

Prognostic Parameters and Risk Stratification in Intensive Care Patients with Severe Liver Diseases

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Abstract

Background and Aim: Acute or chronic liver failure is associated with numerous complications and patients may require intensive care treatment, which is complex, time-consuming and often highly resource-intensive. Thus, it is necessary to identify clinical parameters that allow quick risk stratification. **Methods:** In 117 patients with acute or chronic liver failure requiring ICU admission, the clinical parameters, risk scores and results of microbiological examinations were documented and correlated with the outcome (survivor vs. non-survivor). **Results:** Predictors of outcome were: Child-Pugh-Score ($p < 0.01$), MELD-Score ($p < 0.01$), SAPS-II-Score ($p < 0.05$), bilirubin ($p < 0.01$), Glasgow Coma Scale (GCS) ($p < 0.02$), urine output ($p < 0.01$), requirement of catecholamine administration ($p < 0.004$), serum creatinine ($p < 0.01$). The strongest predictors of outcome were in a multivariate model GCS ($p = 0.006$) and MELD-score ($p = 0.001$). **Conclusions:** Risk stratification in our patient collective was feasible. Apart from parameters to assess kidney function and circulation, various scoring systems that had previously not been evaluated for this kind of patient collective seem to be the main predictors of outcome.

Key words

Liver failure – ICU admission – prognostic parameters – risk stratification – Child-Pugh score – MELD score – Glasgow Coma Scale.

Introduction

A variety of disorders can lead to acute or chronic liver

failure. Alcohol, viral hepatitis, autoimmune diseases, vascular diseases, acute intoxications and inherited disorders of metabolism may damage the liver. In addition, in some patients the cause of liver damage cannot be determined although newer data indicate that in a large proportion of these patients non-alcoholic steatohepatitis (NASH) may be the cause [1-7].

Acute or chronic liver failure is associated with numerous complications and patients may require intensive care treatment, which is complex, time consuming and often highly "resource intensive".

The most important reasons for intensive care unit (ICU) admission are hemorrhage, infections and hepatic encephalopathy. Further complications include hepatorenal syndrome, hepatopulmonary syndrome, malnutrition and cachexia [8-10]. Many of these complications occur in combination, which makes the management of these patients rather complex. Despite the use of sophisticated diagnostic and therapeutic approaches including expensive microbiological evaluations, many of these patients do not survive.

Therefore, it seems necessary to identify clinical parameters that allow risk stratification at time of ICU admission. There are several algorithms used to predict the prognosis in patients with acute or chronic liver failure.

Over the last two decades several studies have tried to evaluate prognostic parameters in patients with acute or chronic liver failure admitted to ICU. Zimmermann et al showed that APACHE III accurately stratifies risk in critically ill patients with cirrhosis because it accounts for many of the factors known to influence prognosis [11]. Cholongitas et al showed that cirrhotics admitted to ICU with three or more failing organ systems have 90% mortality and that SOFA (Sequential Organ Failure Assessment) and MELD were better predictors than APACHE II or Child-Pugh scores [12]. Finally, Mackle et al demonstrated that patients who were ventilated but required no other organ support survived to hospital discharge. However, the requirement for any other organ support, or a raised creatinine (>120 micromol/L) in the first 24 h, reduced the hospital survival to $<15\%$ [13].

Our study aimed to answer the following questions:

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which easily accessible parameters allow risk stratification in patients with acute or chronic hepatic failure at the time of ICU admission? Can scores that have been established for other patient groups, be used in hepatic ICU patients? Do expensive microbiological examinations help in managing these patients? Does the exact knowledge of the involved microbiological spectrum and its location improve the outcome?

Patients and Methods

One hundred and seventeen patients were included in our study. They all had severe liver disease and were treated at the non-cardiac internal ICU at the Grosshadern Clinic, University of Munich, between 2005 and 2007.

The end-point of our study was the 30-day-mortality after ICU admission: patients that died within this time range were counted as non-survivors; all other patients were counted as survivors.

