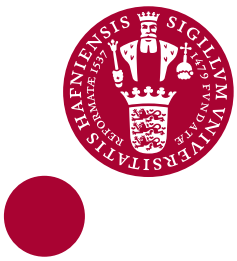

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Cold, Frederik; Schiødt, Frank Vinholt; Pott, Frank Christian; Strandkjær, Nina; Christensen, Erik

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Sepsis-related Organ Failure Assessment Score is a strong predictor of survival in acute-on-chronic liver failure

Frederik Cold[1], Frank Vinholt Schiødt[1], Frank Christian Pott[2], Nina Strandkjær[2] & Erik Christensen[1]

ABSTRACT

INTRODUCTION: The mortality of patients with an exacerbation of decompensated liver cirrhosis is high even if treated in the intensive care unit (ICU), and the criteria for referral to ICU are not well defined. The objective of this study was to identify variables associated with mortality.

METHODS: A single-centre retrospective cohort analysis was conducted in a university-affiliated ICU. A total of 53 adult patients with decompensated alcoholic liver cirrhosis were admitted from January 2012 to June 2015. Variables associated with survival were identified using Cox regression analysis.

RESULTS: The ten-day, 30-day, 90-day, and one-year mortality were 36%, 57%, 66%, and 80%, respectively. Univariate Cox regression analysis showed that mortality was significantly associated with a low oxygen saturation, low diastolic blood pressure, terlipressin treatment, high Acute Physiology And Chronic Health Evaluation II score, high Simplified Acute Physiology Score II score, high Sepsis-related Organ Failure Assessment (SOFA) score and high Model For End-Stage Liver Disease score, but only a high SOFA score and old age were independently associated with increased mortality. These two variables were combined to the Age-SOFA index to predict the probability of surviving a given period.

CONCLUSIONS: The mortality was high in these severely ill patients, even when they received optimum supportive therapy in the ICU. The finding that the SOFA score and age best predicted mortality shows that the increased mortality was caused mainly by insufficiency of organs other than the liver.

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Acute-on-chronic liver failure (ACLF) is the condition of acute decompensation of chronic liver disease (cirrhosis) associated with organ failures and a high short-term mortality [1].

The mortality of patients suffering from ACLF who are being treated in an intensive care unit (ICU) is high, both during the ICU admission and in the first year of follow-up [2-6].

Since it has been shown that the prediction of survival of patients with ACLF is more effectively calculated by using ICU-specific scoring systems than scores focusing only on liver function [1, 6], great efforts have been made to develop new scoring systems to assist the clinicians. The most recent score is the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) scoring system [1, 7].

Despite progress in the prediction of mortality in the ICU [2, 4, 6, 8], the criteria for transfer to the ICU may still be improved.

The aim of this study was to investigate the survival of patients with ACLF referred to the ICU and to identify those variables that hold the best prognostic information for prediction of a poor outcome despite all the supportive measures taken in the ICU to improve the condition.

METHODS

We conducted a retrospective single-centre cohort analysis of patients suffering from an acute exacerbation of decompensated alcoholic liver cirrhosis admitted to the multidisciplinary ICU at Bispebjerg Hospital, Denmark, which is a tertiary 500-bed hospital.

All patient data were extracted from a computerised clinical information system used at the ICU and from the patients records in the days up to the referral to the ICU. During the 42-month study period (from 1 January 2012 to 31 June 2015), 53 patients with clinical or histological diagnosis of alcoholic liver cirrhosis were included. For patients admitted more than once to the ICU, only data from their first ICU admission were included. There were no formalised criteria for ICU referral and admission at the hospital in this period. ICU admission occurred if the referring doctor and the ICU doctor agreed that this was indicated.

The study included patients who had a diagnosis of alcoholic liver cirrhosis (DK 70 diagnoses in the International Classification of Diseases) who were referred to the ICU due to a complication related to their cirrhosis.

The diagnosis of alcoholic cirrhosis was initially registered by the ICU doctors. By searching the ICU patient records system, all patients with this specific diag-

ORIGINAL ARTICLE

1) Centre of Abdominal Disease K, Section of Medical Gastroenterology and Hepatology, Bispebjerg Hospital
2) Department of Anaesthesia and Intensive Care Medicine, Bispebjerg Hospital, Denmark

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TABLE 1

Reasons for referral to the intensive care unit (ICU)[a].

