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Outcome prediction for patients with cirrhosis of the liver in a medical ICU: a comparison of the APACHE scores and liver-specific scoringsystems

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Abstract *Objective*: To find the most adequate prognostic scoring system for predicting ICU-outcome in patients with decompensated liver cirrhosis in a medical intensive care unit (ICU).
Design: Retrospective analysis of patients' records over a 10-year period.
Setting: A medical ICU at the university medical center of Vienna.
Patients and participants: 94% ($n = 198$) of all patients with cirrhosis admitted to our medical ICU throughout the 10-year study period.
Interventions: None.
Measurements and results: From data obtained at admission and at 48 h after admission, scores were calculated using the following scoring systems: Acute Physiology and Chronic Health Evaluation (APACHE) II and III, Scale for Composite Clinical and Laboratory Index Scoring (CCLI), Mayo Risk Score, and Child's Classification. Statistical analysis for the prognostic variables was performed using the chi-square test, *t*-test, Youden index, and area under a receiver operating characteristic (ROC) curve. APACHE III was found to be the most reliable outcome predictor at admission and after 48 h for patients with decompensated liver cirrhosis (AUC = 0.75 and 0.8, respectively).
Conclusions: To predict the outcome for patients with decompensated cirrhosis of the liver admitted to a medical ICU liver failure alone is not decisive. Liver-specific scoring systems (Mayo Risk Score, CCLI) are adequate, but the APACHE II and III proved to be more powerful, because they include additional physiologic parameters and therefore also take into account additional complications associated with this liver disorder.

Key words Liver cirrhosis · ICU · APACHE · ROC curve

Introduction

The prognosis for patients with decompensated cirrhosis of the liver is generally poor. The mortality for patients with cirrhosis and chronic liver disease admitted to a medical intensive care unit (medical ICU) was found to be as high as 64% [1]. As a comorbid factor in trauma patients, cirrhosis led to a significant increase in mortality. Prognosis depended on the degree of hepatic insufficiency [2].

To estimate the prognosis for patients after admission to a medical ICU, to evaluate the use of hospital resources, and to compare the efficacy of intensive care in different hospitals or over time, various prognostic scoring systems have been developed. The Acute Physiology and Chronic Health Evaluation (APACHE) II score is widely used and generally accepted [3]. Based upon APACHE II

the APACHE III score was developed [4]. Both APACHE II and APACHE III use physiology, age, and chronic health to calculate prognosis. They differ in total score, the number of physiologic variables (12 vs. 17), and in how chronic health status is assessed. Specific parameters of liver function are missing (APACHE II) or are included only to a minor extent (APACHE III) in these severity-of-disease classification systems. Therefore, we wondered if it was possible to estimate the prognosis for patients with cirrhosis admitted to a medical ICU using these severity-of-disease classification systems, comparing them with specific hepatic prognostic systems.

Patients and methods

Approval of the Institutional Review Board was not required because of the retrospective design of the study.

All patients admitted to the medical ICU between January 1981 and December 1990 were reviewed retrospectively. Patients categorized under the ICDM-3 index for chronic liver disease with cirrhosis (No. 571) were selected for further analysis. The diagnosis of hepatic cirrhosis was confirmed by the medical history, clinical examination, biopsy ($n = 36$), and/or clinical imaging ($n = 198$). The clinical criteria were esophageal varices verified by endoscopy and the presence of jaundice (bilirubin >3 mg/dl) and ascites. In the nonsurviving group, the diagnosis was confirmed by autopsy.

The following details were recorded: age, sex, APACHE II and III scores, the Scale for Composite Clinical and Laboratory Index Scoring (CCLI) [5], Mayo Risk Score [6], Child's classification [7], cause of cirrhosis, reason for admission, and outcome. Patients with multiple medical ICU admissions during the study period were reviewed only for their initial admission. Further exclusion criteria were a stay in a medical ICU less than 24 h and age under 16 years.

The values for the different scoring systems were calculated from data obtained at admission and after 48 h, even though the APACHE II system is not validated for time intervals beyond admission. For missing physiologic and laboratory parameters (3% at admission; 6% 48 h after admission) we assumed a normal value.

