Diplomarbeit

Simple risk stratification for patients with decompensated cirrhosis upon hospital admission

eingereicht von

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zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr^{in}. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Klinischen Abteilung für Gastroenterologie und Hepatologie

Universitätsklinikum Graz

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Graz, 07.02.2017

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Danksagungen

An dieser Stelle möchte ich Assoz. Prof.in Priv.-Doz.in Dr.in med.univ. Vanessa Stadlbauer-Köllner und Dr.med.univ. Dr.scient.med. Walter Spindelböck für die Möglichkeit zur Erstellung dieser Diplomarbeit und für die großartige Unterstützung während der Entstehung derselbigen meinen Dank aussprechen.

Weiters danke ich den Personen, die an der Erhebung und Auswertung der Daten mitgewirkt haben, hierbei möchte ich besonders Assoz. Prof.in Priv.-Doz.in Dr.in med.univ. Ines Zollner-Schwetz für die Hilfestellung bei der Auswertung der infektiologischen Daten danken.
Ebenfalls möchte ich mich bei all jenen Personen bedanken, die vorab zur Entstehung der vorliegenden Arbeit beigetragen haben.

Insbesonders gilt mein Dank meiner Familie und Freunden, die mich während meiner gesamten Studienzeit bedingungslos, sowohl in guten als auch schweren Zeiten, unterstützt haben. Besonders hervorheben möchte ich hierbei meine Eltern, die mein Studium ermöglicht haben.

Abstract

Background:

Accurate assessment of the disease severity and prognosis of decompensated cirrhosis is crucial to establish an optimal therapeutic management, but it remains challenging to accomplish. Currently, well-established scoring systems for liver impairment, such as the Model of End stage Liver Disease (MELD) score or the Child-Turcotte-Pugh (CTP) score are used to assess the short-term and long-term mortality in patients with cirrhosis. However, there is growing evidence that in patients with decompensated cirrhosis the mortality rate is dependent on superimposed organ failure/s and the presence of systemic inflammatory response syndrome (SIRS) rather than isolated liver failure – which these widely used scoring systems do not assess for. Consequently, there is a growing interest in evaluating predictive parameters reflecting multiple organ failure and SIRS alongside liver impairment, as these will potentially provide a more reliable mortality risk assessment in patients with decompensated cirrhosis.

Aims:

The aim of the present study is to propose a simple risk stratification system for the short-term as well as for the long-term mortality rate in patients with decompensated cirrhosis.

Material and methods:

Clinical and laboratory data were collected from the database of the Hospital of the Medical University of Graz. 165 patients diagnosed with cirrhosis and hospitalized due to acute decompensation of their underlying liver disease between January 2008 and December 2011 were retrospectively enrolled. Multivariate and univariate binary logistic regression analysis were carried out to evaluate potential predictive variables for mortality at day 30, day 90 and 1 year. The Youden's index was used to calculate the best diagnostic cut-off values.

Results:

In the cohort of this study, the average CTP and MELD scores were respectively 10 ± 2 and 21 ± 8 and the most frequent etiology of cirrhosis was chronic alcohol consumption (89%). Short-term mortality (at day 30 and day 90) was best predicted by albumin levels <2,55g/dL, CRP levels >31mg/L, MELD >23 and the presence of ACLF (any grade). CRP levels >31mg/L and MELD >23 best predicted long-term mortality (1 year). When combining the MELD score or the presence of ACLF (independent of the grade) with the most predictive variables we obtained four 2-variable models for risk stratification that were accurate mortality predictors: the combination of ACLF and albumin (**'ACLF-Albumin model'**) was predictive for the thirty-day mortality, while the ninety-day mortality was best predicted by the combination of MELD score and CRP (**'MELD-CRP model'**); for the one-year mortality, both the combination of MELD score and CRP (**'MELD-CRP model'**) and the combination of ACLF and CRP (**'ACLF-CRP model'**) were similarly predictive. Importantly, these models showed improved accuracy when compared with the MELD score or the presence of ACLF (any grade) alone.

Conclusion:

The newly defined 2-variable models 'ACLF-Albumin model', 'MELD-CRP model' and 'ACLF-CRP model' allow for simple risk stratification of patients with decompensated cirrhosis into groups with low, intermediate and high short-term mortality, as well as long-term mortality rates. Importantly, these models show improved accuracy when compared with the original scores. Applying these models, and depending on the mortality risk, either discharge, ward admission or ICU admission may be recommended. Taking our results into account, establishing scoring systems that combine liver impairment with other predictive parameters reflecting SIRS and extrahepatic organ failure is required for the adequate assessment of disease severity in patients with decompensated cirrhosis.

Zusammenfassung

Hintergrund:

Eine präzise Beurteilung der Prognose bei Patienten mit dekompensierter Leberzirrhose ist wegweisend für ein optimales Therapiemanagement, aber dennoch oft schwierig zu realisieren. Der Model of End stage Liver Disease (MELD) Score und der Child-Turcotte-Pugh (CTP) Score sind etablierte Prognosescores bei Leberfunktionsstörungen, die zur Beurteilung der Kurzzeit- und Langzeitmortalität eingesetzt werden. Es gibt allerdings zunehmend Hinweise, dass bei Patienten mit dekompensierter Zirrhose die Mortalität hauptsächlich vom Vorliegen zusätzlicher Organversagen und eines systemisch inflammatorischen Response-Syndroms (SIRS) und nicht vom alleinigen Leberversagen abhängt. Es besteht daher Interesse zur Evaluierung prognostischer Parameter, die hinweisend sind für multiple Organversagen und SIRS zusätzlich zur Leberfunktionsstörung bei Patienten mit dekompensierter Zirrhose.

Ziel:

Das Ziel der Studie besteht darin, ein einfaches System zur Risikostratifizierung für die Kurzzeit- und Langzeitmortalität bei Patienten mit dekompensierter Leberzirrhose vorzuschlagen.

Material und Methoden:

165 Patienten, die aufgrund akuter Dekompensation bei bereits diagnostizierter Leberzirrhose hospitalisiert wurden, konnten retrospektiv eingeschlossen werden. Der Untersuchungszeitraum erstreckte sich von Dezember 2008 bis Jänner 2011. Es wurden klinische und laborchemische Daten mithilfe einer Recherche in der elektronischen Datenbank des Universitätsklinikums Graz erhoben. Die statistische Auswertung der potentiell prognostischen Parameter für die Mortalität zum Tag 30ig, 90ig und einem Jahr wurde unter anderem mit multivariat und univariat binärer logistischer Regressionsanalyse durchgeführt. Der Youden's Index wurde zur Berechnung der diagnostisch besten Cut-off Werte herangezogen.

Ergebnisse:

In der vorliegenden Studienkohorte zeigte sich ein CTP und MELD Score von 10 ± 2 bzw. 21 ± 8. Die häufigste Ursache der Leberzirrhose war mit 89% Alkoholabusus.

Albumin-Werte <2,55g/dL, CRP-Werte >31mg/l, ein MELD Score >23 und das Vorliegen von ACLF (unabhängig vom Grad) erwiesen sich am geeignetsten zur Prognose der Kurzzeitmortalität (Tag 30 und Tag 90). CRP-Werte >31mg/l und ein MELD Score >23 zeigten die beste Aussagekraft zur Prognose der Langzeitmortalität (1 Jahr). Die Kombination von MELD Score oder vorliegendem ACLF mit den prädiktiv besten Parametern ermöglichte eine einfache Risikostratifizierung der Patienten hinsichtlich Mortalität. Folgende 2-Parameter Modelle erwiesen sich als aussagekräftig: Die Kombination von ACLF und Albumin (**'ACLF-Albumin model'**) war prädiktiv für die Mortalität nach 30 Tagen, wohingegen die Kombination von MELD Score and CRP (**'MELD-CRP model'**) für die Mortalität nach 90 Tagen die beste Aussagekraft zeigte. Sowohl die Kombination von MELD Score und CRP (**'MELD-CRP model'**) als auch die Kombination von ACLF and CRP (**'ACLF-CRP model'**) waren gleichermaßen prädiktiv für die Mortalität nach einem Jahr. Beim Vergleich mit dem ursprünglichen MELD Score und dem ACLF (unabhängig vom Grad) konnte eine Verbesserung der prognostischen Aussagekraft durch die 2-Parameter Modelle gezeigt werden.

Schlussfolgerung:

Die neu definierten 2-Parameter Modelle 'ACLF-Albumin model', 'MELD-CRP model' und 'ACLF-CRP model' ermöglichen eine einfache Risikostratifizierung in Gruppen mit niedriger, mittlerer und hoher Kurzzeit- bzw. Langzeitmortalitätsrate bei Patienten mit dekompensierter Zirrhose. Abhängig vom Mortalitätsrisiko könnte entweder eine Entlassung, eine Krankenhausaufnahme auf eine Normalstation oder Intensivstation in Erwägung gezogen werden. Die 2-Parameter Modelle zeigen eine Verbesserung der prognostischen Aussagekraft beim Vergleich mit den ursprünglichen Prognosescores. Unsere Ergebnisse weisen daraufhin, dass zur Abschätzung des Mortalitätsrisikos bei Patienten mit dekompensierter Leberzirrhose Scoring Systeme nötig sind, die sowohl leberspezifische Parameter, als auch Parameter hinweisend für SIRS und extrahepatische Organversagen beinhalten.

Table of contents

List of abbreviations

WHO	World Health Organization
NAFLD	nonalcoholic fatty liver disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HSCs	hepatic stellate cells
HE	hepatic encephalopathy
AD	acute decompensation
SBP	spontaneous bacterial peritonitis
UTI	urinary tract infection
MRI	magnetic resonance imaging
CT	computed tomography
LB	liver biopsy
resp.	respectively
bzw.	beziehungsweise
TE	transient elastography
APRI	AST-to-Platelet-Ratio-Index
AST	aspartate aminotransferase
ULN	upper limit of normal
GGT	gamma-glutamyltransferase
ELF	Enhanced Liver Fibrosis
kPa	kilopascal
PH	portal hypertension
HVPG	hepatic venous pressure gradient
CSPH	clinically significant portal hypertension
INR	international normalized ratio
CTP	Child-Turcotte-Pugh
MELD	Model of End stage Liver Disease
$MELD_{(i)}$	initial Model of End stage Liver Disease
PSS	portosystemic shunt
OHE	overt hepatic encepahlopathy
TIPS	transjugular intrahepatic portosystemic shunting
MHE	minimal hepatic encepahlopathy

CHE	covert hepatic encepahlopathy
GABA	gamma- aminobutyric-acid
BBB	blood-brain-barrier
RNA	ribonucleic acid
SIRS	systemic inflammatory response syndrome
WHVP	wedged hepatic venous pressure
VEGF	vascular endothelial growth factor
NO	nitric oxide
EGD	esophagogastroduodenoscopy
ADH	antidiuretic hormone
SAAG	serum-ascites albumin gradient
HRS	hepatorenal syndrome
ACLF	Acute-on-Chronic-Liver-Failure
NLR	neutrophil-to-lymphocyte ratio
MPV	mean platelet volume
LBP	lipopolysaccharide-binding protein
CRP	C-reactive protein
PCT	procalcitonin
CLD	chronic liver disease
vWF	von Willebrand factor
aPTT	activated partial thromboplastin time
HCC	Hepatocellular carcinoma
AASLD	American Association for the Study of Liver Disease
EASL	European Association for the Study of the Liver
BCLC	Barcelona Clinic Liver Cancer
CT	Child-Turcotte
TIPSS	transjugular intrahepatic portosystemic stent shunt
UNOS	United Network for Organ Sharing
APASL	Asia-Pacific Association for the Study of the Liver
CLIF-SOFA	Chronic LIver Failure-Sequential Organ Failure Assessment
SOFA	sepsis organ failure assessment
CLIF-C OF	CLIF Consortium Organ Function
CLIF-C-ACLF	Chronic LIver Failure - Consortium - ACLF
WBC	white blood cells

ICU	intensive care unit
BMI	body mass index
GCS	Glascow Coma Scale
SD	standard deviation
ROC	receiver operating characteristics
AUROC	Area Under the Receiver Operating Characteristics
OR	odds ratio
CI	confidence intervall
vs.	versus
e.g.	for example
APACHE	Acute Physiology and Chronic Health Evaluation
IL-6	interleukin 6
OPTN	Organ Procurement and Transplantation Network
MR-proADM	mid regional fragment of pro-adrenomedullin
suPAR	soluble urokinase plasminogen activator receptor
bac DNA	bacterial DNA
CLIF-C Ads	CLIF-Consortium score for AD

List of figures

List of tables

1 Introduction

1.1 Cirrhosis

1.1.1 General

Liver cirrhosis develops in response to chronic liver injury with different etiologies. It is histologically characterized by diffuse hepatic fibrosis, necrosis of parenchyma cells and development of nodular regeneration. The degree of hepatic architectural destruction and the cirrhosis etiology influence the clinical manifestations as well as the prognosis. (1)

In developed countries, cirrhosis is an increasing cause of morbidity and mortality ranking the 14th position in causes of deaths worldwide, but it occupies the 4th position in central Europe. According to the World Health Organization (WHO), cirrhosis accounts for 1,03 million deaths per year worldwide and for 170 000 (1,8%) of all deaths in Europe. Data on the prevalence and incidence of liver cirrhosis in Europe are lacking and studies in different countries covering that topic frequently present disparate study designs that curtails data comparison. These studies show considerable geographical variations within Europe. The prevalence of cirrhosis was found to be 4,5% in Denmark and 6% in Finland compared to 10% in Italy and 0,3% in France. (2–5) The incidence ranges from 14 to 26 per 100 000 people per year in Europe. (6,7) In contrast to the understanding of the last two centuries generally accepted progressive 'end-stage' character of this disease, the natural history of cirrhosis has changed significantly in recent years showing dynamic potential of both progression and regression. As therapeutic possibilities have enhanced, long-term survival with clinical and histological improvement depending on etiology and stage were observed. (7,8)