Reason	Patients, n
Liver coma	43
Sepsis	16
Variceal bleeding	10
Respiratory insufficiency	8
Pneumonia	6
Aspirational pneumonia	5
Hepatorenal syndrome	4
Alcoholic hepatitis	2
Hyponatraemia	1
Spontaneous bacterial peritonitis	1
Acidosis	1

a) ≥ 1 reasons for referral to the ICU were retrospectively evaluated through records from the ICU and referring department at the time of referral.

nosis were identified. Then the patient record data was examined thoroughly to confirm the diagnosis. The patient record was also examined to ascertain that the transfer to the ICU was, indeed, related to the cirrhosis.

The following data were recorded for all patients: demographic characteristics, reason for ICU admission, clinical and laboratory data required for calculation of severity scores, indication for ICU admission, need for vasopressors while treated at the ICU including terlipressin, mechanical ventilation and continuous renal replacement therapy. Retrospectively, the records from the ICU doctors and the doctors from the referring department were assessed to ascertain the reason/reasons for referral.

The Acute Physiology And Chronic Health Evaluation (APACHE) II score, the Simplified Acute Physiology Score (SAPS) II, the Sepsis-related Organ Failure Assessment or Sequential Organ Failure Assessment (SOFA) score and the liver-specific Model For End-Stage Liver Disease (MELD) score were calculated on the day of admission to the ICU.

Laboratory variables were recorded on the day of admission to the ICU and included the international normalised ratio (INR), creatinine, sodium, albumin, bilirubin, lactate, pH, partial arterial pressure of oxygen, inspired oxygen concentration and blood pressure.

All records of patients with alcoholic cirrhosis were reviewed independently by a clinical assistant and a junior doctor (specialist registrar in internal medicine – gastroenterology).

The study was approved by the Danish Health Authority and the Danish Data Protection Agency (3-3013-1198/1/). The authorities waived the need for informed consent from patients because the study was retrospective and involved no intervention in patient care.

The survival after the date of admission to the ICU was calculated using the Kaplan-Meier method. In particular, the ten-day, 30-day, 90-day, and one-year mortality were calculated.

The association of variables with survival was studied using the Cox model for censored survival data [9]. The full observation period up to one year was used in the calculations to obtain maximum power in the analyses. For variables having a markedly skewed distribution, their logarithmic value was used in the Cox regression analyses to fulfil the assumption of proportional hazards [9]. Variables with a $p < 0.10$ in univariate analysis were further analysed in a multivariate Cox model where insignificant variables were eliminated using the backward elimination technique. In the analysis, a few missing values were replaced by the mean value of the variable in question. $p \leq 0.05$ was considered statistically significant.

Based on the multivariate Cox model, a pocket chart for easy estimation of the value of a prognostic index was devised [9]. This index could then be translated to the probability of surviving a given time span as described elsewhere [9].

Trial registration: not relevant.

RESULTS

From January 2012 to June 2015, a total of 53 patients with complications to decompensated alcoholic cirrhosis were admitted to the ICU for the first time. The most frequent reasons for referral to the ICU were liver coma, sepsis, variceal bleeding, respiratory insufficiency and pneumonia or a combination of these conditions (**Table 1**).

The patients were severely ill at the time of arrival at the ICU with the following median sores: APACHE II 32.5, SAPS II 60, SOFA 9.5 and MELD 23.1 (**Table 2**). The overall survival was estimated by the Kaplan-Meier method. The overall mortality was 36% at ten days, 57% at 30 days, 66% at 90 days and 80% at one year.

A low oxygen saturation, low diastolic blood pressure, high APACHE II score, high SAPS II score, high SOFA score and a high MELD score at the day of ICU admission and terlipressin treatment at the ICU were all significantly associated with an increased mortality (**Table 3**).

Only age (marginally significant) and the SOFA score showed independent associations with survival (Table 3). The association of the SOFA score with mortality was remarkably strong ($p = 0.000006$). Based on the regression coefficients of these two variables, a prognostic index could be devised (the Age-SOFA Index). To make it easy to calculate this index, we prepared a pocket chart (**Figure 1**). For example, for a patient who is 51 years old and has a SOFA index

of 15, the Age-SOFA Index can be calculated to 9 + 15 = 24.

The estimated probability of surviving ten, 30, 90 and 365 days using the Age-SOFA Index is shown in **Figure 2**. Using Figure 2 for the above patient with an Age-SOFA Index of 24, the estimated probability of surviving ten, 30, 90 and 365 days can be read as 0.5, 0.2, 0.1 and 0.02, approximately.