Area under receiver operating characteristic (ROC) curves were prepared to test the ability of the various scoring systems to separate survivors and nonsurvivors. Each score value obtained of the different scoring systems was used to calculate the different true positive (sensitivity) and false positive (1-specificity) rates to create the ROC-curves. For the different scoring systems tested, the sensitivity, specificity, overall correctness of prediction, positive predictive value, and negative predictive value were calculated and the cutoff point giving the best Youden index was determined [8]. This cutoff point was also used to calculate the predicted and observed outcome for patients (see Table 4). Because mathematical equations for APACHE III have not been published and for APACHE II this equation is available only for admission, these equations have not been used to calculate the relative risk of death. We wanted to test the accuracy of single-score values.

Bivariate statistical analysis for the prognostic variables was performed using the chi-square test and t-test. A p value less than 0.05 was considered statistically significant. Data are expressed as mean ±standard deviation (SD). Sensitivity, specificity, overall correctness of prediction, positive predictive value, and negative predictive value were calculated using the score value giving the best Youden index [8]. The variables were also entered into analysis with ROC curves [9, 10] to compare their ability to discriminate survivors and nonsurvivors.

Results

Of 210 patients with decompensated cirrhosis of the liver who were admitted to the medical ICU in the observation period, 198 (94%) patients were selected for further retrospective analysis. Of these 198 patients [72 females (36%) and 126 males (64%)], 103 died and 95 survived, yielding an overall mortality of 52%. In comparison, the mortality for all admissions to our medical ICU in this period was 24.7%.

The mean age of the patients was 51 ± 11.5 years (range 17–78 years): survivors, 51.6±11.3; non-survivors, 50.1±12.1 ($p > 0.05$). There was no difference in age between women (50.1±12) and men (51.2±11.5) ($p > 0.05$).

The diagnoses were 135 patients with alcoholic cirrhosis (68%), 21 patients with cirrhosis due to previous hepatitis (11%), and 42 patients with other causes of liver dysfunction (21%) (Table 1). The main reasons for admission were hepatic encephalopathy (25%), acute renal failure (22%), and upper gastrointestinal bleeding (17%) (Table 2). The length of stay in the medical ICU for survivors was 6.7±5.4 days and for nonsurvivors, 10.2±12.4 days ($p < 0.05$).

Table 3 reports the average scores at admission and after 48 h. After 48 h there was a significant decrease in the APACHE II and APACHE III scores ($p < 0.05$). Comparing the score on admission with that after 48 h for survivors only, a significant decrease was found in both scores ($p < 0.005$). The changes in the Mayo Risk Score were not statistically significant ($p > 0.05$) (Table 3).

To evaluate to what extent these scoring systems were valid for prediction of patients' mortality, the sensitivity, specificity, overall correctness of prediction, positive predictive value, and negative predictive value were calculated. Table 4 shows these data calculated at the cutoff point

Table 1 Cause of cirrhosis

	Nonsurvivors (n)	Survivors (n)	Mortality (%)
Alcoholic cirrhosis	74	61	55
Posthepatic cirrhosis	11	10	52
Cardiac	3	0	100
Cryptogenic	8	16	33
Other causes[a]	7	8	47

[a] Hemochromatosis, primary biliary cirrhosis, Morbus Wilson, secondary biliary cirrhosis, chronic biliary cirrhosis, immunologic, porphyria, toxic

Table 2 Reasons for admission to ICU

	Nonsurvivors (*n*)	Survivors (*n*)	Mortality (%)
Hepatic coma	23	26	47
Renal failure	28	15	65
Pulmonary failure	13	10	57
Upper gastrointestinal bleeding	16	18	47
Postoperative	8	17	32
Sepsis	3	2	60
Primary multiple organ failure	3	0	100
Other causes[a]	9	7	56

[a] Heart failure, cerebral, bleeding after biopsy, thrombosis, evaluation for transplantation, preoperative, cystic fibrosis, intoxication, St. p. CPR, posttraumatic, acute abdomen, shock

Table 3 Average scores on APACHE II and III, Scale for Composite Clinical and Laboratory Index (*CCLI*), and Mayo Risk Score (*R*)

	All patients	Nonsurvivors	Survivors
APACHE III[a]	73.5 ± 26.6	85 ± 27.3	61 ± 19.6*
APACHE III[b]	67.4 ± 27.8***	81 ± 28.1	52.5 ± 18.2***
APACHE II[a]	20.9 ± 7.9	23.5 ± 8.4	18 ± 6.2*
APACHE II[b]	19.2 ± 7.8***	22.7 ± 7.8	15.3 ± 5.6***
CCLI[a]	19.5 ± 3.3	20.5 ± 2.6	18.4 ± 3.6*
R[a]	10.5 ± 1.9	11.1 ± 1.8	9.7 ± 1.7*
R[b]	10.3 ± 1.7	10.7 ± 1.6	9.7 ± 1.7*

