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Outcome of patients with cirrhosis requiring intensive care unit support: Prospective assessment of predictors of mortality

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Abstract: Determinants of outcome and the utility of the Child-Pugh score and the acute physiology and chronic health evaluation (APACHE) II score as predictors of outcome were prospectively assessed in 54 consecutive patients with cirrhosis requiring intensive care unit (ICU) management. Overall mortality in the ICU was 43% (23/54). Child-Pugh scores did not differ between survivors or nonsurvivors (12.8 versus 12.3, $P = 0.26$), however APACHE II scores ($P = 0.007$), acute physiology scores ($P = 0.006$), and Karnofsky scores ($P = 0.001$) were significant predictors of outcome. By univariate analysis, requirement of mechanical ventilation analysis ($P = 0.001$), duration of mechanical ventilation ($P = 0.001$), pulmonary infiltrates ($P = 0.0001$), infections ($P = 0.047$), gastrointestinal bleeding ($P = 0.005$), and serum creatinine >1.5 mg/dl ($P = 0.0005$) were significantly associated with mortality. By logistic regression analysis only pulmonary infiltrates ($P = 0.0001$) and renal dysfunction ($P = 0.041$) were independent predictors of mortality. When controlled for the severity of illness (APACHE II scores), the mortality in patients with cirrhosis caused by alcohol was significantly lower than that in patients with liver disease not caused by alcohol ($P = 0.01$). Our study not only identified predictors of poor outcome in patients with cirrhosis requiring ICU care but also provided data that may have implications for optimal timing for transplantation.

Key words: cirrhosis, intensive care unit, hepatitis C, prognosis, liver transplantation

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Introduction

Intensive care unit (ICU) care is an integral part of the management of patients with complications of cirrhosis. A number of medical complications, e.g., hepatic encephalopathy, coagulopathy predisposing to hemorrhage, variceal bleeding, pulmonary edema, infections, or cardiac complications, may prompt admission to the ICU in patients with endstage liver disease. These critically ill patients also comprise a significant proportion of those who eventually undergo liver transplantation.

Factors that adversely influence survival in critically ill patients have been assessed in a number of medical conditions, including hematologic malignancies,[1] bone marrow and organ transplantation,[2–4] and respiratory diseases.[5] Child-Pugh scores were initially developed for the assessment of hepatocellular functional reserve in patients undergoing surgical treatment for variceal bleeding, and have since been widely used for the assessment of the severity of illness in patients with endstage liver disease.[6,7] Child-Pugh scores predicted outcome in a retrospective study of patients with cirrhosis and chronic liver disease admitted to the ICU.[8] However, these criteria have not been uniformly shown to be optimal predictors of survival in patients with cirrhosis and were of limited value for discriminating the high-risk patients for transplantation.[9,10] Acute physiology and chronic health evaluation (APACHE) scores were determined to be of prognostic significance in a study in ICU patients with cirrhosis; however, neither Child-Pugh scores nor etiology of liver disease were assessed in that study.[11] No study, to our knowledge, has prospectively evaluated Child-Pugh scores and APACHE scores concurrently as predictors of outcome in critically ill patients with cirrhosis.

Pervious studies on ICU outcome in patients with endstage liver disease were conducted prior to the routine testing of hepatitis C virus (HCV).[8,11–13] HCV has

emerged as a significant cause of cirrhosis and is one of the leading indications for liver transplantation; an estimated 3.5 million people in the United States have chronic HCV infection and each year 8000–10000 chronically infected patients with HCV die of liver-related complications.

We prospectively followed consecutive patients with cirrhosis requiring ICU care at our institution over a 2-year period. The primary objectives of this study were: to determine the outcome and the prognostic factors associated with poor outcome in patients with cirrhosis admitted to the ICU and to determine whether standardized severity-of-illness scoring systems, e.g., Child-Pugh score and APACHE II scores, predicted the outcome in these patients.