In 100 patients (85.5%) the reason for ICU admission was liver cirrhosis with various etiologies (alcoholic, viral hepatitis B or C, combination of alcohol and viral hepatitis, hemochromatosis, Wilson's disease or primary biliary cirrhosis). The remaining 17 patients (14.5%) did not have cirrhosis, but were admitted to the ICU for other reasons such as hepatocellular carcinoma, primary sclerosing cholangitis or acute liver failure.

Various established clinical scores were used for patient risk stratification. One of the most well-known scores is the Child-Pugh-Score. Patients are allocated to the three risk groups by using five clinical and biological parameters. This score correlates well with long-term prognosis in patients with chronic liver disease but is usually not used to predict survival in an acute setting [14-16]. The MELD (Model of End-Stage Liver Disease) score is another important score for risk stratification in patients with liver diseases. It uses a special mathematical formula which includes serum bilirubin, creatinine and INR. This score is currently used to allocate donor livers [17]. The SAPS-II Score (Simplified Acute Physiology Score II) is a score not restricted only to patients with hepatic diseases, which allows the assessment of patient mortality in patients undergoing treatment in the ICU. It contains parameters such as serum sodium and potassium levels, heart rate, urine output etc [18].

Binary logistic regression was used to evaluate the correlation between parameters and outcome in a multivariate model. All parameters that proved significant in bivariate analysis were added stepwise into the multivariate model until the model delivered the best prediction of outcome.

Patient data was collected and documented in an intensive care database. Analysis of the data was carried out with Microsoft Excel 2003 and SPSS 15 and 16. Statistical tests applied were the unpaired student's t-test, chi-square-test, Mann-Whitney-U-test and Exact Fisher test. For multivariate analysis binary logistic regression was used. At a p value of ≤ 0.05 differences were considered statistically significant.

Results

Age, gender, mean hospital stay

The characteristics of the study cohort are shown in Table I.

Table I. Baseline characteristics of the study cohort (n=117)

Parameters	
Age (yrs) (mean \pm SD)	54.9 \pm 11.5
Male (no, %)	77 (65.8%)
Duration of ICU stay (days) (mean \pm SD)	6.8 \pm 7.3
Non-survivors (no, %)	38 (32.5%)
Liver cirrhosis patients (no, %)	100 (85.5%)

Out of the 117 patients, 38 died. The most important causes of death were sepsis 44.7% (17 patients) and hemorrhage (44.7%, 17 patients). Further causes of death were the progress of the underlying disease (8.0%, 3 patients) and cerebral edema (2.6%, 1 patient).

Survivors and non-survivors did not differ with respect to age (survivors: 55.3 \pm 11.8 years, non-survivors: 54.0 \pm 10.9 years; ns), gender distribution (female non-survivors: 30.0%, male non-survivors: 33.8%; ns) or length of stay in the ICU (survivors: mean 6.1 days range 1-39 days, non-survivors: 8.1 days range 1-25 days; ns).

Underlying diseases

The study population was divided into five subgroups (Table II): hepatic failure without cirrhosis (n=17), alcoholic cirrhosis (n=57), viral B or C cirrhosis (n=15), alcoholic plus viral B or C cirrhosis (n=5) and cirrhosis caused by other diseases (n=23).

Table II. Non-survivors and survivors according to underlying disease (p=0.245)

Underlying disease	Group	
	Non-Survivor no (%)	Survivor no (%)
No liver cirrhosis	3 (17.7%)	14 (82.3%)
Alcoholic cirrhosis	24 (42.1%)	33 (57.9%)
Viral B or C cirrhosis	5 (33.3%)	10 (66.7%)
Mixed alcoholic and viral cirrhosis	1 (20.0%)	4 (80.0%)
Cirrhosis with other etiology	5 (21.7%)	18 (78.3%)
Total	38 (32.5%)	79 (67.5%)

There was no statistically significant correlation between the underlying disease and the outcome (p=0.245). However, when the cohort was divided into those with and without alcoholic cirrhosis as underlying disease, we observed that 25 of the 62 patients (40.3%) with alcoholic cirrhosis died, whereas in the group of non-alcoholic cirrhosis 13 of 55 patients (23.6%) died (p=0.054).