1.1.2 Etiology

The main causes of cirrhosis in Europe comprise chronic alcohol consumption, viral hepatitis C and B as well as nonalcoholic fatty liver disease (NAFLD). (6) Due to the geographical variation, chronic hepatitis B virus (HBV) infection is the leading cause of cirrhosis in the Asia-Pacific region. The most common causes of cirrhosis in the Western world comprise alcoholic liver disease and hepatitis C virus (HCV) infection. (6,9) During the last years, NAFLD has become a main cause of cirrhosis as a consequence of the significantly increasing metabolic syndrome. (10) In contrast to other hepatotoxins, alcohol is not strictly dose-dependent. Nevertheless, an amount of more than 60-80g per day in men and more than 20g per day in women over a period of more than 10 years is associated with increased risk of developing cirrhosis. (11) HCV infection in combination

with alcohol potentiates the hepatotoxic effect. (12) There are less frequent causes of cirrhosis comprising autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. Many different inherited and metabolic diseases may cause cirrhosis, the most frequent being hemochromatosis and Wilson's disease. (13)

1.1.3 Pathogenesis

A varying degree of scarring and regeneration as well as clinical complications are observed due to different etiologies of cirrhosis. Nevertheless, the pathophysiological mechanisms at the cellular level show similarities independent of the underlying disease. (1) Main processes in the development of cirrhosis are inflammation, apoptosis and compensatory regeneration of hepatocytes and activation of hepatic stellate cells (HSCs) inducing fibrogenesis. (13) The microvascular changes taking place result in sinusoidal remodelling, angiogenesis with intrahepatic shunts and hepatic endothelial dysfunction. (14) Enhanced capillarization and defenestration of liver sinusoidal endothelial cells induce insufficient release of vasodilatators and abnormal substrate exchange contributing to hepatic dysfunction. Structural and functional changes lead to increased intrahepatic vascular resistance, which act as the most important factor to induce portal hypertension secondary to cirrhosis. In the case of disease progression, damage of the lobular and vascular architecture may result in liver insufficiency and increased resistance to portal blood flow inducing portosystemic shunts. (8) Vasodilatation in the splanchnic circulation induces an increased blood flow in the splanchnic organs as to reduce vascular resistance in the portal hypertensive state. Nevertheless, the subsequent increase in portal venous inflow contributes to portal hypertension and the development of ascites and hepatorenal syndrome. (15) The formation of intrahepatic shunts as a consequence of angiogenesis and loss of parenchymal cells promotes the development of hepatic encephalopathy (HE) and impaired first-pass effect of orally given drugs. (7)

1.1.4 Clinical manifestation

The clinical manifestations of cirrhosis are often unspecific and remain unsuspected until complications occur. On the basis of clinical complications cirrhosis can be classified into a compensated and decompensated stage. The presence of ascites, HE, variceal hemorrhage and/or non-obstructive jaundice characterize the decompensated stage indicating poorer prognosis. (9,16) Patients with compensated cirrhosis may be asymptomatic or present increased fatigue, weakness, weight loss or gastrointestinal

complaints. (17) There are findings on physical examination potentially associated with cirrhosis such as ascites, spider angioma, palmar erythema, umbilical collateral veins (caput medusae) or a glazing tongue. Due to endocrine disorders the development of hypogonadism and gynecomastia in men and anovulation in women may occur. Reduced synthesis of proteins results in malnutrition, muscular atrophy and ascites. Disturbances in the carbohydrate metabolism may present as glucose intolerance and result in diabetes onset. Bacterial infections are frequent and seen as a potential precipitating event for the development of acute decompensation (AD). The pattern of bacterial infections shows regional differences, and varying rates of specific infections are reported in the literature. The most common bacterial infections are spontaneous bacterial peritonitis (SBP) (10-54%), pneumonia (14-21%) followed by urinary tract infection (UTI) (7-41%) and bacteremia associated with iatrogenic interventions (4-21%). (9,18–20)

1.1.5 Diagnosis

In many cases imaging by abdominal ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT) of an irregular, nodular and small liver combined with disorders of the liver function is sufficient for the diagnosis of liver cirrhosis. As cirrhosis is seen as a dynamic process, the progression should be analyzed with etiology-driven mechanisms in mind, including the potential outcome of invasive and non-invasive tests. The final diagnosis should comprise the determination of significant cirrhosis, the etiology and the presence of potential complications (e.g. jaundice, hepatic encephalopathy and/or portal hypertension). The clinical manifestation of complications allows for the classification of cirrhosis as being compensated or decompensated stage, which are associated with distinct prognoses. (7,21)

Liver biopsy (LB) has traditionally been regarded as the gold standard for determining the extent of tissue damage, such as hepatic fibrosis, in patients with chronic liver disease. The main indications include diagnosis, contribution to therapeutic management decision and disease staging. A biopsy, to be diagnostically conclusive, should be 2-3cm in length, 16 gauge in caliber and contain at least 11 portal tracts. For diagnosing cirrhosis, liver biopsy is only recommended in cases with an atypical presentation. According to the underlying disease there are different semiquantitative scoring systems available for assessment of the prognosis. (22) Scoring systems developed from Knodell, Scheuer or METAVIR incorporate five stages of fibrosis (stage of fibrosis 0 to 4; F0-F4). The scoring system from Ishak comprises seven stages of fibrosis (stage of fibrosis 0 to 6; F0-F6) assigned for

grading and staging chronic viral hepatitis. The stages METAVIR F2-F4 (resp. Ishak F3-F6) are designated as significant fibrosis, F3-F4 (resp. Ishak F4-F6) as severe fibrosis and the stage F4 (resp. Ishak F5-F6) is classified as cirrhosis (table 1). (23)

Table 1 Histopathological classification system for fibrosis (22–24)

Stage of fibrosis	Knodell	Scheuer	METAVIR	Ishak
0	No fibrosis	No increase in fibrosis	No fibrosis	No fibrosis
1	Portal fibrosis	Portal fibrosis, no septa	Portal fibrosis	Fibrosis of isolated portal areas with or without short septa
2	n.d.	Incomplete or complete portoportal septa, architecture preserved	Portal fibrosis with scattered septa	Increased fibrosis in most portal areas with or without short septa
3	Portoportal or portocentral septa	Fibrosis with septum formation and architectural disorder, no evidence of complete cirrhotic change	Numerous septa without cirrhosis	Portal fibrosis with portoportal septa
4	Cirrhosis	Probable or definite cirrhosis	Cirrhosis	Portal fibrosis with marked portoportal or portocentral septa
5	n.d.	n.d.	n.d.	Marked septum formation (portoportal or portocentral) with some nodule formation (incomplete cirrhosis)
6	n.d.	n.d.	n.d.	Probable or definite cirrhosis

n.d., not defined

One of the main limitations of LB is the sampling error caused by the inhomogeneous distribution pattern of many liver diseases at early stages or too small biopsy samples. Furthermore, there may occur substantial interobserver variation especially if biopsy interpretation is not performed by a liver pathologist. All currently available scoring systems determine cirrhosis as a histopathological end stage disregarding the discrimination of a potential reversible fibrogenic process in contrast to an advanced irreversible stage. This dynamic character of cirrhosis requires different treatment for each stage. Additionally, LB is costly and as an invasive procedure there are potential complications of which post-interventional hemorrhage and bile leakage are the most common. (22,24,25) These limitations of LB strengthen the need for non-invasive procedures for assessment of the fibrosis stage and methods that allow continuous measurement in order to adapt treatment with regard to the current stage of disease (progressive, static, regressive). (21,24) Non-invasive methods comprise indirect serum biomarkers (combination of widely available laboratory parameters, listed in table 2), direct serum biomarkers (extracellular matrix proteins) and different imaging such as transient elastography (TE). (23)

Table 2 Indirect serum biomarkers for non-invasive measurement of liver fibrosis (26–29)

Non-invasive methods	Calculation	Diagnostic range	Sensitivity	Specificity
APRI (AST-to-Platelet-Ratio-Index)	(AST/ULN)/ platelet count [10^9/L] x 100	Significant fibrosis: >1,5 Cirrhosis: >2	38-57%	87-93%
Forns-Index	7,811–3,131 x ln(platelet count)+ 0,781 x ln(GGT) + 3,467 x ln(age) – 0,014 x (cholesterol)	Significant fibrosis: > 6,9	30%	95%
Fibrotest ®	4,467 x log[alpha 2 makroglobulin (g/L)] – 1,357 x log[haptoglobin (g/L)] + 1,017 x log[GGT (IU/L)] + 0,281 x [age (years)] + 1,737 x log[bilirubin (µmol/L)] – 1,184 [apolipoprotein A1 (g/L)] + 0,301 x sex (0 for female, 1 for male) – 5,540	Significant fibrosis: 0,6-1,0	50%	93%

ULN, upper limit of normal; AST, aspartate aminotransferase;
GGT, gamma-glutamyltransferase

Among tests that include direct serum biomarkers, hyaluronic acid, the Fibrospect II ®, the ELF ® (Enhanced Liver Fibrosis) and the FibroMeter ® belong to the most common used tests. The main strengths of direct and indirect serum biomarkers are the high applicability, the inter-laboratory reproducibility and common availability. However, the fact that none of these parameters is exclusively liver specific may result in false positive or false negative findings. (24)

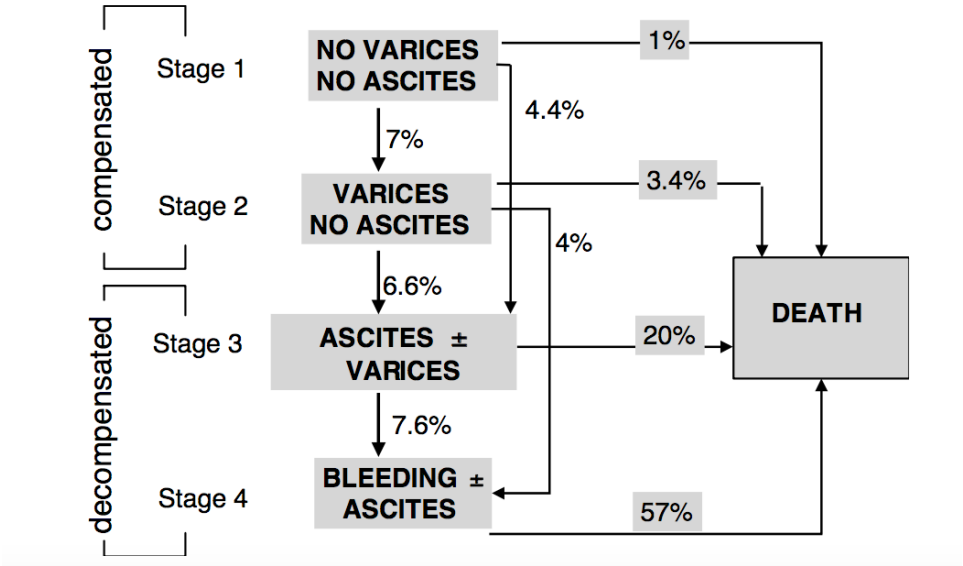
Transient elastography (TE, e.g. FibroScan) is an ultrasound procedure for the staging of liver fibrosis through determination of liver stiffness. The transthoracic placed transducer measures the velocity of a low-frequent elastic shear wave propagating through the liver. Liver stiffness is related to the speed of the reflected wave. Values range from 1,5 to 75 kilopascals (kPa) with a value of about 5 kPa in the normal liver. Transient elastography has been validated for varying liver diseases, which show different cut-off values according to the etiology of the underlying liver disease. The cut-off value for cirrhosis in patients with alcoholic liver disease is about 22,6 kPa, whereas a value of about 12,5 kPa

indicates cirrhosis in patients with HCV infection. (30,31) The applicability is not possible in the case of ascites or obesity. The TE is the most common used and validated non-invasive procedure showing good reproducibility. Both serum biomarkers and TE show high accuracy in determining significant fibrosis or cirrhosis, whereas non-invasive procedures cannot distinguish between intermediate stages of fibrosis. (21,24) Staging liver disease in viral hepatitis with a combination of serum biomarkers and TE is recommended. Only in the case of a mismatch of the two combined non-invasive tests liver biopsy is required. There is strong evidence that non-invasive methods, especially TE have a high prognostic value for predicting hepatic complications, disease progression and death. Measurement of liver stiffness is independently related to the stage of fibrosis and seems to be superior to liver biopsy in predicting clinical outcome. (32–34) It is recommended that non-invasive methods should reduce, but not replace the application of liver biopsy. An integrated system, which includes individually non-invasive and invasive methods with continuous measurement enables optimal therapeutic management, adapted to different stages of cirrhosis (progressive, static, regressive). (21)

1.1.6 Staging Classification

Cirrhosis as a dynamic process shows wide differences in life expectation depending on the stage of disease progression. The classification into either a compensated or a decompensated stage of cirrhosis shows survival time of >12 years in the compensated stage while decompensated cirrhosis is associated with a survival time of approximately 2 years. Nevertheless, cirrhosis should not be assumed as a single disease stage with simple progression from compensated to decompensated stage. (16,21) Clinical manifestation of jaundice, variceal hemorrhage, HE and/or ascites indicates decompensation. In 2006 a prognostic clinical subclassification with 4 stages has been established (figure 1). Each of the 4 stages is marked by different clinical characteristics appearing in the course of cirrhosis. Stage 1 (compensated with no esophageal varices or ascites) indicates a one-year mortality of only 1% and stage 2 (compensated with esophageal varices) has an estimated one-year mortality rate of 3,4 %. In contrast, stage 3 (decompensated with ascites and/or esophageal varices) and stage 4 (decompensated with gastrointestinal hemorrhage and/ or ascites) indicate high mortality rates of 20% and 57% per year. (16) Additionally, the introduction in the classification system of a fifth stage with the presence of renal failure and infection has been proposed. Stage 5 indicates a one-year mortality rate of 67 %. (35,36)

Figure 1 One-year mortality according to the clinical stage (16)



Recently, a redefinition of stage 3 and 4 has been proposed, where stage 3 comprises gastrointestinal hemorrhage without ascites and stage 4 is characterized by ascites with or without gastrointestinal hemorrhage. (37) According to the stages in cirrhosis there are different prognostic predictors available for the compensated or decompensated stage. Portal hypertension (PH) is one of the main contributors to the development of hepatic complications that mark the transition from the compensated to decompensated stage. Measurement of the hepatic venous pressure gradient (HVPG) is the diagnostic procedure for detecting portal hypertension. A HVPG value ≥6mmHg indicates cirrhosis, whereas clinical manifestations of PH are observed when HVPG is ≥10mmHg. (38) The HVPG ≥10mmHg is determined to be 'a clinically significant portal hypertension (CSPH)', because this value is associated with the development of esophageal varices, clinical decompensation and hepatocellular carcinoma in stage 1 of compensated cirrhosis. (39,40) Although robust predictors of disease progression, especially in the early-compensated stage of cirrhosis, are important, HVPG is limited due to the impossibility of continuous measurement and the narrow interval from ≥6mmHg to ≥10mmHg. (21) In the compensated stage additionally to the HVPG, age, the international normalized ratio (INR) and the Child-Turcotte-Pugh (CTP) score are significant prognostic predictors. In the decompensated stage the Model of End stage Liver Disease (MELD) score and the CTP score have been found to be useful in the prediction of mortality. (16)

1.2 Decompensated Cirrhosis

The decompensated stage of cirrhosis comprises the clinical manifestation of jaundice, hepatic encephalopathy, portal hypertension, hematologic abnormalities and the development of hepatocellular carcinoma. In further consequence portal hypertension may induce the development of ascites, esophageal varices and/ or hepatorenal syndrome. The decompensation of cirrhosis is associated with an adverse prognosis.

