Predictors of Mortality and Resource Utilization in Cirrhotic Patients Admitted to the Medical ICU*

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Background and objective: Cirrhotic patients admitted to the medical ICU (MICU) are associated with high mortality rates and high resource utilization. This study identifies specific predictors of increased mortality and resource utilization and uses them to develop and validate prognostic models in cirrhotic patients admitted to the MICU.

Methods: Cirrhotic patients admitted to the MICU were identified from the Critical Care Section database (January 1993 to October 1998). Clinical data were extracted from chart review including hospital course variables, mortality, and length of stay (LOS). Total cost per case (TCPC) was obtained from the Transition System Inc. Multivariate logistic and linear regression analyses identified the independent predictors of increased mortality and resource utilization used for model building (MB) and model validation (MV).

Results: A total of 582 cases were randomized to the MB and MV groups. Each group contained 240 cases after exclusion criteria were applied. The MICU mortality rate was 36.6%, and the in-hospital mortality rate was 49.0%. Acute physiology, age, and chronic health evaluation (APACHE) III score (odds ratio [OR], 4.7; 95% confidence interval [CI], 2.70 to 8.16; p < 0.001), mechanical ventilation (OR, 4.57; 95% CI, 2.35 to 8.34; p < 0.001), and the use of pressors (OR, 7.57; 95% CI, 4.35 to 13.18; p < 0.001) were independent predictors of MICU mortality. APACHE III score (OR, 4.96; 95% CI, 2.97 to 8.29; p < 0.001), the use of pressors (OR, 6.55; 95% CI, 3.66 to 11.72; p < 0.001), and acute renal failure (ARF) (OR, 4.31; 95% CI, 2.41 to 7.71; p < 0.001) were independent predictors of in-hospital mortality. Increased LOS in the MICU was associated with mechanical ventilation, ARF, bronchoscopy, bacteremia, use of pressors, transjugular intrahepatic portosystemic shunt (TIPS), and never received cardiopulmonary resuscitation (CPR) (p < 0.005). Source of admission, platelet transfusion, bacteremia, pneumonia, and never received CPR were independently associated with increased total LOS (p < 0.001). Mechanical ventilation, platelet transfusion, bronchoscopy, TIPS, sepsis, and never received CPR were independent predictors of increased TCPC (p < 0.001).

Conclusion: Simple prognostic models for mortality and resource utilization have been developed for cirrhotic patients admitted to the MICU.

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Key words: cirrhosis; cost; end-stage liver disease; intensive care; length of stay; mortality; outcome; resource utilization

Abbreviations: APACHE = acute physiology, age, and chronic health evaluation; ARF = acute renal failure; CI = confidence interval; LOS = length of stay; MB = model building; MICU = medical ICU; MV = model validation; OR = odds ratio; ROC = receiver operating characteristic; TCPC = total cost per case; TIPS = transjugular intrahepatic portosystemic shunt

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Cirrhosis is the 10th leading cause of death in the United States and the most common cause of mortality among the nonmalignant digestive diseases.1 Cirrhotic patients admitted to the medical ICU (MICU) have an increased mortality (40 to 90%) and a poor prognosis.2–5 Several prognostic models have been proposed, but few have been validated.1,5,6,9–13 Because cirrhotic patients admitted to the MICU have high mortality rates and resource consum-
tion, predictive models could be very important decision-making tools.

To this end, we identified clinicodemographic variables that could independently predict mortality and increased resource utilization in patients with cirrhosis who are admitted to the MICU.

**Materials and Methods**

**Patient Population**

Consecutive patients admitted to the MICU from January 1, 1993, through October 31, 1998, with a diagnosis of liver failure, cirrhosis, chronic liver disease, variceal bleeding, hepatic encephalopathy, or hepatorenal syndrome were identified from the database maintained by the Critical Care Medicine section at the Cleveland Clinic Foundation. Patients had to have histologically proven or clinically diagnosed cirrhosis (eg, portal hypertension with ascites, esophageal varices, or encephalopathy) to be included in the study. Exclusion criteria included age <18 years, acute liver failure, and patients who had received prior liver transplantation.