DISCUSSION

The results of this retrospective study confirm the poor prognosis of patients suffering from an acute exacerbation of decompensated alcoholic liver cirrhosis even when treated intensively in the ICU [2-6]. It has previously been difficult to identify patients who will most likely benefit from supportive treatment in the ICU, and those patients who despite all supportive therapy will not benefit but will deteriorate fatally. This emphasises a need for better criteria for admitting patients to the ICU. The purpose of this study was to identify patient characteristics associated with mortality in the ICU in order to improve the selection for ICU treatment.

The strength of this study is that we had one year of follow-up on survival, which can be used to identify predictors showing the strongest association with survival in this seriously ill patient group.

The greatest weakness of the study is that we had no data to calculate the CLIF-SOFA score, since we did not have data on vasopressor treatment at the time of ICU referral. Furthermore, there is a risk of selection bias, since we only recorded data on patients for whom the ICU doctors registered a diagnosis of alcoholic liver disease at the time of their ICU admission.

TABLE 2

Characteristics of the patients at the first day in the intensive care unit, N = 53.

Age, median (range), yrs	58 (35-84)
Gender, male/female, %	62/38
Ascites, no/yes, %	53/47
Encephalopathy, grade 0/1/2/3/4, %	8/2/17/38/35
Systolic blood pressure, median (range), mmHg	109 (47-178)
Diastolic blood pressure, median (range), mmHg	57 (30-90)
Bilirubin concentration, median (range), µmol/l	73 (7-636)
Albumin concentration, median (range), g/l	28 (17-48)
International normalised ratio, median (range)	2.05 (1-7)
Sodium concentration, median (range), mmol/l	132 (107-157)
Creatinine concentration, median (range), µmol/l	107 (30-827)
Lactate concentration, median (range), mmol/l	2.7 (0.5-14.5)
PaO_2, median (range), kPa	10.8 (7.2-23)
O_2 saturation, median (range), %	95 (67-100)
APACHE II score, median (range)	32.5 (19-51)
SAPS II score, median (range)	60 (28-108)
MELD score, median (range)	23 (0-47)
SOFA score, median (range)	9.5 (3-21)
Continuous renal replacement therapy, no/yes, %	70/30
Mechanical ventilation, no/yes, %	34/66
Norepinephrine administered, no/yes, %	51/49
Terlipressin administered, no/yes, %	47/53

APACHE = Acute Physiology And Chronic Health Evaluation; MELD = Model For End-Stage Liver Disease; PaO_2 = partial arterial pressure of O_2; SAPS = Simplified Acute Physiology; SOFA = Sepsis-related Organ Failure Assessment.

TABLE 3

Results of Cox regression analyses.

	Beta coefficient	Standard error	p-value
Univariate analysis[a]			
Age, yrs	0.0316	0.0174	0.069
Bilirubin concentration, µmol/l	00213	0.00111	0.055
Creatinine concentration, ln(µmol/l)	0.326	0.173	0.059
Diastolic blood pressure, mmHg	−0.0325	0.0153	0.034
O_2 saturation, %	−0.103	0.029	0.0005
APACHE II score	0.0570	0.0234	0.015
SAPS II score	0.0322	0.0122	0.008
MELD score	0.0414	0.0149	0.006
SOFA score	0.1852	0.0410	0.000006
Terlipressin administration, no/yes	0.614	0.316	0.053
Multivariate analysis using the backward elimination technique			
Age, yrs	0.0321	0.0169	0.058
SOFA score	0.1817	0.0402	0.000006

APACHE = Acute Physiology And Chronic Health Evaluation; MELD = Model For End-Stage Liver Disease; SAPS = Simplified Acute Physiology; SOFA = Sepsis-related Organ Failure Assessment.
a) Only results with p < 0.10.

Moreover, the retrospective collection of substantial parts of the data, the relatively small group of patients and the fact that we had no recordings of liver transplantations in the follow-up period warrant cautious conclusions. However, the mortality data are in concordance with data from a similar study on a similar patient group from another ICU in Denmark [6]. The striking finding in this paper was that the SOFA score has a very strong association with mortality.