1.2.1 Hepatic encephalopathy (HE)

1.2.1.1 General

Hepatic encephalopathy (HE) is defined as a potential reversible brain dysfunction and constitutes a serious complication caused by liver insufficiency and/or portosystemic shunt (PSS) associated with poor survival and severe risk of relapse. (41) It is associated with acute or chronic liver failure. Clinical presentation shows a broad range of neurological or psychiatric abnormalities characterized by subclinical symptoms up to coma. (42) There are differences in prevalence and incidence according to the severity of the underlying liver disease and PSS. At the time of cirrhosis diagnosis, the prevalence of overt HE (OHE) is 10-14% in general, compared to 16-21% in patients with decompensated cirrhosis or 10-50% in patients who underwent transjugular intrahepatic portosystemic shunting (TIPS). 30-40% of all patients with cirrhosis develop OHE at any time in the course of the disease with a probability of 5-25% the first episode of OHE to occur within 5 years after diagnosis. (42,43)

1.2.1.2 Clinical manifestation

The manifestation of HE shows a great variety of nonspecific neurological and psychiatric features. These neurological impairments may only be determined with psychometric tests. Due to the presence and severity of clinical features a classification into no, minimal and overt HE can be performed. In the case of minimal HE (MHE) patients present with subtle cognitive deficits and seem to be asymptomatic. On the contrary, the onset of disorientation or flapping tremor marks the transition from MHE to OHE. (41,42,44) Asterixis (synonym: flapping tremor) is a neuromuscular impairment and denotes the failure to actively maintain posture, resulting in bilateral but asynchronous flapping motions of outstretched, dorsiflexed hands. Hyperextension of the wrist with splayed fingers is performed to provoke masked flapping tremor. (42) It may also occur in patients with uremia and severe heart failure. In the more progressed course of HE common clinical findings are impairments in reaction time, concentration, memory, sensory abnormalities

and psychomotor dysfunctions. (45) If the disease progresses, patients may develop sleep-wake abnormalities with excessive daytime sleepiness, mood changes characterized by depression or euphoria. Furthermore, consciousness impairments resulting in somnolence, confusion and even coma may occur. (44,46) There are different precipitating events that promote the development of HE, such as gastrointestinal hemorrhage, diuretic overdose, infections or electrolyte disorders. Moreover, a previous history of recent HE is the most meaningful risk factor for the reoccurrence of an HE episode. (43) The clinical features of HE may not be present or do not progress simultaneously, hence staging of disease severity may be challenging. Although all neurological and psychiatric abnormalities of MHE and OHE are believed to be completely reversible, there is evidence that patients with multiple episodes of OHE suffer from persistent impairment in executive function that manifest as working memory and learning disorders. (47)

1.2.1.3 Classification

In 1998 the Hepatic Encephalopathy Consensus Group at the World Congress of Gastroenterology meeting in Vienna for the first time established a standardization of the definition of different syndromes in HE. (48) Following this, a classification according to the underlying disease, the time course, the severity and the presence of precipitating events may be performed. The clinical profile, the therapeutic management and risk of mortality differ according to the stage. HE can either be related to acute liver failure (HE Typ A), major portosystemic shunting without intrinsic liver disease (HE Typ B) or be associated with cirrhosis or portal hypertension (HE Typ C). Typ A is related to high short-term mortality without liver transplantation. The West Haven criteria scale is a semiquantitative grading system, which estimates the severity of HE by assessing behavioral and neurological function (table 3). The scale comprises 4 grades (Grade I-IV) and is considered the standard for the diagnosis of OHE. (42) In due consideration of the severity of neurological impairment, a division into OHE and covert HE (CHE) can be made. CHE is a term introduced to comprise MHE and grade I of OHE. (49)

Table 3 West Haven Criteria (42)

Grade	Clinical features
Grade I	Lack of awareness Euphoria or anxiety Shortened attention span Altered sleep rhythm
Grade II	Lethargy or apathy Personality change Asterixis Dyspraxia Disorientation for time
Grade III	Somnolence to semistupor Responsive to stimuli Confused Disorientation for time, person, place Bizarre behavior
Grade IV	Coma

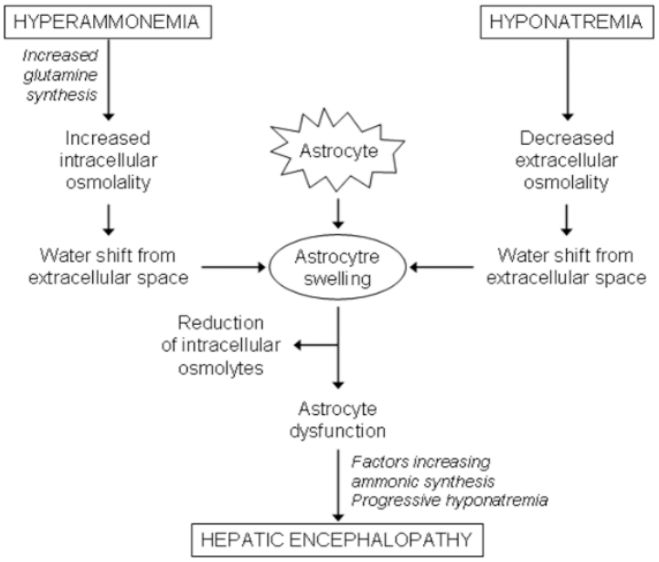
When categorizing by the time course, HE can be described as episodic, recurrent (defined as episodes of HE that occur within a time interval of 6 months or less) and persistent HE (constantly presence of behavioral alterations including episodes of OHE).

1.2.1.4 Pathogenesis

Disorders in normal brain function as a result of hepatic injury represent a wide clinical spectrum caused by functional and morphological impairment of brain cells, brain edema and intracranial hypertension. Although the exact molecular mechanisms of the pathogenesis of HE are unknown, a multifactorial pathogenesis is assumed. One of the main contributors to the development of HE are gut-derived toxins, including ammonia. Furthermore, infections, reactive oxygen species, increased GABAergic (gamma-aminobutyric-acid) neurotransmission and hyponatremia play a role in the pathogenesis of HE. (50) Ammonia is absorbed in the small intestine and transported to the liver where it is converted to urea and excreted by the kidneys. In the case of liver insufficiency, ammonia is not completely metabolized by the liver, gets into the systemic circulation and reaches the brain where it acts as a neurotoxin. Elevated ammonia serum levels may result in

cerebral edema, alterations in neurotransmitter concentrations, astrocytes and neuronal function. (45) Astrocytes eliminate ammonia by amidation of glutamate and producing glutamine. Increased accumulation of osmotic active glutamine results in swelling of astrocytes, cerebral edema and intracranial hypertension. (51) Astrocytes are one of the main constituents of the blood-brain barrier (BBB). Alterations in astrocytic function may therefore induce increased permeability of the BBB allowing more ammonia and other neurotoxins to enter the brain. (52) Furthermore, there is evidence that hyperammonemia induces increased production of reactive oxygen species and nitrogen oxide species resulting in multiple protein and ribonucleic acid (RNA) modifications and alterations in neuronal excitability. (53) Although there is strong evidence that ammonia plays a key role in the pathogenesis of HE, there is not always a consistent correlation between the serum ammonia level and the occurrence of overt symptoms of HE. Consequently, other factors play important roles on the development and progression of HE. Infection and systemic inflammatory response syndrome (SIRS) induce a deterioration of HE by supporting the cerebral effects of ammonia. (45) The observation that grade 3/4 of HE is related to the presence of infection/SIRS and not to the serum level of ammonia in patients with cirrhosis strengthens the importance of infection and inflammation. (54) Hyponatremia as a frequent complication of advanced liver disease contributes to an increase in astrocyte swelling in consequence of reduced extracellular osmolality (figure 2).

Figure 2 Astrocyte swelling due to hyponatremia and hyperammonemia (55)



1.2.1.5 Diagnosis

HE is a diagnosis of exclusion that requires the determination of underlying cirrhosis, acute liver failure or portosystemic shunt combined with any mental impairment or change in psychometric tests. Additionally, other potential causes of HE have to be excluded. The presence of a precipitating event strengthens the diagnosis of HE. The choice of an appropriate diagnostic procedure differs depending on the degree of impairment. (42,50) Clinical scales such as the West Haven criteria scale are used to make the diagnosis of OHE. Nevertheless, other causes of encephalopathy such as uremia, hyponatremia, alcohol abuse, psychiatric diseases or (side-) effects of drugs have to be excluded. The difficulty of making the diagnosis of CHE or MHE is the absence of clinical symptoms. There are psychometric and neurophysiological tests available. Two different of these psychometric and/ or neurophysiological tests should be applied for establishing the diagnosis. Testing for and making the diagnosis of MHE and CHE are of major importance because of the potential development of OHE associated with poor quality of life and prognosis. Blood-ammonia alone is assumed to be inaccurate for establishing the diagnosis, staging or prognosis of HE due to possible absence of correlation between the serum ammonia level and presence of HE. (42,50,51)

1.2.2 Portal hypertension

1.2.2.1 General

Portal hypertension (PH) is a pathological increase in portal pressure and represents a potential life-threatening hallmark of progressive cirrhosis and paves the way to lethal complications such as ascites, HE, hepatorenal syndrome and development/hemorrhage of esophageal varices. Direct measurement of portal pressure is invasive and clinically impractical. Hence, the most commonly used parameter is the hepatic venous pressure gradient (HVPG), which describes the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure. The HVPG represents the gradient between the portal vein and the intra-abdominal portion of the inferior vena cava. The normal HVPG is 1-5mmHg; the presence of a HVPG value ≥6mmHg is defined as portal hypertension. HVPG 6-10mmHg indicates subclinical portal hypertension.

HVPG ≥10mmHg is suggestive for development of complications of PH (e.g. esophageal varices) and it is termed ‘clinically significant portal hypertension‘ (CSPH). Further elevation above 12mmHg indicates the possibility of variceal hemorrhage. (7,50)

1.2.2.2 Pathogenesis

PH results from an increased intrahepatic vascular resistance and in the case of disease progression it is aggravated by an elevated portal-venous blood inflow. In further consequence, collateral blood flow contributes to the development of esophageal varices or portal hypertensive gastropathy. (56,57) The pathological processes inducing an increased intrahepatic resistance include massive structural changes of hepatic stellate cells (HSCs) and liver sinusoidal endothelial cells (LSECs). Besides, increased vascular tone is caused by contraction of vascular smooth muscle cells, myoblasts and HSCs. The functional intrahepatic abnormalities are characterized by decreased production of vasodilators and increased response to endogenous vasoconstrictors. Intrahepatic angiogenesis develops in response to activated LSECs (activated by HSCs themselves), which promote angiopoietin and vascular endothelial growth factor (VEGF) and other angiogenic factors. The proliferation of intrahepatic vessels contributes to the pathologic intrahepatic resistance. (50) As the level of PH increases, portal-collateral circulation develops. The collateral vessels originate from opening, dilatation and hypertrophy of already existing vessels or angiogenesis. The fact that blood from the digestive organs escapes to the collaterals and activates the compensatory increased portal blood flow from the splanchnic circulation. (50,57) The arterial splanchnic and systemic circulatory vasodilatation originates among others from increased production of vasodilators, such as nitric oxide (NO) and vascular hyporesponsiveness to vasoconstrictors. (56)

1.2.2.3 Diagnosis

In early stages of portal hypertension clinical symptoms are usually absent, in the course of disease progression periumbilical collateral veins or palpable splenomegaly may indicate the presence of portal hypertension. Diagnostic steps for evaluating patients with suspected portal hypertension include detection of esophageal varices by endoscopy, assessment of the portal-collateral circulation by imaging and the measurement of portal pressure. (50) Potential imaging modalities include abdominal ultrasound, computed tomography, angiography and magnetic resonance imaging angiography. Portal pressure can be measured directly by catheterization of the portal vein or indirect by hepatic venous catheterization. Due to fewer complications, simplicity and good reproducibility, the indirect measurement is preferred. The hepatic venous pressure gradient (HVPG) is the difference between wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) upon hepatic vein catheterization. Measurement of the HVPG accurately

represents the portal pressure both in alcoholic and viral cirrhosis. (50,58) Since an HVPG level of ≥10mmHg predicts the development of esophageal varices, clinical decompensation and hepatocellular carcinoma, it is used as a prognostic parameter in patients with compensated cirrhosis. (39,40) Moreover, HVPG is used to determine the impact of medical treatment such as beta-blockers. In the case of a decrease in HPVG of ≥20% or a HVPG <12mmHg as a consequence of medical treatment, the risk for development of ascites and variceal hemorrhage is reduced. (59) Medical treatment targets comprise vasoconstriction in the splanchnic circulation on the one hand and vasodilatation of intrahepatic vessels on the other hand. (60) Traditional non-selective beta-blockers (propranolol, nadolol, carvedilol) are used for intrahepatic vasodilatation. Vasoactive drugs (terlipressin, somatostatin, octreotide) are used in the setting of an acute bleeding episode. (61)

