Prospective Evaluation of Factors Affecting the Outcome in Cirrhotic Patients Requiring Intensive Care

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ABSTRACT

Introduction: The short-term prognosis of acutely ill patients with cirrhosis is influenced by the degree of hepatic and extrahepatic organ dysfunction.

Objective: This study intends to find the parameters that influence the outcome in cirrhotics requiring critical care.

Methods: This was a single-centre, prospective, observational study. Prognostic scores were calculated on the day of admission and day 7. The appearance of new events and length of hospital stay was documented. Follow up was done at day 30 in person or by telephone for those who had left the hospital.

Results: Out of 96 subjects 12 were lost to follow up, 84 subjects followed of which 55 expired within 30 days of admission. On multivariate analysis older age, presence of Malena, oliguria, presence of infective foci, hepatic encephalopathy, low platelet count and pH, high lactate, creatinine, bilirubin, serum ferritin were predictors of mortality. Mean serum ferritin levels were significantly higher (p<0.001) in non-survivors (922.95 ± 319.85) as compared to survivors (368.17± 113.87). Lower ROC was observed for liver-specific scores CTP (0.727), MELD (0.79) and MELD Na (0.77) as compared to general ICU scores SOFA (0.808), APACHE II (0.855) on the day of admission.

Conclusions: CLIF SOFA score which is a combination of liver-specific scores and ICU scores should replace CTP and MELD to predict short term mortality in critically ill liver cirrhotics. Serum ferritin as a biomarker has good ability in anticipating the outcome. An ideal score should include ferritin along with the assessment of multi-organ functioning.

Key Words: Cirrhosis, MELD, CLIF- SOFA, Serum Ferritin

INTRODUCTION

Patients with advanced liver cirrhosis frequently require admission to the intensive care unit as they have a poor prognosis, with mortality rates ranging from 36% to 86%.1-3 The short-term prognosis of acutely ill patients with cirrhosis is influenced by the degree of hepatic insufficiency and by dysfunction of extrahepatic organ systems. Sepsis is the presence of cirrhosis is associated with poor prognosis; mortality rates increase with the increasing number of failing organs.5,6 Among the extrahepatic organ failures often encountered in end-stage liver disease, renal failure or dysfunction in cirrhotic patients has been the subject of extensive investigation.7 Stratifying patients help differentiate those who could achieve a better outcome with aggressive treatment from those who would not benefit from admission to the intensive care unit.8

The Child-Turcott score and its subsequent modifications by Pugh are old empirical methods used to assess the degree of liver failure in candidate patients for Portosystemic shunt.9 The discriminatory power of this score relative to mortality in cirrhotic patients admitted to the ICU is inferior to that of general ICU scores like Sequential Organ Failure Assessment (SOFA) or Acute Physiology and Chronic Health Evaluation (APACHE)(10). Model for End-Stage Liver Disease (MELD) score, initially developed for cirrhotic patients treated with Transjugular Intrahepatic Portosystemic Shunt (TIPS), has been applied widely to predict mortality across a broad spectrum of liver diseases (11). MELD score has its
limitations one such is its inaccuracy in predicting survival in 15–20% critically ill patients.  

A modification of SOFA, the Chronic Liver Failure-SOFA (CLIF-SOFA) score, has been proposed for patients with cirrhosis hospitalized for acute decompensation. 13-15  Cirrhotic patients with other organ dysfunction showed increased mortality, increasing with the number of organs affected, 14 reaching 90% in patients with three or more organ dysfunctions. Based on reliable prognostic factors, interventions like liver assist devices or plasmapheresis can be initiated for critically ill cirrhotics. Whenever patients with cirrhosis are critically ill the question of utility and/or futility of placing them in ICU arise, especially in resource-constrained settings. 16,17

This is a challenging situation and needs good scoring systems which can predict the utility of ICU. The present study is intended to find the parameters that influence the outcome in cirrhotics requiring critical care so that available resources can be put to best use.

**MATERIALS AND METHODS**

The study was a single-centre, prospective, observational study conducted between January 2015 and January 2016 at Department of Medical Gastroenterology, Nizam’s Institute of Medical Sciences (NIMS), Hyderabad after obtaining approval from Institutional Ethics Committee. Consecutive patients of liver cirrhosis requiring intensive care were recruited. The primary endpoint was a reassessment of scores at day 7 and mortality up to day 30.

**Inclusion Criteria:**

Consecutive patients more than 18 years of age with liver cirrhosis of any aetiology requiring intensive care were recruited.

**Exclusion Criteria**

- Acute liver failure
- Post-liver transplantation
- HIV infection
- Established case of hepatocellular carcinoma
- Presence of severe comorbidities in the form of cerebrovascular accident, chronic kidney disease, severe cardiopulmonary insufficiency, ischemic heart disease, chronic obstructive pulmonary disease.
- Post - hepatobiliary surgery

**Procedure**

The diagnosis of cirrhosis was based on clinical, radiological and laboratory parameters. History, physical examination, haematological and biochemical parameters, and imaging studies were done. Patient demographics and an indication of ICU admission were noted. Presence of co-morbid disease was documented. Prognostic scores were calculated on the day of admission and day 7. The appearance of new events and complications during the hospital course was noted. Length of ICU and hospital stay were documented. Standard of care was provided to all patients. Follow up was done at day 30 in person or by telephone for those discharged.