Methods

The study samples comprised patients with cirrhosis referred to the liver transplant service of the Pittsburgh Veterans Affairs Medical Center between January, 1993 and December, 1994. Consecutive patients requiring ICU admission at any time between their referral and transplantation or death were considered as an ICU admission. For the purpose of this study, each ICU admission was considered a separate patient, as reported previously.[14] All ICU admissions were followed until discharge from the ICU or until death.

The following variables were recorded for each patient on admission to the ICU: age, sex, etiology of liver disease, data of hospital admission, data and reason for ICU admission, presence of co-morbid illness (diabetes, hypertension, heart disease, malignancy, renal failure), and Child-Pugh score. Admission vital signs, Karnofsky score, and laboratory data (complete blood count, BUN, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase, gamma glutamyl transpeptidase, prothrombin partial thromboplastin times, serum cholesterol, albumin, and electrolytes) were also recorded. The APACHE scoring system is the most widely employed severity-of-illness scale in the ICU studies.[15] The APACHE II score was calculated at the time of the ICU admission by adding the acute physiology score (APS), chronic health points, and age points.[15] It has also been shown that preadmission functional status of the patient is an important determinant of the outcome in critically ill patients.[15,16] We employed the Karnofsky performance score to assess the functional status of the study patients.[17]

During the ICU stay, the following variables were recorded: invasive procedures (requirement for pulmonary artery catheter, arterial line, tracheostomy, endoscopy, bronchoscopy); total parenteral or enteral nutrition; inotropic or vasopressor support; requirement for and duration of mechanical ventilation; dialysis; infections; and presence of pulmonary infiltrates and their etiology. The criteria for diagnosing nosocomial pneumonia,[16] adult respiratory distress syndrome,[18] pulmonary edema,[19] and peritonitis[20] were as previously reported.

Statistical analysis. Patient demographics and laboratory values were entered into a database (Prophet, BBN Systems and Technologies, Cambridge, MA, USA). Contingency tables were analyzed using the χ^2 or Fisher exact test. Continuous variables were compared using the *t*-test or Mann-Whitney test. Multivariate logistic regression analysis was done in stepwise fashion with variables being entered to the equation if the significance level was less than 0.1 and removed from the equation if greater than 0.15.[21]

The pool of variables available for analysis was chosen from variables that were significant by univariate analysis and considered to be of clinical importance (factors that could possibly be altered by management in the ICU).

Results

Characteristics of the study population

There were 54 ICU admissions in 40 patients with cirrhosis during the study period; 30 patients had 1 admission, 8 patients had 2 admissions, 1 patient had 3 admissions, and 1 patient had 5 admissions to the ICU. The mean age of the patients was 48 years (range, 28–69 years). The underlying liver diseases in these patients are outlined in Table 1. Comorbid illnesses included diabetes mellitus in 20% (11/54), hypertension in 9% (5/54), coronary artery disease in 9% (5/54), and malignancy in 11% (6/54) of the patients. The reasons for ICU admission were hepatic encephalopathy, 52% (28/54); gastrointestinal bleeding, 20% (11/54); status post-surgical procedure; 9% (5/54); hypotension/sepsis, 6% (3/54); respiratory distress, 6% (3/54); and miscellaneous, 7% (4/54), i.e., chest pain 1, platelet transfusion reaction 1, seizure 1, and disseminated intravascular coagulation 1.

The duration of ICU stay ranged between 1 and 39 days (mean, 9 days); 39% of the patients had an ICU length of stay greater than 7 days and 22% stayed for 14 days or more. The study patients had been hospitalized a mean of 23 days (range, 0–129 days) before being admitted to the ICU.