1.2.2.4 Complications of portal hypertension

1.2.2.4.1 Esophageal varices

The development and growth of esophageal varices occur in 7% of patients with cirrhosis and no pre-existing varices per year. The risk of first variceal hemorrhage is 12% per year. After the first episode of variceal hemorrhage, the high risk of recurrence within 1 year (60%) and the high 6-week mortality rate (15-20%) indicate the poor prognosis of this complication of cirrhosis. Esophageal varices occur in the course of portal hypertension if the HVPG is ≥10mmHg. Among the portal collateral circulation, esophageal varices have an exceptional position due to the possibility of rupture. Esophageal hemorrhage presents the most frequent lethal complication of cirrhosis. Different clinical events in the course of cirrhosis and portal hypertension are predictors of potential variceal hemorrhage. The presence of ascites, advanced liver failure and a large diameter of varices with a thin wall are related to a high risk of hemorrhage. Furthermore, there are endoscopic features of varices such as ‘red-signs’ acting as predictive factors. Esophagogastroduodenoscopy (EGD) is used for screening, diagnosis and local therapies, such as variceal ligation, sclerotherapy or obturation. (62) The first endoscopic screening for esophageal varices is performed after the diagnosis of cirrhosis. According to size, varices can either be classified as small or large (>5mm). (63) Besides portal pressure, reducing systemic therapies and local endoscopic procedures, surveillance is one of the main cornerstones in the management of all varices due to their high reoccurrence rate. (61–64)

1.2.2.4.2 Ascites in cirrhosis

The term ‘ascites’ (Greek: askos for bag or sack) describes the pathologic fluid accumulation in the abdominal cavity. A variety of diseases may cause ascites in the course of their progression including most frequently cirrhosis, followed by heart failure, malignancy or tuberculosis. It is the most common complication of cirrhosis as a consequence of a HVPG ≥10mmHg. Among patients with compensated cirrhosis approximately 60% develop ascites during 10 years. Once hepatic decompensation with the development of ascites takes place the 1-year mortality rate is 20%. (16) In the course of progressive portal hypertension, splanchnic arterial vasodilatation leads to reduced effective arterial blood flow. At the beginning, a compensatory increase in cardiac output ensures arterial pressure and effective arterial blood volume. In the case of disease progression, compensatory mechanisms can no longer maintain adequate arterial pressure leading to the activation of vasoconstrictor systems. In response to vasoconstrictive and antinatriuretic factors, water and sodium retention in the kidneys is induced. A main mechanism is the increased release of antidiuretic hormone (ADH) (in response to a reduced effective arterial blood flow), resulting in the inability to normally excrete free water and leading to the development of hyponatremia. Consequently, patients who have cirrhosis with ascites typically show urinary sodium retention, increased total body sodium, increased total body water and hypotonic hyponatremia. The increase in free water retention causes excess of extracellular fluid, which mostly accumulates in the peritoneal cavity and in the interstitial tissue mainly of the legs due to high pressure of the capillaries in lower extremities. Storage of extracellular fluid in the peritoneal cavity is caused by portal hypertension that induces high pressure of the splanchnic capillaries. Diagnostic steps include physical examination, abdominal ultrasound, laboratory investigation of liver function and renal function. Furthermore, a diagnostic paracentesis with analysis of the ascitic fluid may be performed upon first presentation to rule out other causes of ascites. The serum-ascites albumin gradient (SAAG) is used to determine whether the ascites is related to portal hypertension or to another cause. A SAAG value ≥1,1g/dL and a total protein concentration of <2,5g/dL indicate that the ascites is caused by portal hypertension with a 97% accuracy. (65,66) Total ascitic fluid protein concentration <1,5g/dL is associated with an increased risk of developing spontaneous bacterial peritonitis (SBP). SBP is a frequently occurring infection in patients with cirrhosis. The prevalence of SBP is 1,5-3,5% in outpatients and 10% in hospital treated patients. Diagnostic paracentesis is performed to confirm a suspected bacterial infection of ascites. Diagnosis of SBP is

verified if the neutrophil count in the ascitic fluid is >250/mm^3. (66,67) Due to clinical features ascites may be classified into uncomplicated ascites or ascites presenting with complications, such as refractory ascites, SBP, hepatorenal syndrome or hyponatremia. Due to the severity of ascites a quantitative grading system (Grade 1 to 3, table 4) is used in patients with uncomplicated ascites. It is determined whether no treatment up to large volume paracentesis combined with restriction of sodium intake and diuretics is necessary. (67,68)

Table 4 Grading of ascites (67)

Grade of ascites	Clinical definition	Treatment
Grade 1	Mild ascites Detectable by ultrasound	No treatment
Grade 2	Moderate ascites Moderate, symmetrical distension of the abdomen	Restriction of sodium intake and diuretics
Grade 3	Large ascites Marked abdominal distension	Large volume paracentesis Restriction of sodium intake and diuretics

The most accurate factors in predicting poor prognosis of patients with ascites are the presence of hyponatremia, low arterial pressure, low urine sodium and increased serum creatinine. The term refractory ascites indicates that ascites does not respond to any medical treatment or reoccurs shortly after large-volume paracentesis. Patients who suffer from refractory ascites may be evaluated for liver transplantation due to a median survival of only 6 months. (50,68)

1.2.2.4.3 Hepatorenal syndrome (HRS)

The hepatorenal syndrome (HRS) is a functional renal failure due to a variety of pathologic conditions in advanced cirrhosis. Other causes of functional or structural renal failure have to be excluded. An average median survival time of only 3 months of patients developing HRS is indicative of the poor prognosis of the condition. (69,70) Two types of HRS can be differentiated due to the clinical course. Type 1 HRS represents as a rapidly progressive acute renal failure with a serum creatinine twice as high than the initial level measured. The level of serum creatinine has to be higher than 2,5mg/dL to meet diagnostic criteria. In contrast, type 2 HRS is characterized by a permanent but moderate impairment of kidney

function. (71) In advanced liver cirrhosis a variety of conditions lead to the development of HRS. Splanchnic arterial vasodilatation and decreased cardiac output lead to effective hypovolemia. As a consequence, a compensatory activation of vasoconstrictor systems such as the renin-angiotensin system, the sympathetic nervous system and ADH take place. These compensatory mechanisms induce intrarenal vasoconstriction and hypoperfusion of the kidneys and contribute to the development of HRS. (70,71) The most common precipitating event in patients with HRS is SBP. The type of HRS and the MELD score are two independent predictive values for the prognosis in patients with HRS. Interestingly, patients with type 1 HRS combined with a high MELD score of ≥20 showed a median survival of only 1 month. In contrast the presence of type 2 HRS indicates better prognosis than in patients with type 1 HRS and the same level of MELD score. (69)

1.2.3 Bacterial infections in cirrhosis

Bacterial infections in cirrhosis are very common, representing one of the most frequent causes of admission and indicate poor prognosis. The pattern of bacterial infections shows regional differences and varying rates of specific infections are reported in the literature. The most common bacterial infections worldwide are spontaneous bacterial peritonitis (SBP) (10-54%), pneumonia/respiratory tract infection (14-21%), urinary tract infection (UTI) (7-41%) and bacteremia related to iatrogenic interventions (4-21%). SBP is the best investigated infection in cirrhosis, whereas other infections are understudied. (20) A number of studies conducted in Europe report the urinary tract to be the leading site of infections, whereas SBP represents a minor percentage. (72,73) Urinary tract infections occur very frequently. There is evidence that the risk of developing an UTI is associated with progressing age rather than the severity of liver disease. (74) Patients with advanced cirrhosis presenting UTI often show or develop additional bacterial infections (in 38%), a circumstance that indicates poor 90-day survival (only 29%). (75) The prevalence of SBP in outpatients without symptoms is reported to be as low as 3,5% or even below that percentage. (76,77) In the case of hospitalized patients, the prevalence increases and ranges from 10 to 30%. (78) Furthermore, in the space of the first year after the first episode, SBP shows a high recurrence rate of 69%. (79) Patients with ascites presenting with pneumonia have the highest risk of mortality among cirrhotic patients with bacterial infections. (80) The increased mortality of cirrhosis and bacterial infections is related to the potential development of infection-related complications such as HE, gastrointestinal hemorrhage, renal failure or Acute-on-Chronic-Liver-Failure (ACLF). Infections lead to hospital admission in patients with cirrhosis in 30 to 50%. Additionally, nosocomial infections

develop in 15 to 35% of patients with cirrhosis during hospitalization in contrast to 5 to 7% of patients without cirrhosis. There is strong evidence that the presence of infection in cirrhosis significantly increase mortality rates, with 30% of patients who die after infections in the period of 1 month and again 30% die within 1 year. A variety of mechanisms contribute to the pathogenesis of bacterial infections in cirrhosis. The main mechanisms are immune dysfunction, impaired gut microflora, increased intestinal permeability for bacteria and genetic predisposition. (81) The immune deficiency syndrome in cirrhosis is characterized by reduced circulating immune cells except monocytes, impaired function of leukocytes and compromised function of T-lymphocytes. (9,18,19) Bacterial infection may cause acute decompensation in patients with cirrhosis or occur as the most frequent precipitating event (in 33%) of ACLF. Recently, the extension of the staging system of compensated and decompensated cirrhosis has been proposed, by introducing a stage 5 for infections and renal failure. (35,36) Since bacterial infection indicates high mortality rates, there is a strong need for early detection and infection treatment. It is recommended to perform a diagnostic-workup to detect infections in every patient with cirrhosis admitted to the hospital or in case of deterioration in hospitalized patients. (73) Making diagnosis of an existing infection in cirrhosis may be tough. Different clinical and laboratory parameters as well as microbiological testing are used for the diagnosis of bacterial infections. Infection is responsible for a systemic host response, which is classified into 3 stages of different severity. The first stage is termed sepsis, the second severe sepsis (in the case of acute organ failure) and the third septic shock with hypotension that is unresponsive to proper fluid substitution. (82) The systemic inflammatory response syndrome (SIRS) in cirrhosis may be caused by infection or non-infectious condition. Sepsis is defined by the presence of two or more criteria of SIRS and infection. Criteria of the SIRS include a core temperature ≥38°C or ≤36°C, a heart rate ≥90beats/min, tachypnea with ≥20breaths/min or an arterial partial pressure of carbon dioxide ($PaCO_2$) ≤32mmHg and a leukocyte count ≥$12x10^9$/L or ≤$4x10^9$/L or immature neutrophils of >10%. (83) Nevertheless, determination of SIRS shows poor accuracy in predicting bacterial infection. On the one hand not all patients with cirrhosis and infection meet diagnostic criteria of SIRS and on the other hand there are patients with cirrhosis but without infection who fulfill the SIRS criteria. (82) Patients with cirrhosis often present with tachycardia due to hyperdynamic circulation or bradycardia related to medical treatment. Furthermore, HE is associated with tachypnea and hypersplenism that induce reduction in leukocyte count. All these clinical features may misrepresent the systemic

inflammatory response of patients with cirrhosis. (81) Another difficulty in diagnosis of infection in cirrhosis is the fact that only 50-70% of infections are culture positive. In recent years there is strong evidence that a variety of laboratory parameters that are used for the diagnosis of infection are also accurate in predicting infection and mortality in patients with cirrhosis. These laboratory parameters include blood neutrophil-to-lymphocyte ratio (NLR), eosinophil count, mean platelet volume (MPV), lipopolysaccharide-binding protein (LBP) or sCD14. (84–87) Among acute-phase serum proteins C-reactive protein (CRP) and procalcitonin (PCT) are commonly applied early parameters of infection. Although there is evidence that these parameters may be decreased in patients with cirrhosis, they have predictive value of sepsis severity and progression. CRP has found to be an independent predictive value of high short-term mortality in patients with cirrhosis and CTP score ≥8. (88)

1.2.4 Hematologic abnormalities

Hematologic abnormalities in cirrhosis comprise both impairment in corpuscular blood components and coagulopathies. Several complications of cirrhosis such as gastrointestinal hemorrhage or infection are in some extent caused by hematological abnormalities. The most common hematologic abnormalities in patients with cirrhosis are thrombocytopenia and a decrease in coagulation factors. In the course of advanced chronic liver disease (CLD) thrombocytopenia, leukopenia or anemia may occur. Hypersplenism is the pathologic condition of increased sequestration and destruction of platelets, white blood cells and red blood cells due to portal hypertension. A decrease of intrahepatic production of thrombopoietin combined with hypersplenism is the main contributive factor to thrombocytopenia. In patients with advanced cirrhosis chronic gastrointestinal hemorrhage combined with a decreased response to erythropoietin is related to anemia. A variety of conditions such as alcohol and viral hepatitis C and B in cirrhosis induce bone marrow suppression, which in turn causes pancytopenia. (89) Furthermore, patients with a CLD show disorders in the synthesis of all coagulation factors. (50) In contrast, the levels of ‘von Willebrand factor’ (vWF) and factor VIII are elevated. (90,91) Historically, the decrease in procoagulants was believed to be responsible for the risk of gastrointestinal hemorrhage. However, there is now strong evidence that not only procoagulant factors, but also anticoagulant factors such as protein C, antithrombin and tissue factor pathway inhibitor are decreased in equal measure. Hence, the role of hematologic abnormalities as a cause of gastrointestinal and variceal hemorrhage might have been overestimated. Due to an unstable and not always complete equal decrease of pro- and anticoagulant factors as

well as thrombocytopenia in advanced liver disease both gastrointestinal hemorrhage and portal vein thrombosis may be triggered. (92) Global tests such as the international normalized ratio (INR), or the activated partial thromboplastin time (aPTT) test were originally designed for vitamin K antagonist induced coagulopathy. As a consequence, the INR shows a decrease in procoagulants, but not in anticoagulant factors occurring in the course of advanced chronic liver disease. (50) Another consistent observation is that the INR and aPTT poorly represent hemorrhage after liver biopsy. (93) These findings suggest that INR is not a reliable prognostic parameter for hemorrhage in cirrhosis. Other potential mechanisms associated with hemorrhage are hemodynamic alterations in the course of renal failure, bacterial infection and endothelial dysfunction. Nevertheless, the INR is a part of the MELD score used to prioritize patients awaiting liver transplantation. As the coagulopathies of CLD differ from those resulting from vitamin K antagonists, the estimate of severity of hematologic impairment may be inappropriate. Thus, the predictive value of the MELD score may be negatively influenced. (94)