**RESULTS**

Total of 96 patients was enrolled, 12 were lost to follow up. 84 patients (M/F: 77/7) completed the study. Alcohol was the most common aetiology (76.1%) followed by Hepatitis B (8.3%), Hepatitis C (4.7%) and alcohol with viral hepatitis (10.7%). 55 patients expired within 30 days of admission. Mean age amongst survivors was significantly lower than non-survivors (45 ± 9.32) vs. (50±8.067) (p<0.001).

Ascites was the commonest symptom among both non-survivors (87.3%) and survivors (55%) with p =0.794. Jaundice was seen in both the groups of non-survivors (67.3%) and survivors (65.5%) with no statistical significance p=0.873 in predicting the outcome. Oliguria was seen in 24 (43.7%) of non-survivors and 4 (13.8%) of survivors with a p-value of 0.005. Malena was commoner than hematemesis at presentation in both non survivors (45.5% vs. 10.5%) and survivors (27.6% vs. 6.8%) with significant difference (p=0.02) [Table 1].

Mean arterial pressure was significantly different (p=0.007) among both the groups with lower values among non-survivors (69.07 ± 9.2388) than survivors (75.103 ± 9.982)[Table 1]. The requirement of inotrope support for maintenance of pressure was more frequently required in non-survivors (9/55) group than in survivors (3/29).

Among the blood indices haemoglobin (9 ± 1.11 vs 8.85 ± 2.73), and platelet counts (1.286 ± 0.4372 vs 0.9989 ± 0.467 lakhs /cum) were higher among non-survivors while total leucocyte count (13442.41 ± 4569.87 vs 15193 ± 5099.98 / cum) was lower among non-survivors (45 ± 9.32) vs. (50±8.067) (p <0.001).

Table 1: Demographics and Clinical Profile

| Age (in years) | 50 | 45 | P-value |
|---------------|----|----|---------|
| Gender        | M/F: 51/4 | M/F: 26/3 | 0.873 |
| Jaundice      | 37(67.3%) | 19(65.5%) | 0.005 |
| Oliguria      | 24(43.7%) | 4(13.8%) | 0.794 |
| Ascites       | 48(87.3%) | 16(55%) | 0.020 |
| Melena        | 25(45.5%) | 8(27.6%) | 0.40 |
| Hematemesis   | 6(10.9%) | 296.8% | 0.005 |
Table 1: (Continued)

|                      | Non survivors (n=55) | Survivors(n=29) | P-value |
|----------------------|----------------------|-----------------|---------|
| MAP                  | 69.07±9.23           | 75.10±9.98      | 0.007   |
| Grades of HE         |                      |                 |         |
| Grade 1              | 18                   | 5               |         |
| Grade 2              | 15                   | 3               |         |
| Grade 3              | 12                   |                 |         |
| Infection foci       |                      |                 |         |
| SBP                  | 10                   | 3               |         |
| Pulmonary            | 6                    | 3               |         |
| UTI                  | 5                    | 2               |         |
| Cellulitis           | 3                    | 1               |         |

Assessment of liver function tests showed SGOT (126 ± 76.36 vs 96 ± 102.29), SGPT (96 ± 102.29 vs 42 ± 65.43), INR (2.227 ± 0.6665 vs 2.051 ± 0.6593) were higher and albumin was lower in non survivors but significant difference (p=0.000) was noted only for bilirubin (24.265 ± 4.818 vs 17.075 ± 5.587) [Table 2].

Blood urea and serum creatinine were higher among non-survivors (58 ± 32.609 and 2.35 ± 1.147) than survivors (54 ± 45.27 and 1.537 ± 0.348) but statistical significance was seen for serum creatinine (p<0.001) [Table 2]. Significantly higher (p=0.00) mean serum ferritin levels were noted in non-survivors (922.95 ± 319.858) when compared to survivors (368.17 ± 113.873) with a range of 102 to 1746 and 270 to 717 [Table 2].

Table 2: Lab parameters and inflammatory markers

|                   | Non survivors (n=55) | Survivors(n=29) | P-value |
|-------------------|----------------------|-----------------|---------|
| Hemoglobin        | 8.88±2.173           | 9±1.117         | 0.1187  |
| TLC               | 15193.09±5999.58     | 13442.41±4569.87| 0.125  |
| Platelet Count    | 0.0089±0.467         | 1.286±0.4372    | 0.007   |
| Creatinine        | 2.35±1.147           | 1.537±0.3488    | <0.001  |
| Urea              | 58±32.609            | 54±45.27        | 0.679   |
| Total Bilirubin   | 24.26±4.818          | 17.07±5.587     | <0.001  |
| Albumin           | 2.19±0.66            | 2.25±0.382      | 0.659   |
| AST               | 12±2.763             | 96±102.29       | 0.337   |
| ALT               | 54±36.05             | 42±65.43        | 0.795   |
| INR               | 2.27±0.66            | 2.05±0.65       | 0.253   |
| Serum Ferritin    | 922.95±319.85        | 368.17±113.87   | <0.001  |
| pH                | 7.294± 0.07128       | 7.342 ± 0.0978  | 0.011   |
| Lactate           | 3.0745 ± 1.353       | 2.22 ± 1.88     | 0.019   |
| paO2/FiO2         | 360.77± 71.137       | 393.725 ± 79.26 | 0.056   |
| HCO3              | 16.549 ± 3.159       | 22.841 ± 3.897  | 0.235   |

Among the scoring systems that were compared CLIF-SOFA had the highest sensitivity and APACHE II had the highest specificity with the highest AUROC noted with CLIF-SOFA [Figure 1, Table 3].