This association is much stronger than that of the liver-specific variables, including the MELD score [10]. The SOFA score is comprised by six different subscores for the respiratory, cardiovascular, hepatic, coagulation, and the renal and neurological systems, respectively [11]. Thus, the SOFA score reflects both the number of essential functions that are dysfunctional and the degree to which each function is affected. The fact that SOFA outranks the liver-specific variables and scores that we were able to study shows that in the terminal phase of decompensated alcoholic cirrhosis, the prognosis is strongly determined by the detrimental effect of the decreased liver function on other essential organs and functions necessary for survival.

The strong prognostic value of the SOFA score in these severely ill patients has also been found in other studies [12-14]. Since four of the values of the SOFA score are identical to the values of the CLIF-SOFA score, we probably would have found similar associations using this score. Interestingly, in the performed studies, the addition of liver-specific information in the CLIF-SOFA score only increased the predictive value slightly [12-14], showing that this extra information is of relatively limited value at this advanced stage of liver disease.

In addition to SOFA, only age had a marginally additional significant association with mortality in the multivariate Cox regression analysis. Since age is not included in the SOFA score, it seems reasonable to combine age and the SOFA score into the Age-SOFA Index based on the coefficients obtained in the multivariate Cox model using the method described in reference [9]. This index can be calculated in a simple way using the pocket chart (Figure 1), and the obtained value can be used to estimate the probability of surviving ten, 30, 90 and 365 days (Figure 2).

This can provide some idea of the most likely outcome of transferring the patient to the ICU and thus help us decide whether treatment in the ICU would be warranted for the patient in question. An Age-SOFA Index of 26 and above predicts a 30-day survival probability of 0.1 or less (Figure 2).

However, the Age-SOFA Index needs to be validated in a larger sample and compared with the CLIF-SOFA score. Until then, it can only be used as a guide together with other pertinent information in the decision-making about the best course of action for the patient.

In this study, we focused on the treatment at the ICU and the patient characteristics at the time of ICU admission. However, to improve the survival in this seriously diseased group of patients, a close follow-up is important as well as further research into the factors

FIGURE 1

Pocket chart for easy calculation of the Age- Sepsis-related Organ Failure Assessment (SOFA) Index[a].

Age, yrs	Age points
28	5
34	6
40	7
45	8
51	9
57	10
62	11
68	12
74	13
79	14

Age-SOFA (score) -

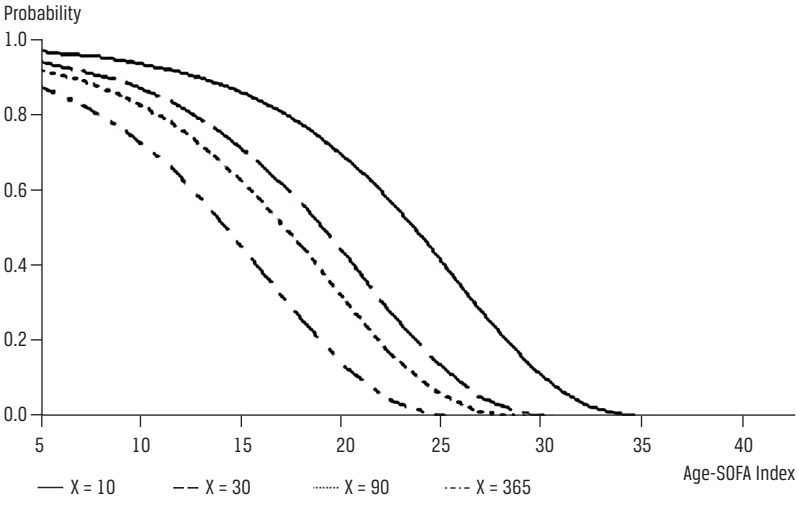
Age-SOFA Index = Age points + SOFA =

For age, only 1 number should be used, and if the age is between those stated, interpolation should be used.

a) To keep the SOFA score as it is, we used regression coefficients scaled with this factor 1/0.1817 = 5.5036 making the coefficient for SOFA = 1. Otherwise, the pocket chart was constructed as described in [9].

FIGURE 2

Probability of surviving X days. Estimated probability of surviving 10, 30, 90 and 365 days by the value of the Age-SOFA Index, based on the Cox model in Table 3 scaled to provide the pocket chart in Figure 1.



SOFA = Sepsis-related Organ Failure Assessment.

that increase survival after discharge from the ICU and the hospital [15].

CONCLUSIONS

Increasing failure of vital organs and old age were found to be independent predictors of non-survival in ACLF patients admitted to the ICU.

CORRESPONDENCE: *Erik Christensen.* E-mail: erik.christensen@ymail.com

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