1.2.5 Hepatocellular carcinoma (HCC)

Primary liver cancer represents the fifth most frequent neoplasm in men and ninth most frequent in women worldwide. Furthermore, it is the second most common cause of cancer-related death. (95) Underlying chronic liver disease (CLD) can be found in more than 80% of patients developing HCC and it is the leading cause of death in cirrhosis. (96) The incidence of HCC is associated with the etiology of the underlying liver disease and it is the highest in cirrhosis caused by viral hepatitis C or B. (97) Chronic HBV infection represents the most important risk factor for HCC worldwide, but in Europe HCV infection and alcohol abuse are the leading hazard factors. (98,99) A variety of genetic changes contribute to the multifactorial pathogenesis. (50,100) In the majority of cases, clinical features are similar to those of the underlying CLD. In more advanced stages of HCC, symptoms such as weight loss, anorexia or abdominal pain may be present. (50) Patients with the diagnosis of HCC at an early, asymptomatic stage and adequate treatment have a 5-year survival rate of more than 50%, whereas the 5-year survival rate in patients with an advanced stage is 0 to 10%. Therefore, surveillance is a cornerstone in disease management. It is performed in patients both with cirrhosis who get an adequate treatment in the case of the diagnosis HCC and in the case of HBV infection without cirrhosis. Screening with ultrasound every 6 months is recommended by the American Association for the Study of Liver Disease (AASLD). (101) In contrast to patients with Child-Turcotte-

Pugh score (CTP) A and B, those with a CTP score of C should receive liver transplantation. (50) The diagnostic algorithm in the case of a lesion or clinical symptoms suspicious for HCC includes MRI, CT and liver biopsy if necessary. (102) These procedures are also used for the staging of HCC. Determination of the prognosis of a patient with HCC is crucial for disease management. In recent years many different staging systems have been developed, which attempt to encompass tumor stage, severity of liver function disorders and cancer-related symptoms. (103) The European Association for the Study of the Liver (EASL) currently suggests the Barcelona Clinic Liver Cancer (BCLC) system which both predicts prognosis and links staging with a treatment recommendation. (104) The BCLC system comprises 5 stages and for the assessment of liver function the CTP score is used. (100,105)

1.2.6 Prognostic scoring systems in decompensated cirrhosis

1.2.6.1 Child-Turcotte-Pugh (CTP) score

In 1964 the Child-Turcotte (CT) score was initially developed and modified in 1973 from Pugh et al. and named Child-Turcotte-Pugh (CTP) score. These original models were used in the limited setting for the evaluation of surgery of portal hypertension (portocaval shunting). (106) The Child-Turcotte-Pugh (CTP) score then became a common used and validated predictor of long-term survival and disease severity in cirrhosis. The score comprises 3 objective laboratory variables (total serum bilirubin, serum albumin and the prothrombin time) and 2 subjective clinical variables (ascites and hepatic encephalopathy). (107)

Table 5 Child-Turcotte-Pugh scoring system for liver cirrhosis (107)

Variable	1 point	2 points	3 points
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3,5	3,5-2,8	<2,8
Prothrombin time (INR)	<1,7	1,7-2,3	>2,3
Ascites	Absent	Mild	Severe
Encephalopathy	Absent	Grade 1 to 2	Grade 3 to 4

Table 5 shows the modified Child-Turcotte-Pugh score for the severity of liver disease according to the degree of the 5 variables. Class A comprises a total CTP score of 5 to 6 points (well-compensated disease), Class B includes 7 to 9 points (significant functional

compromise) and Class C comprises 10 to 15 points (decompensated disease). The different classes correlate with one-year patients' survival. One-year survival rate for cirrhotic patients with a CTP score A is 100%, with a CTP score B it is 80% and for patients with CTP score C the one-year survival rate is 45%. (107) In patients with decompensated cirrhosis, the CTP score is still among the most accurate predictors of death, because even subtle abnormalities in the laboratory variables are predictive for death. Nevertheless, without including parameters of renal dysfunction, the CTP score was replaced by the MELD score for prioritizing liver donor allocation. (16) Critically, one of the model's main weaknesses is that it does not include variables reflecting other organ dysfunctions, which are known to contribute to mortality rates in critically ill cirrhotic patients. (108) The CTP score is considered to be less reproducible compared with the MELD score due to 2 subjective variables (ascites and hepatic encephalopathy).

1.2.6.2 Model for End-stage Liver Disease (MELD) score

The Model for End-stage Liver Disease (MELD) score is a prospectively developed and validated scoring system for the severity and three-month mortality of liver disease. In 2000 the Mayo End-Stage Liver Disease (MELD) score was initially developed to predict mortality in patients with cirrhosis following transjugular intrahepatic portosystemic stent shunt (TIPSS) placement. (109,110) The United Network for Organ Sharing (UNOS) found the MELD score to be superior to the CTP score and decided in 2002 to use the MELD score for prioritization of patients awaiting liver transplantation. The Eurotransplant Board implemented in 2003 the MELD score for liver allocation in Europe. (111) The original model was based on serum bilirubin (mg/dL), serum creatinine (mg/dL), the international normalized ratio (INR) and the etiology of the liver disease (cholestatic or alcoholic versus other etiologies). (109) After modification of the MELD score, the etiology of liver disease was subsequently excluded due to causing difficulties such as how to categorize patients with multiple causes of liver disease. (111,112) The formula of the initial MELD score is:

'$MELD_{(i)}$ = 9,57 * Log_e(serum creatinine) + 3,78 * Log_e(total serum bilirubin) + 11,2 * Log_e(INR) + 6,43' (112)

The Organ Procurement and Transplantation Network (OPTN) stated a policy change for the use of the MELD scoring system related to organ allocation that is in use since January

2016. First, the traditional MELD score (called initial MELD ($MELD_{(i)}$)) is calculated. If the initial $MELD_{(i)}$ score is 11 or more, the MELD score is re-calculated, incorporating the serum sodium (Na) value this time. (113) The formula is:

'MELD = MELD(i) + 1.32 * (137 – Na) – [0.033 * MELD(i) * (137 – Na)]' (113)

In the case of sodium values lower than 125mmol/L, 125 is used for the calculation, and for values greater than 137mmol/L a maximum value of 137 is used. (113)

Total points range from 6 to 40. To avoid negative scores, laboratory values such as serum bilirubin levels that are less than 1mg/dL are rounded up to 1. If the patient has been dialyzed twice within the last seven days, serum creatinine automatically counts 4 points. In proportion to the increase in the MELD score, the risk of three-month mortality increases (table 6). (114)

Table 6 3-month mortality rate according to the MELD score (111)

MELD score	Mortality rate
40 or more	71,3%
30-39	52,6%
20-29	19,6%
10-19	6%
<9	1,9%

The MELD score is considered more reproducible than the CTP score because it does not include subjective variables such as ascites or HE. (16) As predictors of death are different in patients with compensated or decompensated cirrhosis, the MELD score (as a marker for liver and circulatory dysfunction) is a strong predictor of the decompensated stage of cirrhosis. Laboratory variables of the MELD score reflect renal dysfunction, which is caused by liver insufficiency and hemodynamic factors at advanced stages of cirrhosis. (37) Hyponatremia is linked to impaired renal function induced by hemodynamic abnormalities that develop in advanced cirrhosis and implies an increased incidence of complications and a high mortality rate. (115,116) Therefore the implication of sodium is of importance for adequate assessment of the prognosis. Nevertheless, applying the score requires computing and is less practical than the CTP score for individual estimates at the

bedside. (117) One of the main limitations of the MELD score is the underweighting of complications of portal hypertension such as ascites, hepatic encephalopathy, variceal hemorrhage, hepatorenal syndrome, severe malnutrition and bacterial infections. All these complications are associated with a poor prognosis in advanced cirrhosis, however the variables included in the score are not necessarily influenced by these complications. (116) To predict survival in patients with compensated cirrhosis, the MELD score does not seem to be useful, as the laboratory variables only increase with decompensation and significant disease progression. (37) Calculating the MELD score during an acute, but potentially reversible, complication, such as bacterial infection, acute renal failure or gastrointestinal hemorrhage may not accurately predict short-term mortality. (116) Furthermore, initially low MELD score combined with early mortality in patients with cirrhosis strengthens the need for accurate predictors to identify patients with cirrhosis and low MELD score who are at risk of rapid clinical disease deterioration. (73)

1.3 Acute-on-chronic-liver-failure (ACLF)

1.3.1 General

Acute-on-Chronic-Liver-Failure (ACLF) as a frequent syndrome has a prevalence of 30%. (118) The term ACLF was initiated in 1995 for the description of the simultaneous appearance of a chronic underlying liver disease and an acute liver failure. (119) ACLF as an increasingly recognized and life-threatening syndrome strengthened the need for a clear and uniform definition. In 2009 two consensus working definitions were proposed to try to comprise the main characteristics of this syndrome. The first one was established by the Asia-Pacific Association for the Study of the Liver (APASL): 'Acute hepatic insult manifesting as jaundice (serum bilirubin ≥5mg/dL) and coagulopathy (INR ≥1,5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.' (119) The second was decided by the EASL and AASLD: ' Acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure'. (120) As all these definitions are very vague Moreau et al. established diagnostic criteria based on the main characteristics of the syndrome. (18) ACLF occurs most often in young individuals, 30% of hospitalized cirrhotic patients are affected, it is associated with a 28-day mortality rate of 33% and it differs from solitary decompensation of cirrhosis. (18)

1.3.2 Clinical manifestation

The clinical cornerstones of ACLF are acute decompensation (AD) of the patient's liver cirrhosis, presence of organ failure(s) and a high 28-day mortality rate.

There may occur precipitating events directly causing liver injury (alcoholic hepatitis, drug-induced liver injury, superimposed viral hepatitis or portal vein thrombosis), leading to ACLF. (121) Besides, extrahepatic events such as trauma, surgery, variceal hemorrhage or infection often precipitate AD of cirrhosis. Interestingly, in a considerable proportion (43%) no precipitating event could be found. Furthermore, no association between different events or the presence of an event and mortality could be determined. (18) Precipitating events may lead to ACLF by inducing an altered host response to injury that finally causes SIRS predisposing for infection itself. (121,122) The presence and persistence of SIRS is associated with poor outcome in patients with advanced cirrhosis. (123) It is assumed that inflammation in patients with cirrhosis leads to hemodynamic dysregulation resulting in deterioration of portal hypertension and reduced hepatic blood flow. (122) Bacterial infection is a frequent feature in the course of ACLF with an in-hospital mortality rate of 15% (twice as high as in cirrhotic patients with no infection). (121) While SIRS increases predisposition to infection, initial existing infection induce abnormally enhanced pro-inflammatory response that may result in SIRS as well. (122) Sepsis in cirrhotic patients represents a frequent precipitating event inducing HE, renal dysfunction and variceal hemorrhage. (121) The development of organ failure due to sepsis and sepsis related death in patients with cirrhosis is characterized by an abnormal enhanced cytokine production resulting in organ damaging inflammation. (124) Moreau et al. have observed evidence that the leukocyte count and C-reactive protein (CRP) levels were higher in patients with simultaneous existing ACLF than in patients without. However, high leukocyte counts and CRP levels were also measured in patients with ACLF without bacterial infection. (18) In more than in a half of the diagnosis ACLF no prior history of AD was reported or the syndrome developed short after (less than 3 weeks) the AD. This fact strengthens the hypothesis that ACLF is a dynamic syndrome with both the potential to improve and deteriorate. Multiple organ failure seems to be the main cause of death. (18)

1.3.3 ACLF grades

ACLF based on high mortality rate, presence of organ failure(s), systemic inflammation and trigger events is a distinct syndrome developing in cirrhotic patients with acute decompensation. In 2013 Moreau et al. defined the diagnostic criteria for ACLF in the prospective CANONIC study. Diagnostic criteria are reflect the 3 major characteristics of the syndrome: acute decompensation (AD) of liver cirrhosis, presence of organ failure(s) and high 28-day mortality rate (threshold of 15%). Pathophysiological mechanisms contributing to the syndrome are inflammation and immune failure. The 28-day mortality rate is 14,6% in patients with only one organ failure. (18) AD is defined by the development of complications of portal hypertension and/or liver dysfunction (ascites, HE, gastrointestinal bleeding and bacterial infection). (16,18,37)

For determination of organ failure, the Chronic LIver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score is used (table 7). This is an adaptation of the sepsis organ failure assessment (SOFA) score, which is frequently used in intensive care units. (125) The CLIF-SOFA incorporates subscores ranging from 0 to 4 for each of the 6 comprised organ systems (liver, kidneys, brain, coagulation, circulation and lungs). Total points range from 0 to 24 points and the text in bold points out the diagnostic criteria for organ failure. An increase in the CLIF-SOFA score implies more severe organ impairment. (18)

Table 7 CLIF-SOFA Score (18)

Organ system	0	1	2	3	4
Liver (bilirubin, mg/dL)	<1,2	≥1,2 to ≤2,0	≥2,0 to <6,0	≥6,0 to ≤12,0	**≥12**
Kidney (creatinine, mg/dL)	<1,2	≥1,2 to <2,0	**≥2,0 to <3,5 ***	**≥3,5 to <5,0 ***	**≥5,0 ***
Cerebral	No HE	I	II	**III**	**IV**
Coagulation (INR)	<1,1	≥1,1 to <1,25	≥1,25 to <1,5	≥1,5 to <2,5	**≥2,5 or platelet count ≤20x10^9/L**
Circulation (mean arterial pressure, mmHg)	≥70	<70	**Dopamine ≤5 or dobutamine or terlipressin**	**Dopamine >5 or E ≤0,1 or NE ≤0,1**	**Dopamine >15 or E >0,1or NE >0,1**
Lungs					
PaO_2/FiO_2 or	>400	>300 to ≤400	>200 to ≤300	**>100 to ≤200**	**≤100**
SpO_2/FiO_2	>512	>357 to ≤512	>214 to ≤357	**>89 to ≤214**	**≤89**