Mortality

Overall, 43% (23/54) of the ICU admissions were associated with death. Mortality was 100% (3/3) in patients

Table 1. Demographic and clinical characteristics of the study patients

Age, mean (range) years	48 (28–69)
Comorbid illnesses	
Diabetes	20% (11/54)
Hypertension	9% (5/54)
Heart disease	9% (5/54)
Malignancy	11% (6/54)
Underlying liver disease	
Viral hepatitis	35% (19/54)
HCV	28% (15/54)
HBV	7% (4/54)
Alcohol-induced	28% (15/54)
Alcohol and viral hepatitis	26% (14/54)
HCV	24% (13/54)
HCV and HBV	2% (1/54)
Other	10% (6/54)
Child-Pugh score, mean (range)	12 (7–15)
Ascites	
Mild	19% (10/54)
Moderate	37% (20/54)
Severe	41% (22/54)
Encephalopathy	
Mild	33% (18/54)
Moderate	26% (14/54)
Severe	20% (11/54)
Serum bilirubin, mg/dl, mean	11.5 (0.7–52.0)
Creatinine, mg/dl, mean	2.6 (0.7–8.4)
Prothrombin time (s), mean	17.9 (12.4–30.1)

HCV, Hepatitis C virus; HBV, hepatitis B virus
Viral markers for HCV required the presence of HCV antibodies by recombinant immunoblot assay-II assay, and for HBV, the detection of hepatitis B surface antigen (with or without hepatitis Be antigen)

admitted for respiratory distress, 54% (6/11) in those admitted for gastrointestinal bleeding, 67% (2/3) in patients with hypotension/sepsis, and 39% (11/28) in patients admitted for encephalopathy.

Predictors of mortality

Patients who died had shorter length of hospitalization prior to ICU admission than patients who survived (mean, 18 days versus 27 days; $P = 0.07$). A significantly higher number of patients who died were admitted directly to the ICU upon hospital admission than patients who survived (30%, 7/23 versus 6%, 2/31; $P = 0.03$). Child-Pugh score did not differ between survivors and nonsurvivors (11.8 versus 12.3; $P = 0.26$); however, the survivors had significantly higher Karnofsky scores (43 versus 30; $P = 0.001$), lower APACHE II scores (14.5 versus 18.5; $P = 0.007$), and lower APS scores (8.0 versus 11.7; $P = 0.006$) compared with nonsurvivors (Table 2).

Respiratory rate and pulse rate on admission did not differ significantly between survivors and nonsurvivors; however, nonsurvivors were significantly more likely to have an abnormal temperature ($P = 0.039$) and abnormal blood pressure ($P = 0.06$) than survivors. Mental status was not a predictor of outcome; coma scores (part of APACHE II scores) and percentage of patients with

Table 2. Association of clinical and laboratory variables with outcome in the study patients

Variables	Survivors ($n = 31$)	Non-survivors ($n = 23$)	P value
Age, years (mean)	47.35	49.0	NS
Child-Pugh score	11.8	12.3	NS
Karnofsky score	43	30	0.001
APACHE II score	14.5	18.5	0.007
APS score	8.0	11.7	0.006
Coma score	2.8	2.7	NS
Abnormal temperature[a]	10% (3/31)	35% (8/23)	0.039
Abnormal blood pressure[a]	165 (5/31)	39% (9/23)	0.057
Abnormal pulse[a]	39% (12/31)	43% (10/23)	NS
Abnormal respiration[a]	48% (15/31)	56% (13/23)	NS
Creatinine >1.5 mg/dl	68% (12/31)	100% (23/23)	0.0005*
Mechanical ventilation	29% (9/31)	74% (17/23)	0.001
Pulmonary infiltrates	12% (4/31)	83% (19/23)	0.0001*
Gastrointestinal bleeding	16% (5/31)	52% (12/23)	0.005
Length of ICU stay (days)	6.3	13.2	0.07
Infections	26% (8/31)	52% (12/23)	0.047

* By multivariate analysis, pulmonary infiltrates ($P = 0.0001$) and renal dysfunction ($P = 0.041$) were independent predictors of mortality
APACHE, Acute physiology and chronic health evaluation; APS, acute physiology score; ICU, intensive care unit
[a] Abnormal temperature, >37.7°C or <35.5°C; abnormal pulse, <60 or >90 beats/min; abnormal respiration, <8 or >16/min; abnormal blood pressure, systolic <90 mmHg, or >160 mmHg, diastolic <60 or >90 mmHg

alert mental status (48% versus 30%; $P = 0.184$) did not differ significantly between patients who lived and those who died.