Clinical scores and outcome

As expected (Table III), the Child-Pugh-Score correlated well with survival ($p < 0.01$, information only available for 83 patients). Similarly, the MELD-Score differed significantly between survivors and non survivors (survivors: 23.4 ± 8.6 , non-survivors: 32.2 ± 7.8 , $p < 0.01$). A ROC curve was performed and an AUC of 77% was calculated. Finally, the SAPS-II Score was 51.7 ± 15.6 in the non-survivor group and 39.7 ± 15.2 in the survivor group ($p < 0.05$). Out of the 15 sub-parameters used to calculate the SAPS-II Score only bilirubin, GCS and urine excretion were able to predict outcome ($p < 0.02$, see the other parameters in Table IV). ROC curves were performed for GCS and SAPS-II and AUCs of 70% and 72% were calculated, respectively.

Table III. Non-survivors and survivors according to the Child-Pugh-Score ($p < 0.010$)

	Group	Group	
		Non-Survivor no (%)	Survivor no (%)
CHILD	Child A	0 (0%)	8 (100%)
	Child B	2 (11.76%)	15 (88.24%)
	Child C	26 (44.83%)	32 (55.17%)
	Total	28	55

Table IV. SAPS-II score parameters and correlation with the outcome (not significant for all groups)

Parameters	SAPS-II Score	
		p-value
Age		0.556
Serum bicarbonate		0.067
Serum urea		0.123
Previous illness		0.808
Heart rate		0.565
Serum potassium		0.114
Leucocyte number		0.184
Serum sodium		0.517
PaO ₂ /FiO ₂		0.284
Blood pressure		0.163
Temperature		0.458

Serum creatinine and catecholamine demand

On admission to the ICU the mean serum creatinine in the non survivor group was 2.9 ± 1.7 mg/dl compared to 1.9 ± 1.4 mg/dl in the survivor group ($p = 0.01$). Another strong predictor was the maximal catecholamine requirement during the ICU stay. Mortality differed significantly ($p = 0.024$) between the groups defined by catecholamine requirement: no catecholamine demand - 26.1%; < 1 mg/h - 22.9%; 1-3 mg/h - 40.0%; > 3 mg/h - 62.5% (Fig. 1).

Microbiological findings

In all patients, microbiological analyses were performed, i.e. blood cultures in 43.6%, cultures from ascites in 51.3%, from urine in 53.8%, lung in 60.7%, and catheter tips in

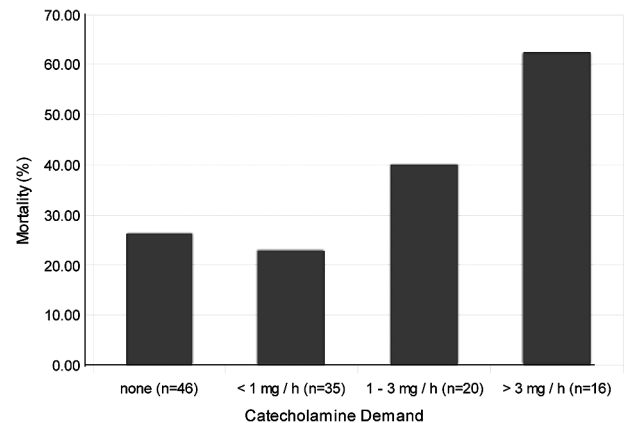


Fig 1. Mortality in correlation to the catecholamine demand ($p = 0.024$)

70.1%. Positive findings were obtained in 76 patients (65.0%) and 41 different pathogens were detected. The most common pathogens were coagulase negative Staphylococcus ($n = 38$), Candida albicans ($n = 33$), gram positive cocci ($n = 32$), gram negative bacilli ($n = 18$) and Staphylococcus aureus ($n = 18$). The mortality in the subgroup with no identified pathogens was 25% (4/16 patients), while the mortality in the subgroup with pathogens detected was 39.5% (30/76 patients). The difference between these groups was not significant ($p = 0.395$).

In a further analysis we compared the mortality in the subgroups with positive and with negative microbiological evaluation sorted by location (Table V). Although mortality was somewhat lower if no pathogene was detected, the difference between groups did not reach statistical significance for any location.