*** or use of renal replacement therapy**; HE, hepatic encephalopathy; E, epinephrine; NE norepinephrine; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; SpO_2, pulse oxymetric saturation

Based on the number of organ failure(s) additional to present AD, 4 subgroups with different 28-day and 90-day mortality rates can be defined. One of the prognostic indicators of a high mortality rate is the type of organ failure as it is reflected in the subgroup 'patients with a non-kidney organ failure' in the group 'No ACLF'. The mortality rate is higher than 15% in patients with kidney failure in comparison to patients with a single non-kidney failure where it is less than 15%. These findings imply that a single liver failure is expendable for the diagnosis ACLF. Furthermore 2 or more organ failures predict a high 28-day mortality rate as well as high serum creatinine or HE (grade I or II) combined with a non-kidney failure. (18)

1. No ACLF

This group incorporates 3 subgroups: (1) patients with no organ failure, (2) patients with a single 'non-kidney' organ failure who had a serum creatinine level <1,5mg/dL and no hepatic encephalopathy, and (3) patients with single cerebral failure who had a serum creatinine level <1,5mg/dL. The 28-day and 90-day mortality rates are 4,7% and 14% in this group of patients. (18)

2. ACLF grade 1

This group incorporates 3 subgroups: (1) patients with single kidney failure, (2) patients with single failure of the liver, coagulation, circulation, or lungs with a serum creatinine level ranging from 1,5 to 1,9mg/dL and/or mild to moderate hepatic encephalopathy, and (3) patients with single cerebral failure with a serum creatinine level ranging from 1,5 and 1,9mg/dL. The 28-day and 90-day mortality rates are 22,1% and 40,7% in this group. (18)

3. ACLF grade 2

This group comprises patients with 2 organ failures. The 28-day and 90-day mortality rates are 32% and 52,3%, respectively. (18)

4. ACLF grade 3

This group comprises patients with 3 organ failures or more. The 28-day and 90-day mortality rates are 76,7% and 79,1%, respectively. (18)

Independent risk factors for the development of ACLF, associated with high mortality rate in patients with AD are a high CLIF-SOFA score, ascites and the degree of inflammatory reaction. (16,18) The probability of death is related to high leukocyte count used for the estimation of severity of inflammatory reactions. On the other hand, the cause of inflammation has no predictive value for the mortality associated with ACLF. (18)

In comparison to other frequent used prognostic scores, the CLIF-SOFA score showed slightly superior accuracy to the CTP and similar accuracy to the MELD score in predicting 28-day mortality. (18) A modified version of the CLIF-SOFA score for the diagnosis and grading of ACLF was established by the European Association for the Study of the Liver (EASL). The simplified CLIF Consortium Organ Function (CLIF-C OF) score (table 8) comprises 3 subscores for each organ system correlating with the risk of dying at 28-days.

Total points range from 6 to 18 and the text in bold defines diagnostic criteria of organ failure. Though, the score allows a simple stratification of patients with clinical and prognostic significance, predictive accuracy is not superior to the original CLIF-SOFA score. (118)

Table 8 The CLIF Consortium Organ Function (CLIF-C OF) score (118)

Organ system	1	2	3
Liver (bilirubin, mg/dL)	<6	≥6 and<12	**≥12**
Kidney (creatinine, mg/dL)	<2	**≥2 and <3,5**	**≥3,5 or renal replacement**
Cerebral (West-Haven Grade for HE)	Grade 0	Grade I-II	**Grade III-IV***
Coagulation (INR)	<2,0	≥2,0 and <2,5	**≥2,5**
Circulation (mean arterial pressure, mmHg)	≥70	<70	**Use of vasopressor**
Lungs			
PaO_2/FiO_2 or	>300	≤300 and >200	**≤200****
SpO_2/FiO_2	>357	>214 and ≤357	**≤214****

* Patients with the need of mechanical ventilation because of HE were considered as having a cerebral failure, not respiratory failure
** Patients with mechanical ventilation are considered as presenting a respiratory failure

The Chronic LIver Failure - Consortium - ACLF (CLIF-C-ACLF) score is a specific prognostic score for patients presenting with ACLF developed by combining the CLIF-C-OF score with the two variables age and white blood cell count (WBC) aimed to improve the predictive value of the frequent used scores. Total points range from 0 to 100, which predict the mortality with a high accuracy. (118,123)

'CLIF-C-ACLF score = 10x (0,33x CLIF-C-OFs + 0,04x Age + 0,63x ln(WBC count) - 2)' (118)

The cut-off value of 40 points or lower implies a 90% negative predictive value and 97% sensitivity, whereas a value of 60 or higher indicates an 82% positive predictive value and 94% specificity.

The CLIF-C-ACLF score is superior in predicting short-term and long-term mortality to the frequent used MELD score, CTP score as well as to original CLIF-SOFA and CLIF-C-OF score.

2 Material and methods

2.1 Hypothesis and aims

Accurate assessment of disease severity and prognosis in patients with decompensated cirrhosis is crucial for establishing an optimal therapeutic strategy. A simple risk stratification system that takes into account several laboratory and clinical parameters to estimate the prognosis in patients with decompensated cirrhosis should assist with therapeutic management and decision making for organ allocation.

Findings in recent studies show that mortality in decompensated cirrhosis is not mainly dependent on isolated liver failure but rather on precipitating events and organ failure/s superimposed on liver impairment. (18) Furthermore, the presence of SIRS (with or without bacterial infection) is considered to have important prognostic relevance. It indicates an increase in mortality, complications of portal hypertension and HE in cirrhotic patients with or without renal impairment. (122,123,126) On the one hand SIRS may induce immune dysregulation contributing to the development of infection. On the other hand, occurring infection may cause a pro-inflammatory response leading to SIRS. (123,127) The widely used CTP and MELD scores neither incorporate parameters representing multi-organ failure nor parameters reflecting SIRS. Crucially, in cirrhotic patients with low CTP and MELD scores presenting with organ failure/s alongside the liver or SIRS, disease severity may therefore be underestimated. (122,123,126) Considering the importance of SIRS and extrahepatic organ failure/s it is important to include parameters reflecting these events in prognostic models. In recent studies, surrogate parameters of infection/inflammation in cirrhosis were proposed to have prognostic significance (84–87,128,129). Within these parameters, there is strong evidence that CRP is an appropriate marker reflecting SIRS and predicts short-term and long-term mortality in patients with cirrhosis. (88,126) There is evidence that increased levels of CRP without the presence of SIRS indicates poor prognosis as well. In patients who do not meet the criteria for SIRS it has been proposed that CRP may act as a sensitive marker for hidden systemic inflammation, which can not be detected by clinical SIRS criteria. (18,88)

It is of importance that the risk stratification system shows some main characteristics. For the application in clinical setting, the different parameters considered have to be diagnostically conclusive, easily and inexpensive to obtain. Therefore, we only included routine laboratory parameters measured upon admission of patients presenting with decompensated cirrhosis. Subjective clinical features, such as ascites and HE should be

avoided due to subjectivity and reproducibility concerns. The risk stratification system has to be based on complications and organ systems most predictive for short-term and long-term mortality. Different cut-off levels have to predict the mortality rate and be associated with a recommendation on how to proceed regarding patient therapeutic management. Additionally, the stratification system should present an improved predictive accuracy compared to already existing prognostic scores.

In the present study, the aim is to propose a simple risk stratification system for the mortality in patients who were admitted to the hospital due to decompensated cirrhosis. Therefore, a variety of laboratory and clinical parameters were evaluated in order to determine their predictive value for mortality.

2.2 Study design

This is a retrospective single-center prognosis study carried out at the Medical University of Graz. The study includes 165 patients. By the use of a database research in the time interval from January 2008 to December 2011 we retrospectively enrolled patients who were admitted to the hospital due to acute decompensation of their underlying liver cirrhosis. The study was conducted in due consideration of the Declaration of Helsinki and the study protocol was acknowledged by the ethical review committee of the Medical University of Graz. The ethical commission of the Medical University in Graz consented to the study protocol (reference number: 23-285 ex 10/11).

2.3 Study population

The term ‘liver cirrhosis’ was used on the electronic database of the hospital (MEDOCS) to identify medical records of patients who were admitted to a Department of Internal Medicine or an Intensive Care Unit (ICU) between January 2008 and December 2011. We investigated the medical records of all patients with cirrhosis found by the database search. Patients were admitted to a Department of Internal Medicine or a medical ICU according to disease severity. Only those patients presenting with acute decompensation of their liver cirrhosis were considered for further investigations and data collection. The inclusion of a patient was independent of the etiology of cirrhosis or the different manifestations of acute decompensation (gastrointestinal hemorrhage, ascites, jaundice, HE, hepatorenal syndrome, infection or combinations).

2.3.1 Inclusion criteria

- men and women aged between 18 and 80 years
- established diagnosis of liver cirrhosis
- hospital admission due to acute decompensation of liver cirrhosis

2.3.2 Exclusion criteria

- elective hospital admission of cirrhotic patients
- patients with a previous liver transplant
- missing clinical or laboratory data
- malignant neoplasm of any origin (e.g. hepatocellular carcinoma)

2.4 Clinical data and laboratory parameters

All data presented here reflect the situation upon hospital admission unless stated otherwise. The following data were collected from patients: sex, age, height, weight, body mass index (BMI), blood pressure, heart rate, breathing rate and body temperature. Furthermore, the presence and grade of HE, ascites and the score of the Glasgow Coma Scale (GCS) were of particular interest. The severity of ascites was graded as mild (grade 1), moderate (grade 2) or large (grade 3). The grading system used for the severity of HE comprises 4 grades, with grade 4 being defined as 'coma due to HE'. The type of acute decompensation of cirrhosis and the etiology of cirrhosis were evaluated. The presence of esophageal varices was determined. The clinical data were collected from medical records upon admission. Laboratory data were collected from the laboratory investigations performed at hospital admission. Laboratory parameters required include platelet count, neutrophil count, lymphocyte count, eosinophil count, neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV), total serum bilirubin, creatinine, INR, albumin and CRP. The CTP score, MELD score and the presence of SIRS were determined using the clinical and laboratory parameters upon admission. According to the presence and number of organ failures every patient was retrospectively classified into the ACLF grades 0 to 3. The CLIF-SOFA score was used to determine the presence and severity of organ failure/s. The primary endpoint is both death and liver transplantation after hospital admission.

2.5 Evaluation of the presence of infection

Due to the fact that infection in patients with cirrhosis indicates poor prognosis, the presence of infection was of particular interest. Microbiological diagnostic workup was performed at the Laboratory for Clinical Microbiology, Department of Internal Medicine, Medical University of Graz. We investigated the microbiological results comprising central and peripheral blood cultures (aerobic and anaerobic), urine cultures, stool cultures, ascitic fluid analyses and bronchoalveolar lavage cultures. In order to diagnose thoracic infections, thoracic radiography and/ or CT were used. Infections were diagnosed by the microbiological proof of a pathologic amount of bacteria, fungi, viruses or other microorganisms in a body site. After reviewing medical records, all infections were identified and documented. Infections were classified into community acquired (infection diagnosed from day 0 to 2 of hospitalization) or hospital acquired (infection diagnosed at day 3 of hospitalization or later). Infections with different microorganisms at different body sites diagnosed simultaneously were considered as independent infections. An infectious disease consultant re-evaluated all microbiological tests and medical records concerning infection.

2.6 Statistical analyses

Metric variables are expressed as mean ± standard deviation (SD); categorical variables are displayed as numbers (n) and percentage (%). In dual group analyses, groups showing a normal distribution were compared with an independent t-test and the Mann-Whitney test was performed if groups did not show a normal distribution. The chi-squared test or Fisher's exact test was conducted in the case of categorical variables. Diagnostic accuracy of scoring systems or laboratory parameters was assessed by the calculation of Receiver Operating Characteristics (ROC) and the Area Under the Receiver Operating Characteristics (AUROC). Table 9 displays different cut-off values of the AUROC indicating if the parameters or scoring systems tested show excellent, good, fair or poor results. (130) The Youden's index (Y= sensitivity + specificity - 1) was used to calculate the best diagnostic cut-off values. Binary logistic regression analysis was calculated to analyze potential mortality variables.

Table 9 Cut-off values of the AUROC related to test performance

AUROC	Test performance
0,9-1	excellent
0,8-0,9	good
0,7-0,8	fair
0,6-0,7	poor
0,5-0,6	fail

AUROC, Area Under Receiver Operating Characteristics

Potential variables for the prediction of the mortality included in the multivariate logistic regression analyses were as follows:

- Sex
- Age
- BMI
- Platelet count
- Neutrophil count
- Lymphocyte count
- Eosinophil count
- Neutrophil to lymphocyte ratio (NLR)
- Mean platelet volume (MPV)
- Albumin
- C-reactive protein (CRP)
- ACLF grade 0 to 3
- MELD score
- CTP score
- Infection upon hospital admission
- Systemic inflammatory response syndrome (SIRS)

Before the potential variables were entered in binary logistic regression analysis, the correlation between the different variables was determined. Parameters showing a Spearman's coefficient <0,5 were assumed to have a low correlation and thus entered in logistic regression analysis. In an attempt to define independent predictors for short-term (at day 30 and day 90) and long-term mortality (at 1 year) univariate and multivariate

analyses (with backward and forward elimination of variables, exclusion at p=0,10; maximum iterations: 20) of potential variables were conducted. All variables that were related to short-term or long-term mortality with a statistical significance in multivariate analyses were entered into univariate logistic regression analyses in order to determine the explained variance for each variable by using the Nagelkerke R squared. Tests were performed at a 5% significance level ($p \leq 0,05$). Results with a $p \leq 0,05$ are defined as statistically significant, those with a $p \leq 0,01$ as high significant and those with a $p \leq 0,001$ as highest significant. Statistical analyses were conducted using the SPSS 22 software (IBM® Corporation, USA).