An admission to the MICU during an episode of hospitalization was considered as one case, and readmission during the same hospitalization was included in the same case. Two MICU admissions during different hospitalizations for the same patient were counted as two cases. Accordingly, 582 cases involving 511 patients were identified from the database.

**Data Collection**

Two investigators (A.A. and J.P.O.) reviewed hospital charts according to a predefined set of guidelines. Their data collection template included various admission and hospital course variables. A total of 202 variables were included (Table 1).

**Outcomes**

Assessed outcomes included mortality and health resource utilization. Follow-up was censored on December 31, 1998. MICU and in-hospital mortality was determined by reviewing hospital records. Causes of death were determined from the National Death Index plus. Health-care resource utilization was assessed by determining the length of stay (LOS) and total cost per case (TCPC). LOS was determined by chart review, and the TCPC was obtained from the Transition System Inc. (TSI; Boston, MA), which includes all costs for professional services, laboratory tests, and diagnostic and therapeutic interventions. MICU LOS was defined as the number of days the patient spent in the MICU and included all MICU readmissions during the same hospitalization. The in-hospital LOS was defined as the total number of days the patient spent in the hospital starting from the day of the index MICU admission up to the day of discharge from the hospital or death.

**Statistical Analysis**

*Model Building and Model Validation Groups:* The cases identified from the database were randomized into two groups stratified by year of admission to guarantee an even and balanced distribution of the two groups over time. This helped control for confounding influences of advances in MICU care and changing therapeutic strategies over the study period. The two groups included the model building (MB) group and the model validation (MV) group. The MB group was used to identify predictors that were independently associated with an outcome. The MV group was used to confirm this association. We used a forward stepwise selection procedure of predictors on the cases in the MB group and then added all original variables to the model to determine their significance (p < 0.05). Only those variables with <5% missing from the database were included. The final MB model was applied to the MV group, and only those predictors that remained significant in both models (p < 0.025 [one-tailed test in the direction of their effect in the MB model]) were considered to be significant for the final model. This allowed us to account for the type I error inherent in the use of many potential predictors while maintaining the flexibility necessary to build models in the MB group. The type I error for each variable was 0.00125 (0.05 multiplied by 0.025). The MV group also was used to test the predictive ability of the variables included in the final model by using the final predictors in the MB group to predict the outcomes in the MV group.

As a binary outcome, mortality was evaluated with area under the receiver operating characteristic (ROC) curve (a combined measure of sensitivity and specificity used to quantify discrimi-
nation) and Hosmer-Lemeshow tests (to test model fit to assess calibration). The Hosmer-Lemeshow test compares the actual mortality rates observed in the MV group with the rates predicted by the MB group. The continuous hospital utilization variables (LOS and TCPC) were evaluated with $R^2$, which measures the percentage of variation accounted for by the variables in the final model. The most important $R^2$ value is that measured between the observed measures of the MV group and that predicted by the model using the MB group. These efforts yielded many models and subsequent measures, but the central conclusions of the study are based on the models constructed on all cases, and the best estimates of their applicability are the measures of model performance (ie, the area under the curve and $R^2$) among the validation cases.

Because patients could be utilized more than once as multiple cases, we used repeated measures logistic regression (by using generalized estimating equations for mortality) and analysis of variance (for LOS and TCPC). These repeated measures approaches allow the use of multiple admissions per patient, without violating the assumption of independence between observations. Therefore, the use of multiple admissions per patient is accounted for in the analysis and does not weight the data from individuals with more admissions more heavily than those with single admissions. Rather than including only the first admission of each patient, the inclusion of all admissions allows the results to be applicable to a wider range than the subset of patients without a previous admission. LOS and TCPC values were base-10 log-transformed to reduce the influence of outliers and to reduce heteroscedasticity (eg, more variability with greater values). Because of the log-transformations, the antilogarithms of the regression coefficients were used to illustrate the effect of significant variables as the relative percentage of change. The odds ratios (ORs) for mortality and regression estimates for log-transformed continuous outcomes were calculated. All the data were entered into a database (Oracle; Oracle Corporation; Redwood Shore, CA). Computer software (SAS, version 8; SAS Institute Inc; Cary, NC) was used for statistical computations.