Table V. Mortality according to negative and positive pathogen detection sorted by location

Location	Mortality		p-value
	(no pathogen detected)	(pathogen detected)	
	% (no/total)		
Blood culture	32.4% (12/37)	42.9% (6/14)	0.520
Ascites	39.2% (20/51)	55.6% (5/9)	0.470
Urine	31.6% (12/38)	43.8% (7/16)	0.530
Lung	22.2% (2/9)	51.4% (19/37)	0.150
Tip of catheter	36.0% (9/25)	50.0% (5/10)	0.470

Multivariate analysis

Glasgow coma scale (GCS) and MELD proved to be the main predictors of outcome in the multivariate model, when adjusted to the other parameters (Cox & Snell R-Square 0.347, Nagelkerke R-Square 0.486, GCS $p = 0.006$, MELD $p = 0.001$) (Tables VI, VII).

Discussion

Previous studies [19-21] demonstrating that patients with chronic or acute liver failures die of sepsis or gastrointestinal

Table VI. Classification table, percentage of correct predictions by the model after each step

Classification Table*					
Observed		Predicted			
		Survivor		Percentage correct	
		non-survivor	survivor		
Step 1	Survivor	non-survivor	10	10	50.0
		survivor	6	37	86.0
	Overall percentage				74.6
Step 2	Survivor	non-survivor	15	5	75.0
		survivor	5	38	88.4
	Overall percentage				84.1

*The cut-off value is .500

Table VII. Variables in the equation after each step. Wald statistic and Odds Ratios

Variables in the equation								95% C.I. for EXP(B)	
		B	S.E	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1 ^a	MELD	-.134	0.040	11.325	1	0.001	0.875	0.809	0.946
	Constant	4.695	1.266	13.750	1	0.000	109.356		
Step 2 ^b	GCS	-.159	0.058	7.530	1	0.006	0.853	0.762	0.956
	MELD	-.155	0.048	10.599	1	0.001	0.857	0.781	0.940
	Constant	6.062	1.620	14.006	1	0.000	429.088		

a. Variable(s) entered on step 1: MELD; b. Variable(s) entered on step 2: GCS

bleeding were confirmed in our study. Age and gender did not predict outcome although some of these parameters are part of other scores - APACHE [22], the Mayo Risk - [23] and SAPS-II [18].

Furthermore, there was no correlation between the underlying disease (alcoholic cirrhosis, viral cirrhosis, primary biliary cirrhosis etc.) and outcome. This could be due to the fact that many different diseases lead to the same clinical manifestations of acute or chronic hepatic failure, which then predicts outcome. This is in line with a study in a cohort of liver transplanted patients [24].

All major scoring systems evaluated in this study showed an excellent correlation with the outcome of our patients, although none of these scores was developed to predict outcome in patients with liver failure admitted to an ICU.

Choi et al proved the predictive value of the MELD and Child-Pugh scores and showed that the inclusion of the plasma sodium concentration into the MELD-score even improved its performance [25]. In our patients, plasma sodium did not predict outcome neither alone nor in combination with the MELD-Score.

Chen et al demonstrated the prognostic value of the SAPS-II Score in patients with a pyogenic liver abscess [26]. Although the SAPS-II Score predicted outcome in our population, only 3 of 15 parameters showed a direct correlation to the outcome: GCS, bilirubin and urine output.

Glasgow coma scale was primarily intended to assess the state of trauma patients. However, Bastos et al suggested

that it may also be used as a tool to predict mortality in all ICU patients [27]. This was confirmed in our study.

Bilirubin was a good parameter to predict patients' survival although various limitations should be kept in mind. Even in advanced hepatic disease, bilirubin levels may be normal [28]. On the other hand, elevated levels are often very unspecific and can point to many different diseases, severe and harmless [29]. Still, in patients with liver disease elevated levels of bilirubin point to a worse outcome [28]. Thus, bilirubin levels may at least provide some estimate of mortality in patients with liver disease admitted to an ICU.