3 Results

3.1 Study population

165 cirrhotic patients met the inclusion criteria, representing 44 women (27%) and 121 men (73%) with an age ranging from 26 to 80 and a mean age of 56 ± 12. Table 10 shows the clinical characteristics, scoring systems, mortality rates at different endpoints and the infectiological evaluation. The laboratory parameters upon admission are displayed in table 11. 115 patients (70%) were primarily referred to a Department of Internal Medicine, whereas 50 patients (30%) were hospitalized at the Intensive Care Unit. The disease severity determined by the CTP score and MELD score was significantly worse in patients admitted to the ICU than in patients initially admitted to the general ward (Child-Pugh score: 11 vs. 10; MELD score: 22 vs. 20; p=0,044; p=0,046). The most frequent etiology of cirrhosis was chronic alcohol consumption (n=147; 89%). The main types of decompensation in descending order were as follows: ascites (n=63; 38%), upper gastrointestinal bleeding (n=47; 29%), alcoholic steatohepatitis (n=17; 10%), acute kidney injury (n=17; 10%), HE (n=10; 6%) and bacterial infection (n=7; 4%). According to the CTP score, the study population was categorized into class A (n=5; 3%), B (n=59; 36%) and C (n=101; 61%). ACLF according to the definition of Moreau et al. was seen in 50 patients (30%). 22 patients (13%) presented with ACLF grade 1, 12 patients (7%) with grade 2 and 16 patients (10%) presented with grade 3. As evidenced by microbiological tests 28 patients (17%) showed an infection upon hospital admission and 33 patients (20%) developed an infection during hospitalization. In total, any kind of infection was diagnosed in 52 patients (32%), the most common infections were urinary tract infection (n=24; 15%), followed by bacteremia (n=21; 13%), pneumonia (n=12; 7%), gastrointestinal infection (n=6; 4%) and spontaneous bacterial peritonitis (n=5; 3%). In 18 patients (11%) more than one type of infection was diagnosed.

Table 10 Clinical and laboratory characteristics of 165 patients

Characteristics		
Age	yrs	56 ± 12
Sex (female/male)	n (%)	44 (27)/ 121(73)
BMI	kg/m^2	26 ± 5
Etiology of cirrhosis		
Alcohol	n (%)	147 (89)
Chronic hepatitis C (CHC)	n (%)	15 (9)
Unknown	n (%)	3 (2)
Type of decompensation		
Ascites	n (%)	63 (38)
Upper gastrointestinal bleeding	n (%)	47 (29)
Alcoholic steatohepatitis	n (%)	17 (10)
Acute kidney injury	n (%)	17 (10)
Hepatic encephalopathy	n (%)	10 (6)
Bacterial infection	n (%)	7 (4)
Others	n (%)	4 (3)
Admission general ward	n (%)	115 (70)
Admission ICU	n (%)	50 (30)
Scoring systems		
CTP score upon admission	points	10 ± 2
MELD score upon admission	points	21 ± 8
ACLF grade upon admission		
Grade 0	n (%)	115 (70)
Grade 1	n (%)	22 (13)
Grade 2	n (%)	12 (7)
Grade 3	n (%)	16 (10)
Infection		
Infection upon admission *	n (%)	28 (17)
Infection during hospitalization **	n (%)	33 (20)
Type of infection		
Urinary tract infection	n (%)	24 (15)
Bacteremia	n (%)	21 (13)
Pneumonia	n (%)	12 (7)
Gastrointestinal infection	n (%)	6 (4)
SBP	n (%)	5 (3)
Others	n (%)	5 (3)
SIRS upon admission	n (%)	44 (27)
Mortality		
Mortality at 30 days	n (%)	33 (20)
Mortality at 90 days	n (%)	45 (27)
Mortality at 182 days	n (%)	55 (33)
Mortality at 1 year	n (%)	61 (37)
Mortality at 2 years	n (%)	69 (41)

All variables reflect the condition upon admission.
Categorical variables are expressed as numbers (n) and percentage (%).
Metric variables are expressed as mean ± standard deviation.

* Infection upon hospital admission (=community acquired) was defined as infection diagnosed from day 0 to 2 of hospitalization.
** Infection during hospitalization (=hospital acquired) was defined as infection diagnosed starting from day 3 or during any time of hospitalization.
BMI, body mass index; CHC, chronic hepatitis C infection; ICU, intensive care unit; MELD, Model of End-stage Liver Disease; ACLF, Acute-on-Chronic Liver Failure; SIRS, systemic inflammatory response syndrome

Table 11 Laboratory parameters of 165 patients

Laboratory parameters		
Platelet count	G/L	124 ± 91
Neutrophil count	G/L	7,4 ± 5,5
Lymphocyte count	G/L	1,2 ± 0,7
Eosinophil count	G/L	0,1 ± 0,2
Albumin	g/dl	2,8 ± 0,7
Creatinine	mg/dl	1,9 ± 6,4
INR		1,9 ± 0,8
Bilirubin (total)	mg/dl	7 ± 8
NLR		7 ± 6
MPV	fl	10,7 ± 1
CRP	mg/dl	40 ± 82

Variables are expressed as mean +/- standard deviation.
INR, international normalized ratio;
NLR, neutrophil to lymphocyte ratio;
MPV, mean platelet volume; CRP, C-reactive protein

3.2 Factors associated with mortality

Table 12 shows factors that are associated with mortality in the 165 patients with decompensated cirrhosis. In the group of patients presenting with ACLF upon admission, the risk of mortality was significant higher at day 30, 90 and 1 year ($p<0,001$; $p<0,001$; $p<0,001$) than in those presenting without ACLF. 46 patients showed more than one type of decompensation upon admission, which also results in significant higher mortality rates at day 30, 90 and 1 year ($p<0,001$; $p<0,001$; $p<0,001$). Furthermore, the presence of more than one kind of infection upon hospital admission or during hospitalization also indicates a significant higher mortality rate at day 30, 90 and at 1 year ($p=0,006$; $p=0,022$; $p=0,025$). In comparison, the presence of a single infection upon admission was associated with high mortality rates at day 30 and 90, and 1 year ($p=0,001$; $p=0,003$; $p=0,015$), whereas the development of any kind of single infection during the hospitalization was not associated with mortality ($p=0,496$; $p=0,190$; $p=0,053$). The presence of SIRS again indicates a high

mortality rate at day 30, 90 and 1 year (p<0,001; p<0,001; p=0,005) in our study population.

Table 12 Factors associated with mortality at day 30 and 90, and 1 year

Factor
ACLF
SIRS
>1 type of decompensation
>1 type of infection
Presence of infection

All factors reflect the condition upon admission.

3.3 Prediction of mortality

3.3.1 Multivariate and univariate data analysis of potential predictive variables

Correlation analyses between the potential variables showed a Spearman coefficient of 0,708 between CTP score and MELD score resulting in exclusion of the CTP score. There was no or only low correlation between the other variables (Spearman coefficient <0,5). The results of the multivariate logistic regression analyses of potential predictive variables for the short-term mortality (at day 30 and day 90) and long-term mortality (at 1 year) are shown in the tables 13-15. Predictive variables for the mortality at day 30 were sex (p=0,046), SIRS (p=0,013) and albumin (p=0,034). ACLF grade 0 (p=0,001) and grade 3 (p=0,001) showed statistical significances, whereas the classification into ACLF grade 1 and 2 was not significant (p=0,481 and p=0,937). The mortality rate at day 30 was 41%, 50% and 56% for patients with ACLF grades 1, 2 and 3, respectively. Sex (p=0,039), SIRS (p=0,027), infection upon hospital admission (p=0,039), MELD score (p<0,001) and platelet count (p=0,021) were the best predictive variables for the mortality at day 90. SIRS (p=0,051), MELD (p<0,001), CRP (p=0,007) and MPV (p=0,024) were identified to be best predictive for the mortality at 1 year. The results of the variables subsequent entered in univariate logistic regression analysis and the Nagelkerke R squared are shown in the tables 13-15. In consideration of multivariate and univariate logistic regression analyses mortality at day 30 was best predicted by the presence of any grade of ACLF, albumin and

the presence of SIRS. MELD score, SIRS, infection upon hospital admission and the platelet count were predictive for the mortality at day 90. The mortality at 1 year was best determined by MELD score, SIRS and CRP.

Table 13 Multivariate and univariate logistic regression analysis of the mortality at day 30

	Mortality (day 30) variable	B	p-value	OR	95% CI	
Multivariate	Sex	1,323	0,046	0,266	0,073-0,977	
	SIRS	1,545	0,013	4,69	1,393-15,791	
	ACLF		0,001			
	ACLF grade 3					
	ACLF grade 2	0,079	0,937	1,082	0,155-7,571	
	ACLF grade 1	-0,619	0,481	0,539	0,096-3,017	
	ACLF grade 0	-2,747	0,001	0,064	0,012-0,33	
	Albumin	-1,038	0,034	0,354	0,135-0,926	
						Nagelkerke R^2
Univariate	Sex	-0,226	0,598	0,798	0,345-1,846	0,003
	SIRS	1,759	0	5,809	2,568-13,138	0,166
	ACLF		0			0,292
	ACLF grade 3					
	ACLF grade 2	-0,251	0,743	0,778	0,173-3,493	
	ACLF grade 1	-0,619	0,352	0,538	0,146-1,982	
	ACLF grade 0	-2,718	0	0,066	0,02-0,219	
	Albumin	-1,742	0	0,175	0,08-0,381	0,228

ACLF grade 0-3: Indicator coding was performed using ACLF grade 3 as the reference category. ACLF grade 0, 1 and 2 were matched against ACLF grade 3 to determine statistical significance.
OR, Odds ratio; CI, Confidence interval; B, regression coefficient;

Table 14 Multivariate and univariate logistic regression analysis of the mortality at day 90

	Mortality (day 90) variable	B	p-value	OR	95% CI	
Multivariate	Sex	-1,151	0,039	0,316	0,106-0,942	
	SIRS	1,193	0,027	3,298	1,145-9,501	
	Infection upon HA	1,279	0,039	3,593	1,066-12,113	
	Platelet count	0,006	0,021	1,006	1,001-1,011	
	MELD score	0,143	0	1,154	1,074-1,239	
						Nagelkerke R^2
Univariate	MELD score	0,139	0	1,149	1,089-1,211	0,277
	SIRS	1,306	0,001	3,69	1,758-7,745	0,101
	Infection upon HA	1,229	0,004	3,419	1,473-7,936	0,069
	Thrombocyte count	-0,002	0,476	0,998	0,994-1,003	0,005
	Sex	-0,154	0,693	0,857	0,4-1,839	0,001

OR, Odds ratio; CI, Confidence interval; B, regression coefficient;

Table 15 Multivariate and univariate logistic regression analysis of the mortality at 1 year

	Mortality (1 year) variable	B	p-value	OR	95% CI	
Multivariate	SIRS	0,945	0,051	2,572	0,995-6,648	
	MELD score	0,121	0	1,128	1,064-1,196	
	CRP	0,014	0,007	1,014	1,004-1,025	
	MPV	-0,543	0,024	0,581	0,362-0,932	
						Nagelkerke R^2
Univariate	MELD score	0,12	0	1,127	1,074-1,182	0,231
	SIRS	1,002	0,006	2,724	1,342-5,532	0,063
	CRP	0,003	0,188	1,003	0,998-1,008	0,019
	MPV	0,016	0,924	1,016	0,73-1,414	0

OR, Odds ratio; CI, Confidence interval; B, regression coefficient;

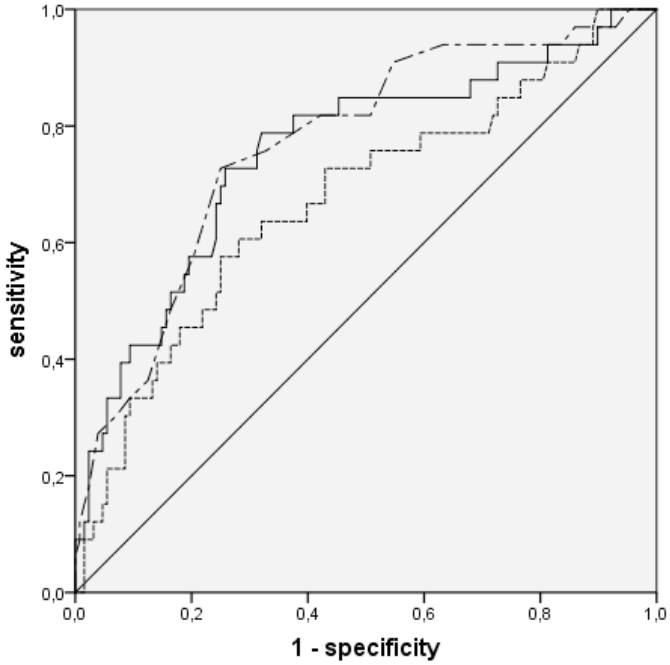
3.3.2 Determination of diagnostic accuracy and Kaplan Meier curves

The Area Under the Receiver Operating Characteristics (AUROC) of the most predictive variables for the mortality at different endpoints including albumin, CRP, MELD, MPV and platelet count was determined. In summary, the results showed albumin to have the best diagnostic accuracy (AUROC: 0,77; 95% CI: 0,680 - 0,860) for the mortality at day 30. MELD score showed the highest diagnostic accuracy for the mortality at day 90 (AUROC: 0,784; 95% CI: 0,698 - 0,870) as well as for the mortality at 1 year (AUROC: 0, 748; 95% CI: 0,669 - 0,827) (table 16,17,22).