[a] Admission
[b] 48 h after admission
* $p < 0.001$ (nonsurvivors vs survivors); ** $p < 0.001$ (p0 vs p1); *** $p < 0.05$ (p0 vs p1)

Table 4 Comparison of the predictive value of the scoring systems

	Cutoff point[a]	Best Youden index	Predicted outcome (%)[a]	Observed outcome (%)[a]	Sensitivity (%)	Specificity (%)	Correct (%)	Predictive value positive (%)	Predictive value negative (%)
APACHE III[b]	80	0.41	35	28	54	86	70	81	64
APACHE III[c]	74	0.51	35	31	59	92	70	89	68
APACHE II[b]	21	0.33	40	29	56	77	66	73	62
APACHE II[c]	17	0.41	52	37.5	72	69	66	72	69
CCLI[b]	19	0.3	57	37	71	59	65	65	65
R[b]	9.88	0.36	63	42	79	57	64	68	70
R[c]	9.15	0.23	77	49	87	36	46	62	69

[a] For the best Youden index
[b] Admission
[c] 48 h after admission

giving the best Youden index. Among the scoring systems tested, the best Youden index was achieved by the APACHE III score. The highest overall correctness of prediction was found for this scoring system also.

Using ROC curves, the APACHE III was found to be the most reliable scoring system to separate survivors from nonsurvivors in patients with decompensated liver cirrhosis. The Area Under the Curve (AUC) for the APACHE III score immediately after admission was 0.75 and it was 0.8 after 48 h (Fig. 1). The AUC for APACHE II was 0.69 at admission and 0.78 after 48 h (Fig. 2) and the Mayo Risk Score 0.72 and 0.66, respectively (Fig. 3). CCLI at admission was 0.68 (Fig. 4).

After 48 h, both APACHE scores (APACHE II: AUC 0.78, APACHE III: AUC 0.8) had a better prognostic value than the Mayo Risk Score (0.66) and, comparing survivors and nonsurvivors, both had a higher significance than immediately after admission.

An increase in the score of each prognostic scoring system was associated with an increase in mortality in patients with decompensated cirrhosis. Using Child's classification, 177 (89%) patients were found to be in Child C. In this group, we assessed a mortality of 55%. Twenty patients (10%) were classified as Child B, with a mortality of 25%. Only one patient was classified as Child A. This patient survived.

Discussion

In patients with decompensated cirrhosis of the liver admitted to a medical ICU, reliable prognostic parameters

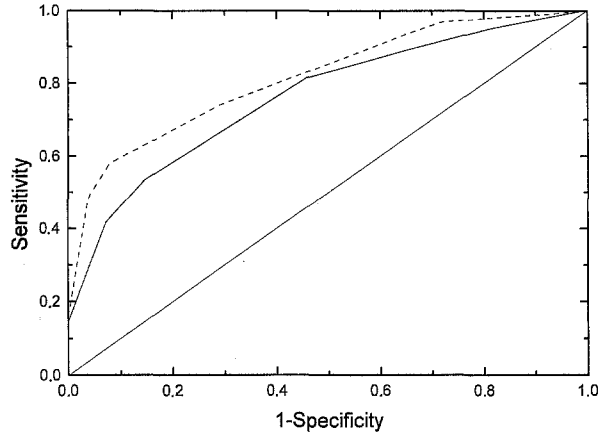

Fig. 1 APACHE III score at admission (*solid curve*) and after 48 h (*dotted curve*). AUC at admission = 0.78 and after 48 h = 0.8