Finally, parameters describing kidney function (urine output and serum creatinine level) showed a tight correlation to outcome. This is also supported by the results of previous studies demonstrating that impaired renal function is accompanied by higher mortality [30-31]. Impaired renal function is a good indicator for disease severity and duration [31, 32]. In contrast, an improvement of these parameters often indicates disease regression [33]. Both urine output and serum creatinine are easily accessible parameters. Confirming the role of serum creatinine level in the prediction of short-term outcome in patients with decompensated liver cirrhosis, Serra et al pointed to the fact that it seems reasonable to combine serum creatinine with other parameters. Indeed, serum creatinine is included in various scores, for example MELD or SAPS-II [34]

Our study also showed that catecholamine demand in the first day in the ICU predicted outcome. Since catecholamines

such as adrenaline, noradrenaline and dopamine are used to stabilize blood pressure and circulation [35], it is little surprising that the use of these substances is directly related to outcome [36].

We also investigated whether positive microbiological cultures predict mortality. In our patient cohort we found a typical spectrum of pathogens. The most frequent pathogens were coagulase negative Staphylococci. It is often hard to decide whether this is only a contamination of the sample or if it is an important finding [37]. Interestingly, our study showed that there was no correlation between the detection of pathogens and the outcome. Even with regard to certain locations (e.g. blood sample, lung, ascites) no influence on survival could be detected. This is in contrast with the results of previous studies, which indicated that the detection of pathogens in patients with hepatic failure is a prognostic factor with worse outcome and increased mortality [38-40].

There are several possible explanations for these contradictory findings. First of all, even though the samples were prelevated under sterile conditions, an accidental contamination with skin flora creating false positive results cannot be ruled out [41]. Second, many of the pathogens detected are opportunistic infectious agents [41-43]. These can only deploy their pathogenic potential when the immune system is compromised. Only detecting these pathogens is not sufficient to make a valid prediction on outcome. The stage of the disease, for example the presence of ascites, hepatic encephalopathy, the ALT and AST levels, bilirubin levels, hepatic venous pressure, C-reactive protein levels and white blood cell count may be taken into consideration and the presence of pathogens should be evaluated in that context.

A recent meta-analysis by Arvaniti et al showed that the presence of infections in cirrhotic patients increased the mortality 4-fold [44]. Indeed, in our cohort one of the main causes of death was sepsis. However, the detection of pathogens may not necessarily be indicative of an active infection, therefore it seems to be difficult to predict the outcome by the detection of pathogens alone. If, however, pathogens and signs of an active infection are detected, valid risk stratification may very well be possible.

A potential limitation of our study is the relatively short follow-up, of 30 days. Therefore, the influence of the microbiological findings on long-term outcome cannot be evaluated. In summary, infections play an important role in patients with severe liver diseases and probably affect outcome [39, 40]. However, the risk stratification on the basis of microbiological findings alone does not seem to be useful. Judging from this perspective, a broad and unselective microbiological screening cannot be justified.

Finally, a multivariate model combining GCS and MELD can best predict outcome in this patient group. This emphasizes again the importance of the scoring systems as useful and readily available tools to quickly stratify the risk in an ICU patient cohort like ours. These scores themselves include several parameters. Thus, for the risk stratification it

seems of extraordinary importance to look at various aspects of the patient's state of health (clinical parameters, biological parameters, microbiological findings etc.) and combine them to obtain a comprehensive picture of the situation. It may be an important step in improving ICU risk stratification in the future.

Conclusions

Several parameters allow the assessment of the patient outcome after ICU admission. The serum creatinine and the demand for catecholamines show a strong correlation with the outcome, underlining the importance of kidney function and normal circulation. The validity of some important scoring systems for ICU liver patients could be proved. Some specific sub-parameters of the SAPS-II (bilirubin, GCS, urine output) show a stronger correlation to the outcome as compared to others, leaving room for the simplification of the score and emphasizing importance of liver and kidney function as well as the conscious state for the risk assessment in these patients. Age and gender related issues do not seem to played an important role. A broad microbiological screening does not bring any advantages for the patient.

In a multivariate model, scoring systems such GCS and MELD played a more important role than any other parameters that were significant in the univariate analysis.

Conflicts of interest

There are no conflicts of interest.

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