non-survivors, the mean C-P and MELD scores were 11.06 and 25.29 respectively. The difference between the mean C-P and MELD scores for survivors and non-survivors was statistically significant (p<0.001). C-P class C constituted 69 (61.6%) of the cases, followed by C-P class B with 30 (26.8%) of cases. Only 13 (11.6%) were in class A. A total of 15 patients (13.4%) had MELD score ≤ 10, 52 (46.4%) had scores of 11-20, 27 (24.1%) had scores of 21-30 and 18 (16.1%) had scores ≥ 31. Mortality rates of 77.1%, 20% and 2.9% for C-P classes C, B and A respectively were obtained in this study and that for the four categories of MELD (≤10, 11-20, 21-30, ≥31) were 2.9%, 40%, 32.9% and 24.2% respectively.

Advanced C-P grading was associated with lower cumulative survival. The mean duration of survival was 7 weeks for classes A and B (95% CI 5, 9) and 4 weeks for class C (95% CI 3, 5). Pair-wise comparison among the 3 classes were not significant for between classes A and B (log rank 0.06, p=0.80), classes A and C (log rank=0.48, p=0.49) but was statistically significant for class B versus C (log rank=4.44, p=0.035).

Higher MELD scores were also associated with lower cumulative survival. The mean survival for MELD score ≤ 10 was 8 weeks (95% CI 7, 11), for score 11-20, it was 6 weeks (95% CI 5, 7). MELD score 21-30 had a mean survival of 4 weeks (95% CI 3, 5) and that for score ≥ 31 was 2 weeks (95% CI 1, 4). In pair-wise comparison, all categories of MELD were statistically, significantly different from each other except for categories 1(MELD ≤ 10) versus 2 (MELD =11-20) (log rank =0.1, p=0.92), 1 versus 3 (MELD 21-30) (log rank = 1.92, p=0.17) and category 3 versus 4 (MELD ≥ 31) (log rank= 2.08, p=0.15) (table 3).
The area under the receiver operator characteristic curve (AUROC) for the MELD score as a predictor of 3-months mortality in CLD was 0.827 (95% CI 0.75-0.91, p<0.0001) (fig 1). Using a cut-off of 15.5, the test had a sensitivity of 80%, specificity of 69%. The positive likelihood ratio (+LR) was 2.6 and the negative likelihood ratio (-LR) was 0.2. These were superior to that of C-P score with AUROC of 0.777 (95% CI 0.689-0.864, p<0.0001) (fig 2). Using a cut-off of 9.5, the test had a sensitivity of 77%, specificity of 64%, LR+ of 2.2 and a –LR of 0.4.
Figure 5

Fig 2: RECEIVER OPERATING CHARACTERISTIC CURVE FOR THE C-P SCORE IN PREDICTING MORTALITY AT 3 MONTHS FOR ALL PATIENTS WITH COMPLETE DATA

Total patients included in analysis = 106.
Number lost to follow-up = 6
Number dead = 70
Number alive = 36
C-P score, AUC = 0.777, with 95% confidence interval 0.689-0.864.
AUC = area under the receiver operator characteristics curve;
C-P = Child-Pugh score.

When only HCC cases were analyzed, the MELD score had an AUROC 0.799 (95% CI 0.62-0.90, P=0.001). Using the same cut-off of 15.5, the sensitivity was 75%, specificity of 83%, LR+ of 4.5 and LR- of 0.3. The C-P score which had an AUROC of 0.807 (95% CI 0.68-0.93, P=0.001), sensitivity of 71%, specificity of 67%, LR+ of 2.1 and LR- of 0.4 using a cut-off of 9.5.

The MELD was superior to the C-P score when subjects with liver cirrhosis only were analyzed. The AUROC was 0.881 (95% CI 0.78-0.98, P=0.000). Using a cut-off of 15.5, the sensitivity was 91%, specificity was 54%, LR+ of 2, and LR- of 0.16. However, when the cut-off was increased to 17.5, the specificity increased to 75%, LR+ was 3.6 and LR- was 0.12. For C-P score, the AUROC was 0.760 (95% CI 0.62-0.89, P=0.002). At a cut-off of 9.5, sensitivity was 91%, specificity 54%, LR+ of 1.98 and LR- of 0.16. The positive predictive value (PPV) and negative predictive value (NPV) of each test is shown in the table below (table 4).