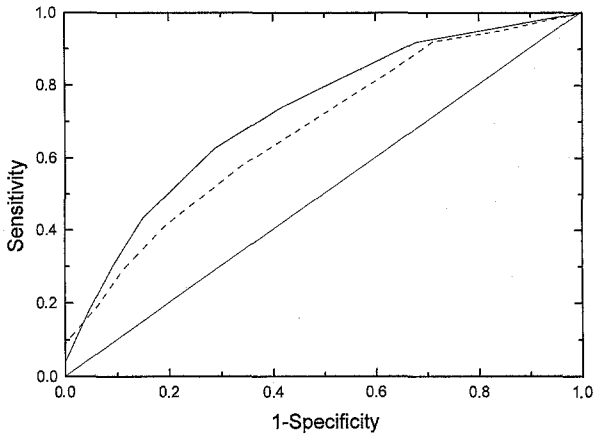

Fig. 3 Mayo Risk Score at admission (*solid curve*) and after 48 h (*dotted curve*). AUC at admission = 0.72 and after 48 h = 0.66

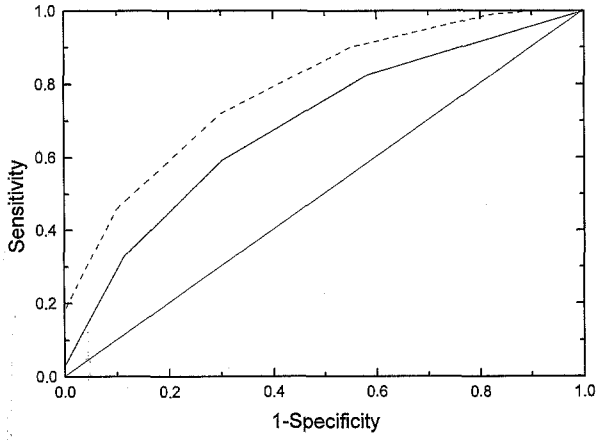

Fig. 2 APACHE II score at admission (*solid curve*) and after 48 h (*dotted curve*). AUC at admission = 0.69 and after 48 h = 0.78

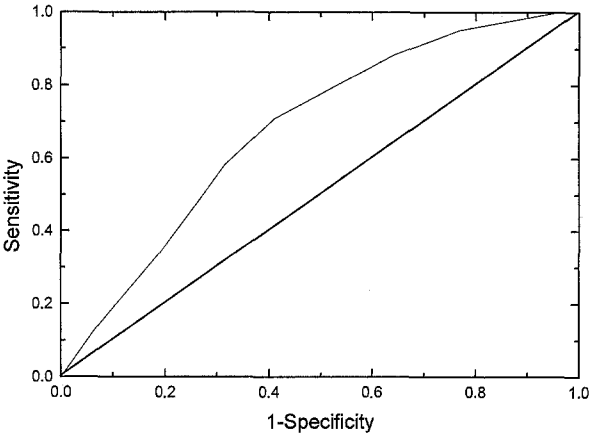

Fig. 4 The Scale for Composite Clinical and Laboratory Index Scoring (*CCLI*) at admission (*solid curve*). AUC = 0.68

have not been well investigated. In these patients, the outcome was found to be poor and the mortality as high as 64% [1]. To estimate the prognosis for patients treated in a medical ICU, to evaluate the use of hospital resources, and to compare the efficacy of intensive care in different hospitals or over time, different prognostic scoring systems have been developed. One of the best known severity-of-disease classification systems is the APACHE II score, which was developed by Knaus et al. [3]. The APACHE III score was then developed, based on the APACHE II [4]. In this scoring system the three groups of variables (physiology, age, and chronic health) provide additional parameters to improve precision. No specific liver function parameters are included in APACHE II and only a few in the APACHE III score.

Therefore, the present study was designed to estimate the prognosis in cirrhotic patients admitted to a medical ICU by use of these general disease classification systems (APACHE II and APACHE III) compared with liver-specific prognostic scoring systems: the Mayo Risk Score [6] and the CCLI [5]. These two scoring systems have liver-dependent parameters to estimate the severity of liver disease.

The Mayo Risk Score was developed for patients with primary biliary cirrhosis. This model aims to improve medical management in selecting patients for, and in the timing of, orthotopic liver transplantation. Relevant parameters are the patient's age, total serum bilirubin and serum albumin concentrations, prothrombin time, and severity of edema.

The CCLI is based on the concept that the severity of the disease is proportional to the number of abnormal clinical and laboratory findings and was developed for patients with alcoholic liver cirrhosis.