Nonsurvivors had significantly higher serum bilirubin (16.0 mg/dl versus 8.4 mg/dl; $P = 0.025$), prothrombin time (19.3 versus 16.9; $P = 0.035$), BUN (54.6 mg/dl versus 9 mg/dl; $P = 0.004$), and white blood count (13.1 versus 9.06/mm^3; $P = 0.05$) and significantly lower hematocrit (25% versus 28.3%; $P = 0.042$) compared with survivors. Mortality was significantly higher in patients with renal impairment, i.e., creatinine more than 1.5 mg/dl (100% versus 58%; $P = 0.0005$).

Forty-three percent (23/54) of the patients required mechanical ventilation. Requirement for mechanical ventilation and duration of mechanical ventilation were significant predictors of mortality. Seventy-four percent of the nonsurvivors, compared with 29% of the survivors, required mechanical ventilation ($P = 0.001$). Patients who died had significantly longer ventilatory support (mean, 7 days versus 1 day; $P = 0.001$).

Twenty percent (11/54) of the patients required dialysis. Patients requiring dialysis had significantly greater severity-of-illness (APACHE II scores, 18.9 versus 15.5; $P = 0.011$), were more likely to develop pulmonary infiltrates in the ICU (91% versus 30%; $P = 0.0004$), and were more likely to have had hypotension at any time during the ICU stay (64%, 7/11 versus 12%, 5/43; $P = 0.001$).

Pulmonary infiltrates developed in 43% (23/54) of the patients. The etiology of pulmonary infiltrates was pulmonary edema in 65% (15/23), acute respiratory distress syndrome in 13% (3/23), atelectasis in 9% (2/23), pneumonia in 9% (2/23), and pulmonary fibrosis in 4% (1/23). Patients developing pulmonary infiltrates were more severely ill, i.e., had higher APACHE II scores ($P = 0.03$), had longer ICU length of stay ($P = 0.034$), and were more likely to have renal impairment, i.e., creatinine more than 1.5 mg/dl ($P = 0.032$). When controlled for the severity of illness, the patients with pulmonary infiltrates were significantly more likely to die than those without pulmonary infiltrates ($P = 0.0002$).

Infections occurred in 30% (20/54) of the patients and bacteremia in 20% (11/54) of the patients; 26% (8/31) of the survivors versus 52% (12/23) of the nonsurvivors developed infections ($P = 0.047$). Spontaneous bacterial peritonitis accounted for 35% (7/20) of all infections in the ICU and was caused by culture-negative neutrocytic ascites in 43% of the episodes, neutrocytic ascites in 29% of the episodes, and bacteriascites in 29% of the episodes. The etiologic agents of bloodstream infections were *Staphylococcus aureus* (27%, 3/11, including one patient with endocarditis), *Klebsiella pneumoniae* (27%, 3/11), *Citrobacter freundii* (18%, 2/11), enterococci (18%, 2/11), and *Pseudomonas aeruginosa* (9%, 1/11). One patient (receiving corticosteroids) had fungemia caused by *Candida albicans*. Patients experiencing infections were more likely to have had gastrointestinal bleeding ($P = 0.035$), creatinine more than 1.5 mg/dl ($P = 0.07$), and to have required dialysis ($P = 0.07$). Mortality was higher in infected (60%, 12/20) versus noninfected (32%, 11/34) patients ($P = 0.047$).

When pulmonary infiltrates, infections, renal impairment, and gastrointestinal bleeding were entered into a logistic regression model, only pulmonary infiltrates ($P = 0.0001$) and renal dysfunction ($P = 0.041$) were independent predictors of mortality. Mortality was 86% when all the above four variables were present and 0% when none of the above was present. Mortality rate was 91% when pulmonary infiltrates and gastrointestinal bleeding were present and 86% when pulmonary infiltrates and renal dysfunction existed.