**Results**

**MB and MV Groups**

A total of 511 patients represented 582 cases. Randomization into the MB and MV groups is illustrated in Figure 1. The application of the inclusion and exclusion criteria yielded a total of 420 patients with 480 cases. The reasons that 91 patients did not meet inclusion criteria included the following: acute liver failure; < 18 years old; prior liver transplant; and no cirrhosis. Incidentally, the MB and MV groups had the same number of cases (240 each). The characteristics of the study population were similar in the MB and MV groups and are presented in Table 2.

**Mortality**

**MICU Mortality:** The MICU mortality rate was 36.6% (154 of 420 patients), and the in-hospital mortality rate was 49.0% (206 of 420 patients). Analyses for the independent predictors of mortality in the MICU indicated the following three variables that were significant in the MB group and maintained their significance in the MV group (Table 3): increasing acute physiology, age, and chronic health evaluation (APACHE) III score ($p < 0.001$); the use of pressors ($p < 0.001$); and the use of mechanical ventilation ($p < 0.001$). Figure 2, top, illustrates that MICU mortality increased as the number of predictors increased. A cutoff on the APACHE III score of
was used for optimum sensitivity and specificity on ROC analysis. Although pressors had the highest OR (7.57), the confidence intervals (CIs) of all three predictors overlapped, so that the three predictors were weighted equally. The ability of these three variables to discriminate was relatively high, with an area under the ROC curve of 90.3%. Additionally, the test of model fit confirmed that predicted mortality was similar to observed mortality (p = 0.84).

**In-Hospital Mortality:** Analysis of the independent predictors of in-hospital mortality produced the following three variables for the final model (Table 3): APACHE III score ≥ 90 (p < 0.001); use of pressors (p < 0.001); and acute renal failure (ARF) (p < 0.001). Figure 2, bottom, illustrates that in-hospital mortality increased as the number of predictors increased. The area under the ROC curve for these three predictors was 90.7%, and model fit tests comparing the number of expected and observed deaths were not different (p = 0.20).

**Causes of Mortality:** A total of 206 patients (49.0%) died in the hospital, of which 154 patients (36.6%) died in the MICU. Ninety-seven of 154 patients (62.9%) who died in the MICU and 137 of all patients who died (66.5%) had liver-related causes of death (eg, alcoholic cirrhosis, nonalcoholic cirrhosis, biliary cirrhosis, viral hepatitis, portal hypertension, variceal bleeding, hepatorenal syndrome, hepatic coma, peritonitis, hepatorenal syndrome, or malignant neoplasm of the liver). Twelve deaths were related to sepsis from varied etiologies (Gram-
negative sepsis, streptococcal sepsis, mycoses, aspergillosis, cryptococcosis, and other), and eight occurred in the MICU. Pulmonary causes of death were identified in six patients, all of whom died in the MICU. There were five deaths from renal failure, again all in the MICU, and six deaths related to cardiac causes, of which five were in the MICU. Four patients died of malignancies other than hepatoma and lung cancer, of whom three died in the MICU. The cause of death was not identifiable from the National Death Index plus in a total of 36 patients, of which 30 had died in the MICU.

**Resource Utilization**

**MICU LOS:** Seven variables were significantly associated with increased LOS (Table 4). About half of the variability observed in MICU LOS ($R^2 = 0.49$) was accounted for by these seven variables. A scoring system also was used to illustrate the effect of these variables on the LOS. Bronchoscopy had a higher estimated effect and was assigned two points, whereas the other variables were assigned one point each. As Figure 3, top, illustrates, an increased number of predictors were associated with longer MICU LOS.

**In-Hospital LOS:** The source of admission and four other variables were significant predictors ($p < 0.001$) of increased in-hospital LOS (Table 4). Patients who were transferred from Cleveland Clinic Foundation nursing floors stayed longer in the hospital than those who were transferred from outside institutions. An increased number of predictors or
points results in a longer in-hospital LOS (Fig 3, middle). These five variables accounted for 23.7% of the observed variability ($R^2 = 0.237$).

**TCPC:** Six variables were significantly associated with TCPC (Table 4). These six variables accounted for 39.6% of the observed variability ($R^2 = 0.396$). The effect of these variables on TCPC is presented in Figure 3, bottom.