The patient population in our study included 94% (n = 198) of patients with cirrhosis admitted to our insti-

tution's medical ICU during a 10-year period. The single score values for each patient were obtained at admission and 48 h thereafter. Comparing these scores, the APACHE III was found to be the most accurate prognostic scoring system (Table 4, Fig. 1), although only two liver-specific parameters are included (albumin and bilirubin concentrations). Though the APACHE II system is not validated and the APACHE III system showed a decreasing explanatory power reflected by a decreasing AUC [11], we have found greater accuracy of the APACHE systems in predicting ICU-outcome 48 h after admission. The prognostic value of APACHE II was found to be as good as the specific hepatic score systems. The prognosis for patients with cirrhosis admitted to a medical ICU did not seem to be dependent exclusively on liver dysfunction but on overall severity of illness. The main reasons for admission were hepatic coma, renal failure, respiratory dysfunction, and gastrointestinal bleeding (Table 2). Therefore, most cirrhotic patients admitted to a medical ICU suffered from multiple-system organ failure. Patients with failure of three or more organ systems have a very high risk of mortality. Liver-specific severity scores do not include parameters for other organ systems. That is why disease-specific severity scores do not reflect severity as accurately as general scores. Severity is now the most important characteristic influencing a patient's outcome. Severity measurement is based on analysis of medical facts – specifically, the nature and type of the patient's physiologic state at ICU admission and how this state changes over time. Knaus et al. found that for the prognosis of hospital mortality risk, physiology is the best predictor (73.1% of relative prognostic information) [12]. If the physiologic state does not change and the individual levels of the APACHE scores do not decrease during the first 48 h, cirrhotic patients do have an increased probability of death. In those patients, treatment cannot stabilize their critical illness, which is also reflected by the length of stay of patients with decompensated liver cirrhosis. Nonsurvivors were treated significantly longer than survivors ($p < 0.05$).

In contrast to disease-specific scoring systems, physiologic parameters are included in APACHE II and III, which improves their prognostic accuracy in predicting mortality during the stay of patients in a medical ICU. The Mayo Risk Score and the CCLI include vital parameters which are exclusively related to liver function. Therefore, abnormalities based on additional organ dysfunction could be better demonstrated by the APACHE scores. Liver-specific scoring systems were found to estimate liver function or dysfunction reliably. In a study reported by Schlichting et al., the main cause of death on a general ward was hepatic failure [13]. In the medical ICU, however, the main cause of death rarely is hepatic failure – in the sense of single organ dysfunction – but rather multiple organ system dysfunction or failure caused by a wide variety of reasons for ICU-admission.

The development of an additional organ failure depends on the degree of the impairment of liver function. Therefore, it was not surprising that the liver-specific scoring systems, although with less power than APACHE II and III, provided statistically significant prognoses for outcome.

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References

1. Shellman RG, Fulkerson WJ, DeLong E, Piantadosi CA (1988) Prognosis of patients with cirrhosis and chronic liver disease admitted to the medical intensive care unit. Crit Care Med 16: 671–678
2. Tinkoff G, Rhodes M, Diamond D, Lucke J (1990) Cirrhosis in the trauma victim. Ann Surg 211:172–177
3. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
4. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, Harrell FE Jr (1991) The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100:1619–1636
5. Orrego H, Kalant H, Israel Y, Blake J, Medline A, Rankin JG, Armstrong A, Kapur B (1979) Effect of short term therapy with propylthiouracil in patients with alcoholic liver disease. Gastroenterology 76:105–115
6. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Landworthy A (1989) Prognosis in primary biliary cirrhosis: model for decision making. Hepatology 10:1–7
7. Pugh RNH, Murray-Lyon MJ, Dawson JL, Pietoni MC, Williams R (1973) Transsection of the oesophagus for bleeding oesophageal varices. B J Surg 60:646–649
8. Youden WJ (1950) Index for rating diagnostic tests. Cancer 3:32–35
9. Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143:29–36
10. Hanley JA, McNeil BJ (1983) A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 148:839–843
11. Wagner DP, Knaus WA, Harrell FE, Zimmerman JE, Watts C (1994) Daily prognostic estimates for critically ill adults in intensive care units: results from a prospective, multicenter, inception cohort analysis. Crit Care Med 22:1359–1372
12. Knaus WA, Wagner DP, Zimmerman JE, Draper EA (1993) Variations in mortality and length of stay in intensive care units. Ann Intern Med 118: 753–761
13. Schlichting P, Christensen E, Fauerholdt L, Poulsen H, Tygstrup N (1983) Main causes of death in cirrhosis. Scand J Gastroenterol 18:881–888