When controlled for the APACHE II scores (APACHE II more than 15), 35% (7/20) patients with alcoholic cirrhosis versus 83% (10/12) of the patients with cirrhosis not caused by alcohol died ($P = 0.01$). Eighty-three percent of the patients without alcoholic cirrhosis had viral hepatitis (HCV 75% and HBV 8%). Serum creatinine (3.3 versus 2.4 mg/dl), bilirubin (5.3 versus 8.4 mg/dl), and frequency of gastrointestinal bleeding (30% versus 50%) were not different between patients with cirrhosis caused by alcohol versus nonalcoholic cirrhosis; however the patients with nonalcoholic cirrhosis were more likely to have required mechanical ventilation (83% versus 35%, $P = 0.008$) and to have pulmonary infiltrates (92% versus 25%, $P = 0.0005$).

Discussion

Assessment of prognosis has become increasingly important in the medical management of critically ill patients. Such data can serve to elucidate factors that portend an unfavorable outcome, but more importantly, identify those variables that may be potentially modifiable or amenable to intervention. In critically ill patients with cirrhosis, such data also have implications regarding optimal timing of transplantation. Mortality in these critically ill patients in our study was 43%. Child-Pugh scores failed to predict the outcome, whereas APACHE II scores, APS scores, and functional status of the patient (Karnofsky score) were more accurate predictors of outcome. The lack of predictive accuracy of Child-Pugh scores is probably because extrahepatic severity-of-illness variables, e.g., renal function, vital signs, and pulmonary status, are not measured by Child-Pugh scores, although these scores

do assess a number of different criteria related to the liver disease.

Of routinely available liver functions tests assessed, only bilirubin and prothrombin time, and not aminotransferases, alkaline phosphatase, albumin, or cholesterol were significant predictors of outcome. The prognostic significance of hyperbilirubinemia and elevated prothrombin time has also been recognized in patients with other medical conditions requiring ICU care. In a study assessing outcome in ICU patients treated with hemodialysis for acute renal failure, serum bilirubin and prothrombin time were significantly associated with mortality; hyperbilirubinemia was an independent predictor of mortality.[22] Bilirubin was also a significant predictor of outcome in transplant recipients requiring ICU care[4] and of early graft failure in liver transplant candidates undergoing transplantation.[23]

We observed a high incidence of renal dysfunction in our patients with cirrhosis admitted to the ICU. Renal impairment (creatinine more than 1.5 mg/dl) was present in 76% of the patients, and 20% of the patients required dialysis. Patients requiring dialysis were significantly more ill (as assessed by APACHE II scores). However, when controlled for the severity of illness, renal impairment ($P = 0.014$) and dialysis ($P = 0.017$) remained significantly associated with mortality in the ICU. The grave prognostic association of renal failure in endstage liver disease was also emphasized in a recent Spanish study. Renal impairment after spontaneous bacterial peritonitis in cirrhosis was reported to be the most significant predictor of hospital mortality.[24] These data have important implications regarding timing of transplantation. Patients with endstage liver disease and renal impairment are at high risk for mortality. However, transplantation should ideally be undertaken before renal failure and the requirement for dialysis ensue. Pretransplant renal dysfunction was an independent predictor of early graft failure after liver transplantation[25,26] and pretransplant dialysis has been identified as a significant risk factor for early posttransplant mortality and infectious morbidity.[27–30]