DISCUSSION

Child-Pugh classification and MELD scores are useful in the assessment of hepatocellular function. Both have been found to correlate with oesophageal variceal size, the presence of endoscopic red signs and response to therapy for varices. Both, but especially the MELD score have been shown to correlate with the development of hepatorenal syndrome, oedema mobilization using salt-poor albumin and survival following liver transplantation. The C-P score and MELD score are also useful guide to prognosis in CLD. In this study, the highest mortality rate was seen in C-P class C and MELD score of 11-20. The apparent reduction in the mortality rate at MELD score >20 maybe due to the fact that scores between 11-20 have been shown to be most sensitive in predicting mortality. This study found the score of 15.5 to have the highest sensitivity and specificity in predicting mortality from CLD.

The predictive abilities of the MELD and C-P score were partly independent of each other and both were predictors of mortality at 3 months. Nonetheless, only the MELD was found to be an independent predictor of short term mortality and is in keeping with previous reports. The AUROC
determines the power of a test to discriminate between subjects having and those not having a particular outcome (mortality). Based on the ROC curve analysis, the MELD was superior to the C-P in all categories of patients except in those with HCC. Moreover, when both scores were subjected to further statistical analysis using the positive likelihood and negative likelihood ratios which describes how many times more likely a person with a particular score will record mortality than someone without the score and how many times less likely a person without the particular score will record mortality than a person with the score respectively, the MELD at a cut-off of 15.5 was superior to the C-P at a cut-off of 9.5 in all categories except for those with liver cirrhosis where its’ performance was the same as that of the C-P score. However, increasing the cut-off for the MELD improved its specificity, positive and negative predictive abilities but the sensitivity remained the same. This is similar to what was obtained in previous studies comparing the performance of the MELD and C-P score in determining short-term survival in liver cirrhosis17,18. However, when creatinine was added to the C-P equation, its performance became identical to that of the MELD18. Heuman19 and colleagues re-examined statistically the traditional cut-off points of C-P classification and considered them as sub-optimal for short-term prognosis. They proposed new C-P classes: A (5-6), B1 (7-8), B2/C1 (9-11), C2 (12-13), and C3 (14-15). They also proposed the addition of serum creatinine and nutritional status both of which are known to influence prognosis in CLD.

The finding in this study contrasts to what was reported in another study in Hong Kong among patients with decompensated chronic hepatitis B. They found the MELD score to be slightly inferior to the C-P score in the prediction of 3-month mortality based on ROC curve analysis15. They attributed their findings to different pathogenic mechanisms involved in the progression of liver disease from different aetiologies. However, this was not confirmed in this study as the MELD remained superior to the C-P when only patients with positive HBsAg result were analyzed.

The value of the MELD score is that it incorporates serum creatinine, a measure of renal function in the prognostic evaluation of patients with CLD which has been recognized for many years to be an important prognostic factor14,18. Its other advantage is that it is a continuous or progressive score, which increases with worsening of its parameters unlike the C-P which is categorized and so have the floor and ceiling effect. However, the MELD is not without its draw-backs. It does not take into account hepatic encephalopathy and serum albumin which are components of the C-P score that reflect hepatic dysfunction. Both hepatic encephalopathy and hypoalbuminaemia also correlate significantly with mortality but only hepatic encephalopathy was shown to be an independent predictor of short-term mortality in this study as was documented in other studies9,16,20. Therefore, it may underestimate mortality in patients with acute on chronic liver disease who develop hepatic encephalopathy. Its variables especially creatinine may be affected by non-hepatic factors like muscle mass. In addition, the relationship between INR used in the MELD score and prothrombin time is not linear and for that reason, INR may not accurately reflect the severity of liver disease21. While it is easy and convenient to calculate the C-P score by the patient’s bedside, one needs an internet connection or a scientific calculator to calculate the MELD score.

In conclusion, The C-P and MELD scores are valid predictors of mortality from CLD irrespective of the aetiology. However, only the MELD score is an independent predictor of short-term mortality. The MELD score demonstrated a higher predictive ability for mortality than the C-P score in CLD generally.

In our environment where internet facilities are not widely available, we recommend that the C-P score be routinely used for individual assessment of patients with CLD in daily clinical practice. On the contrary, the MELD score may be well suited for prioritizing patients who will benefit from liver transplantation.

References
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