**DISCUSSION**

This cohort study assessing predictors of mortality and resource utilization in cirrhotic patients admitted to the MICU is the largest to date.\textsuperscript{1,5,6,15} The study developed and internally validated predictive models for mortality and resource utilization in patients with cirrhosis. The 36.6% MICU mortality rate was lower than previously reported.\textsuperscript{1,6} We attribute this improvement to advances in intensive care during the past decade.

Among the admission and hospital course variables, the APACHE III score\textsuperscript{16,17} and the use of pressors in cirrhotic patients are independently associated with high MICU and in-hospital mortality. It is noteworthy that a widely used liver-specific severity rating (the Child-Pugh score)\textsuperscript{8} is not an independent predictor of mortality. Additionally, laboratory and clinical parameters of liver disease (ie, albumin, prothrombin time, bilirubin, ascites, or hepatic encephalopathy) are not independent predictors of mortality. This finding is consistent with reports by other investigators in both MICU and non-MICU settings suggesting that the Child-Pugh score indicates the severity of underlying liver disease but is not the best tool for predicting mortality or resource utilization in cirrhotic patients with multisystem organ failure.\textsuperscript{5,6,11,14} An increased number of comorbid conditions is thought to contribute to poor prognosis, but the Charlson comorbidity index\textsuperscript{17} did not independently predict either mortality or resource utilization. This further emphasizes

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**Table 4—Regression Estimates for Predictors Included in the Final LOS and Cost Models, and the Percentage of Variability ($R^2$) Explained by the Models\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coefficient, %†</th>
<th>SE, %</th>
<th>p Value</th>
<th>$R^2$, %</th>
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<tr>
<td><strong>MICU LOS</strong></td>
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<tr>
<td>MB set</td>
<td></td>
<td></td>
<td></td>
<td>55.5</td>
</tr>
<tr>
<td>MV set†</td>
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<td></td>
<td>49.4</td>
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<tr>
<td>Overall final model</td>
<td></td>
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<td></td>
<td>50.4</td>
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<tr>
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<td>34.0</td>
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</tr>
<tr>
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<td>3.7</td>
<td>&lt; 0.001</td>
<td></td>
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<td>5.5</td>
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<td>Bacteremia</td>
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<td>3.9</td>
<td>&lt; 0.001</td>
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<td>0.002</td>
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<tr>
<td>TIPS</td>
<td>16.4</td>
<td>3.9</td>
<td>&lt; 0.001</td>
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<tr>
<td><strong>Hospital LOS</strong></td>
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<tr>
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<td>29.1</td>
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<tr>
<td>MV set†</td>
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<tr>
<td>Source of admission</td>
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<td>3.7</td>
<td>&lt; 0.001</td>
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<tr>
<td>Bacteremia</td>
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<td>4.7</td>
<td>&lt; 0.001</td>
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<tr>
<td>Never received CPR</td>
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<td>5.9</td>
<td>&lt; 0.001</td>
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<tr>
<td>Pneumonia</td>
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<td>4.4</td>
<td>&lt; 0.001</td>
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<tr>
<td><strong>Total hospital cost</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MB set</td>
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<td></td>
<td></td>
<td>44.9</td>
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<tr>
<td>MV set†</td>
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<td>Overall final model</td>
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<tr>
<td>Mechanical ventilation</td>
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<tr>
<td>Platelet transfusion</td>
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<td>3.4</td>
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<tr>
<td>Bronchoscopy</td>
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<td>6.1</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Never received CPR</td>
<td>26.9</td>
<td>5.4</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>TIPS</td>
<td>19.1</td>
<td>4.1</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>17.5</td>
<td>4.1</td>
<td>&lt; 0.001</td>
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</table>

*CPR* = cardiopulmonary resuscitation.

†Because outcome was log-transformed, the antilog of the regression coefficient and SE reflects the average percentage increase in utilization created by each significant variable.