Nearly one-third of our patients with cirrhosis in the ICU experienced infections. Spontaneous bacterial peritonitis (SBP) and bacteremia have been reported in 7%–15% and 4%–10% of patients with cirrhosis, respectively.[31] Our incidence of SBP (35%) and bacteremia (20%) was therefore somewhat higher than that reported in cirrhotic patients in general. This was likely reflective of the fact that our patients represented a subgroup of most critically ill patients with liver disease. Although mortality was higher in the infected patients, infections were not an independent predictor of mortality. *Escherichia coli*, *Klebsiella*, and enterococcus were the most frequent causes of culture-positive SBP or spontaneous bacteremia; however, culture-negative neutrocytic ascites was the most frequently observed variant of SBP. Patients with gastrointestinal bleeding, renal impairment, and those requiring dialysis were at significantly higher risk for infections in the ICU. Gastrointestinal hemorrhage has been shown to impair the reticuloendothelial function and facilitate bacterial translocation across the gut.[32,33] Likewise, the association of renal failure with infections is well recognized.

In 20% (11/54) of our patients, a unique presentation characterized by marked leukocytosis (in the absence of any documented infection) with eventual progression to multiple organ system failure, was observed. The white blood cell count of these patients ranged from 16.3 to 25.6/mm^3 (mean, 18.9/mm^3). The mortality in these patients (81%) was comparable to that of patients with documented infections in the ICU (60%). We hypothesize that this clinical presentation may likely be caused by enhanced production and decreased metabolism of cytokines, e.g., tumor necrosis factor-alpha and interleukin (1L)-6, which have been demonstrated in patients with endstage liver disease.[34] A systemic inflammatory response syndrome in patients with cirrhosis of the liver, in the absence of infections, has recently been described, with leukocyte activation in the peripheral blood of patients with cirrhosis and systemic inflammatory response syndrome correlated with the serum levels of 1L-6.[35]

Mental status has been shown to be a significant predictor of outcome in ICU patients in a number of clinical settings, e.g., patients with acute renal failure requiring dialysis and transplant recipients.[4,36] Although encephalopathy was the predominant reason for ICU admission in our patients, no association between the presence or absence of encephalopathy, the degree of encephalopathy (stage I, II, or III) or coma scores (APACHE) was demonstrated in our study. These findings may likely reflect the reversible nature of hepatic encephalopathy with appropriate management in patients with liver disease.

An intriguing finding in our study was that, when controlled for the severity of illness (APACHE II scores), the mortality in patients with cirrhosis caused by alcohol was significantly lower than that in patients with liver disease not caused by alcohol (35% versus 83%; $P = 0.01$). Although Child-Pugh scores, serum bilirubin, creatinine, or the incidence of gastrointestinal bleeding was not different, the patients with liver disease not caused by alcohol may have been more debilitated, as indicated by a significantly greater requirement for mechanical ventilation and a higher incidence of pulmonary infiltrates. Nevertheless, the association of underlying liver disease with outcome has also been noted in transplant recipients. Higher graft

and patient survival was observed in patients undergoing liver transplantation for cholestatic and alcoholic liver disease compared with other liver diseases, including hepatitis.[23] The vast majority of our patients with nonalcoholic liver disease had viral hepatitis caused by hepatitis C virus. It has been proposed that hepatitis C virus is an immunodulatory virus.[37] Greater infectious morbidity in patients with hepatitis C virus compared with patients without hepatitis C virus infection has been documented in transplant recipients.[38] In the nontransplant setting, T-cell-derived cytokine levels were significantly higher in patients with hepatitis C virus compared with normal controls.[39] Whether differences in cytokine profile, level, or expression were contributory variables to differential disease severity in patients with and without viral hepatitis in our study remains speculative.

Despite the high mortality in critically ill patients with cirrhosis, ICU support is not entirely futile in these patients. Of patients in this study who underwent liver transplantation, the 1-year survival was 91% (10/11), the mean Karnofsky score of these transplant recipients at 1 year being 96.

In conclusion, among critically ill patients with cirrhosis, the mortality in the ICU was 43%. Child-Pugh scores, compared to APACHE III scores, were less than optimal predictors of the outcome. Pulmonary infiltrates and renal impairment were identified as independently significant medical complications that predicted mortality in our patients. Future studies validating our findings are warranted, since these data have implications not only for prognosis but for the selection of candidates and timing of transplantation.

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