Figure 1: ROC curve for various scores predicting 30-day mortality.

DISCUSSION

Alcohol was the commonest aetiology seen in 76.1% of our subjects which can be explained by the male preponderance (M:F = 3.2:1) in our study because alcohol consumption is less common among women in this part of the world. In our series, the 30-day mortality was 66.7%. The mean age at presentation was higher among non-survivors compared to survivors. Older subjects had higher mortality possibly due to decreased functional reserves resulting in organ dysfunction with any additional insult.

Amongst the presenting complaints, oliguria and GI bleeding were statistically significant in predicting poor
outcome. Mean arterial pressures and inotrope requirement was significantly different between the two groups reflecting the impact of GI bleed on hemodynamic stability and renal function and thereby the outcome. Similar findings were seen in a study by Chariff et al.\textsuperscript{14,19} SBP was the most common infection followed by pulmonary infections both in non-survivors and survivors. Urinary tract infection, cellulitis, hepatitis A and hepatitis E were other infections that precipitated downhill course. In comparison to previous studies\textsuperscript{17,23} we had a lower incidence of UTI, cellulitis and acute viral hepatitis; however, the mortality was comparable.

The platelet count showed a statistically significant difference between the two groups (p=0.007) indicative of advanced liver disease and portal hypertension in non-survivors. On blood gas analysis the mean levels of pH and lactate were significantly different between survivors and non-survivors [Table 2] indicative of severe ongoing inflammation. Bilirubin and creatinine were significantly different between the two groups again suggestive of decreased hepatic and renal reserves.

In our study mean serum ferritin levels were significantly higher (p<0.001) in non-survivors. Serum Ferritin, an indicator of body iron reserves is also an acute phase reactant and a surrogate marker of the necroinflammatory activity in liver parenchymal cells. Increased levels are known to predict poor outcome in decompensated liver cirrhosis.\textsuperscript{21} Similar results have also been observed in a study by Maiwall et al.\textsuperscript{20}

Although initially derived for predicting post-procedure outcome, CTP and MELD scores have been extrapolated to predict survival in cirrhotic patients.\textsuperscript{21,22} These scores have been used in prioritizing organ allocation in cirrhotics waitlisted for liver transplantation. However when there is the rapid deterioration of the cirrhotic patients due to precipitating factors, prediction of outcome is challenging and CTP, MELD has not fared well in this. We observed lower ROC for liver-specific scores like CTP (0.727), MELD (0.79) and MELD Na (0.77) as compared to general ICU scores. In the present study general ICU scores SOFA (0.808), APACHE II (0.855) fared better in predicting outcome than liver-specific scores in critically ill cirrhotics. Zauner et al. retrospectively compared the prognostic abilities of liver-specific and general scoring systems and found that the APACHE system was the most accurate prognostic system.\textsuperscript{21} However, this study was done before the emergence of SOFA score hence not compared with it. Our study findings resemble a study by Alsheirif et al. stating that SOFA is a better predictor than MELD.\textsuperscript{17} However, there are some limitations to the SOFA. Serum bilirubin, which is one of the parameters in the SOFA does not reflect the full spectrum of liver dysfunction in critical illness and cannot differentiate acute liver dysfunction from the effects of pre-existing chronic disease.\textsuperscript{22} Also, the Glasgow Coma Scale as the variable reflecting neurologic dysfunction has shortcomings. In our study CLIF – SOFA was the best predictor of outcome in critically ill cirrhotics (ROC=0.867) [Figure 1]. This score is a modification of SOFA score and includes additional liver specific parameters like prothrombin time as well as West Haven score to reflect neurologic impairment due to cirrhosis rather than a general neurologic dysfunction score like GCS.

**CONCLUSIONS**

Critically ill cirrhotics have a high mortality rate. Oliguria, GI bleeding, low mean arterial pressures can predict early mortality. Platelet count, bilirubin, lactate, pH and serum creatinine are good predictors of 30-day mortality. The general ICU scores SOFA, APACHE II are better than CTP and MELD in predicting outcome. The CLIF SOFA score which is a combination of liver-specific scores and ICU scores should replace CTP and MELD to predict short term mortality in critically ill liver cirrhotics. Serum ferritin as a biomarker has good ability in predicting the outcome. We hypothesize that the inclusion of ferritin in these scoring systems may improve the predicting power. An ideal score may be the one which includes ferritin along with organ dysfunction scores.

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