‡MV $R^2$ is calculated applying the MB predictions to the MV set and comparing the expected and observed values.
Figure 3. Top: independent predictors of increased MICU LOS. Prediction model for MICU LOS in cirrhotic patients admitted to the MICU. Middle: independent predictors of increased in-hospital LOS. Prediction model for in-hospital LOS in cirrhotic patients admitted to the MICU. Bottom: independent predictors of increased TCPC. Prediction model for TCPC in cirrhotic patients admitted to the MICU (total cost expressed as a multiple of the median total cost unit). For each group, the lower and upper sides of the box are the 25th and 75th percentiles, respectively. The line within the box is the median with a notch for the 95% CI of the median. The lines extending from the box and with the whiskers at the end are 1.5 times the SD. The outliers outside the range are represented by squares outside the SD. + = mean.
the importance of multisystem organ failure over the preexisting comorbid conditions in predicting mortality and resource utilization in cirrhotic patients admitted to the MICU.

We developed a simple prognostic model consisting of three variables to predict MICU or in-hospital mortality. Except for the APACHE III score, which requires extensive data collection, the use of pressors, mechanical ventilation, and ARF are assessed easily at the bedside. The APACHE III score is one of several other generalized severity-of-illness scoring systems as follows: simplified acute physiology score; mortality prediction model; and study to understand the prognosis and preferences for outcomes and risks of treatments model. These complicated models stand in contrast to the simple prognostic scoring systems for cirrhotic patients proposed here, which allow clinicians to provide an accurate prognostic assessment to patients and their families at the bedside.2–4

The cause of death was related to liver disease or its complication in two thirds of the patients. Most of these patients, however, died with multiorgan failure.

Every effort must be made to contain health-care costs today, especially in the ICU where patient care is the most expensive. Previous studies have shown high mortality rates among cirrhotic patients admitted to the MICU, but resource utilization has not been adequately addressed. This study uses LOS and TIPS to estimate resource utilization.

In contrast to the analysis of mortality, the APACHE III score did not accurately predict resource utilization. This is not unexpected because the APACHE III score was developed to assess the disease severity of patients admitted to the MICU and was not designed to assess resource utilization. Organ failure (eg, mechanical ventilation, pressor use, ARF, and bacteremia) and the use of invasive diagnostic and therapeutic procedures (eg, bronchoscopy or transjugular intrahepatic portosystemic shunt [TIPS]) are predictive of longer stays in the MICU. As with LOS, APACHE III score was not an independent predictor of TIPS. Again, bronchoscopy and TIPS were associated with increased TIPS. Besides offering a simple model to predict mortality, our study is the first to report independent predictors of resource utilization.

Our study is limited by a lack of external validation in different settings such as community hospitals. Additionally, the estimates we used for resource utilization may have been less than optimal. This is largely because the sources of data for resource utilization in the United States are poor. Previous studies have used administrative or financial databases (Medicare, Medicaid, and TSI) that are designed for administrative purposes, not clinical research. TSI is considered to be a complex but accurate accounting system that assigns estimates of costs to each resource based on direct acquisition costs for supplies and for costs of labor. Short of more sophisticated and accurate cost data, TSI may be the best financial tracking system, especially for the inpatient setting, as it reflects these estimates more accurately.18 Another limitation is that a large number of variables were utilized in the stepwise procedures. In order to reduce the effect of using numerous and, often, correlated variables, the procedure was used to include only variables that were significant in stepwise procedures and also significant in the validation data set. We used this approach to eliminate variables that were included in the original stepwise regression based on chance alone or in correlation with other variables.

Although it is intuitive that high APACHE III score, the use of mechanical ventilation, the use of pressors, and the presence of ARF are very likely to predict poor outcomes for patients with different diseases, there is a need for studies that identify predictors in specific patient populations like patients with cirrhosis. The predictors of poor outcomes as presented in our study are easily identified and can be used by clinicians to frame discussions with families and possibly to guide limitation of further intervention in these extremely ill patients.

In conclusion, this study confirms that the prognosis for cirrhotic patients admitted to the MICU is poor. We have clarified the predictors that are independently associated with mortality and resource utilization in these patients. By building and validating a simple predictive model, patients, clinicians, and health-care systems can use these data to estimate prognosis more accurately. External validation of these models in different health-care settings will further advance this work.

REFERENCES