3.3.2.1 Short-term mortality at day 30 and 90

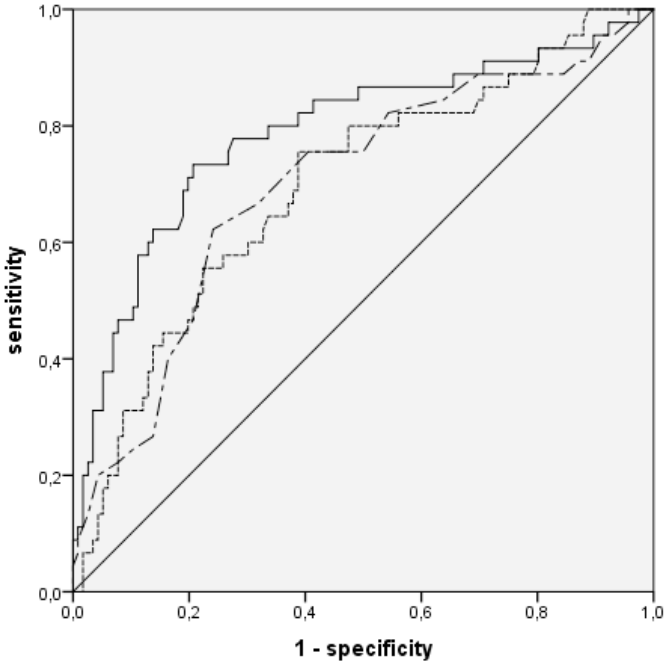
The diagnostic accuracy for the mortality at day 30 in descending order was best performed by albumin (AUROC: 0,77) followed by the MELD score (AUROC: 0,753) and CRP (AUROC: 0,674). The MPV (AUROC: 0,547) and platelet count (AUROC: 0,571) did not show significant diagnostic accuracy (figure 3). The results of the diagnostic accuracy for the mortality at day 90 showed MELD score to be the best predictive variable (AUROC: 0,784) comparable with albumin (AUROC: 0,702) and CRP (AUROC: 0,697). Again the AUROC of the MPV (0,512) and platelet count (0,591) were not notable (figure 4). The best diagnostic cut-off values for the mortality at day 30 and 90, calculated by the Youden's index, are displayed in the tables 16 and 17. As evidenced by the Youden's index the best predictive value of albumin was 2,55g/dl. That of the MELD score was 23 points and the best diagnostic cut-off value chosen for CRP was 31mg/l.

Figure 3 ROC-curve of the mortality at day 30



------- (CRP); ——— (MELD); —-—(ALB);

Figure 4 ROC-curve of the mortality at day 90



------- (CRP); ——— (MELD); —-—(ALB);

Table 16 Diagnostic accuracy and best cut-off values for the mortality at day 30

Mortality (day 30)		
Variable	AUROC	Cut-off value
MELD*	0,753	23 points
CRP*	0,674	31 mg/l
Albumin*	0,77	2,55 g/dl
MPV	0,547	-
Platelet count	0,571	-

AUROC=Area Under the Receiver Operating Characteristics
* The cut-off value was only calculated for variables with a notable diagnostic accuracy.

Table 17 Diagnostic accuracy and best cut-off values for the mortality at day 90

Mortality (day 90)		
Variable	AUROC	Cut-off value
MELD*	0,784	23 points
CRP*	0,697	31 mg/l
Albumin*	0,702	2,55 g/dl
MPV	0,512	-
Platelet count	0,591	-

AUROC=Area Under the Receiver Operating Characteristics
* The cut-off value was calculated for variables with a notable diagnostic accuracy.

According to the different cut-off values, new categorical variables for albumin, CRP and the MELD score were created. The redefined variables are displayed in table 18.

Table 18 Redefined categorical variables for the mortality at day 30 and 90

Variable	Range of values
CRP 1	0 - 31mg/l
CRP 2	>31mg/l
ALB 1	0 - 2,55g/dL
ALB 2	> 2,55g/dL
MELD 1	0 - 23 points
MELD 2	> 23 points

CRP, C-reactive protein; ALB, albumin;
MELD, Model of End stage Liver Disease

The newly defined categorical variables CRP 1/2, ALB 1/2 and MELD 1/2 were again entered in multivariate and univariate logistic regression analyses. As the discrimination of ACLF into grade 1 to 3 did not show any statistically significant prediction for the short-term mortality, there was a new variable defined for ACLF. The new variable ACLF 0/1 only discriminates between no ACLF (ACLF 0) and the presence of ACLF (ACLF 1) of any grade. The results are presented in the tables 19 and 20. After including the categorical variables in the regression analyses, the mortality at day 30 was best predicted by ALB 1/2 ($p=0,017$), ACLF 0/1 ($p<0,001$) and SIRS ($p=0,005$). By comparing the Nagelkerke R^2, the explained variances were 0,285 in ACLF 0/1, 0,231 in ALB 1/2 and 0,166 in SIRS. The variables MELD 1/2 ($p<0,001$), SIRS ($p=0,026$) and CRP 1/2 ($p=0,004$) showed to be significant for the prediction of the mortality at day 90. The Nagelkerke R^2 of MELD 1/2, SIRS and CRP 1/2 in descending order were 0,293, 0,124 and 0,101 respectively.

Table 19 Multivariate and univariate logistic regression analyses of the mortality at day 30

	Mortality (day 30) variable	B	p-value	OR	95% CI	
Multivariate	Sex	-1,384	0,038	0,251	0,068-0,923	
	SIRS	1,694	0,005	5,442	1,661-17,833	
	ACLF 0/1	2,394	0	10,961	3,233-37,164	
	ALB 1/2	-1,422	0,017	0,241	0,075-0,772	
						Nagelkerke R^2
Univariate	ACLF 0/1	2,386	0	10,872	4,518-26,158	0,285
	ALB 1/2	-2,09	0	0,124	0,052-0,294	0,231
	SIRS	1,759	0	5,809	2,568-13,138	0,166
	Sex	-0,226	0,598	0,798	0,345-1,846	0,003

OR, Odds ratio; CI, Confidence interval; B, regression coefficient;

Table 20 Multivariate and univariate logistic regression analyses of the mortality at day 90

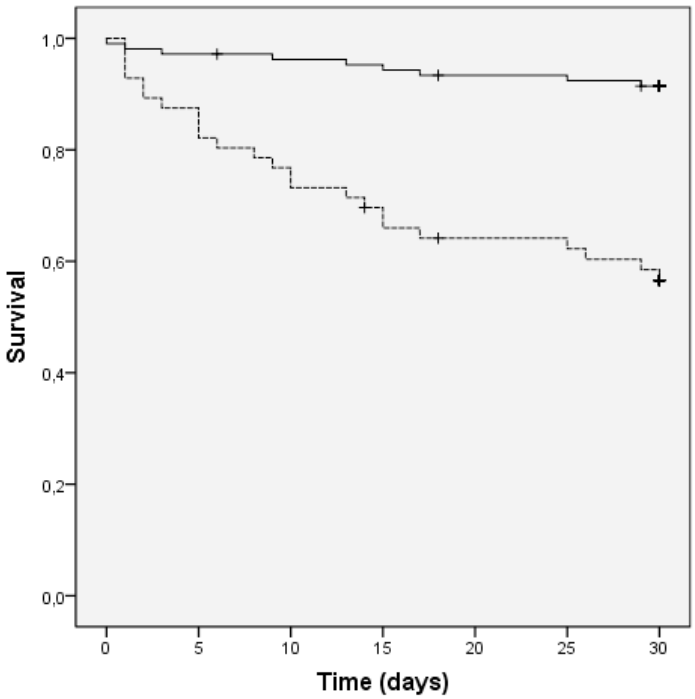
	Mortality (day 90) variable	B	p-value	OR	95% CI	
Multivariate	SIRS	1,168	0,026	3,217	1,151-8,991	
	CRP 1/2	1,463	0,004	3,321	1,591-11,732	
	MELD 1/2	2,27	0	9,683	3,633-25,807	
						Nagelkerke R^2
Univariate	MELD 1/2	2,286	0	9,837	4,46-21,694	0,293
	SIRS	1,306	0,001	3,69	1,758-7,745	0,101
	CRP 1/2	1,419	0	4,132	1,993-8,566	0,124

OR, Odds ratio; CI, Confidence interval; B, regression coefficient;

The best predictive categorical variables of the different endpoints were entered into Kaplan-Meier curves. The survival after 30 days was considerably discriminated by albumin ≤2,55g/dL. Thirty-day mortality for patients with a baseline albumin >2,55g/dL was 8% and 43% for patients with a baseline albumin ≤2,55g/dL (figure 5). The presence of any grade of ACLF was another similar limiting factor of the survival after 30 days with a thirty-day mortality rate of 8% in patients with no ACLF and 48% in patients presenting with ACLF (figure 6). The presence of SIRS also discriminated the thirty-day survival; in patients with no SIRS the thirty-day mortality was 12%, compared with 43% in patients showing SIRS upon admission (figure 7). The ninety-day mortality rate was 11% in the study group of patients with a baseline MELD score of ≤23 points and 56% in patients with a baseline MELD score of >23 points (figure 8). CRP performed comparably with a ninety-day mortality rate of 18% in patients with CRP ≤31mg/l and 48% in those with

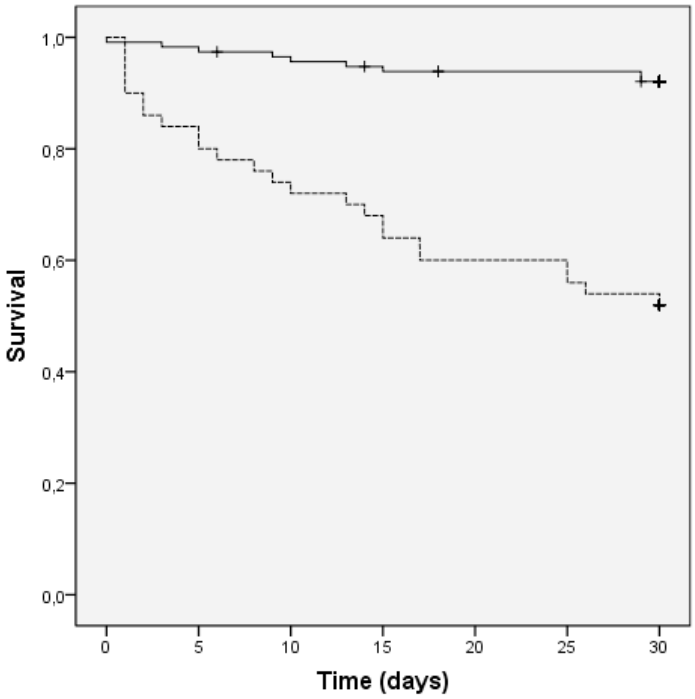
CRP >31mg/l (figure 9). Patients presenting with no SIRS showed a ninety-day mortality rate of 20%, compared to 48% in those with SIRS upon admission (figure 10).

Figure 5 Thirty-day survival according to albumin



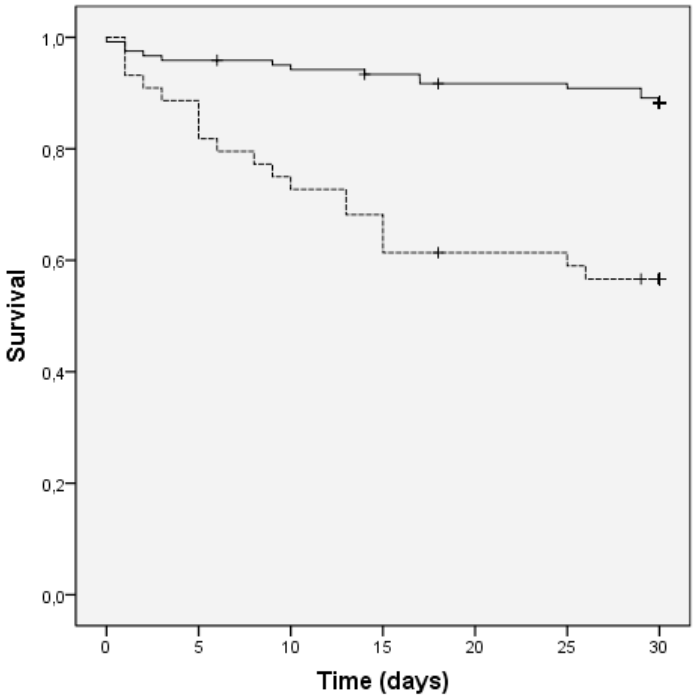
Albumin count >2,55g/dL discriminated the thirty-day survival.
——— Albumin >2,55g/dL (8% mortality)
------- Albumin ≤2,55g/dL (43% mortality)

Figure 6 Thirty-day survival according to the presence of any grade of ACLF



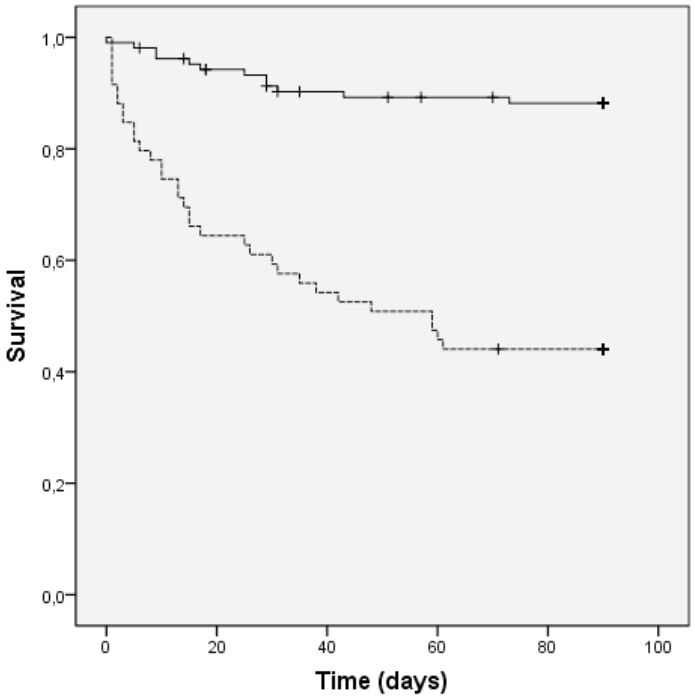
The presence of any grade of ACLF discriminated the thirty-day survival.
—— No presence of ACLF (8% mortality)
------- Presence of ACLF (48% mortality)

Figure 7 Thirty-day survival according to the presence of SIRS



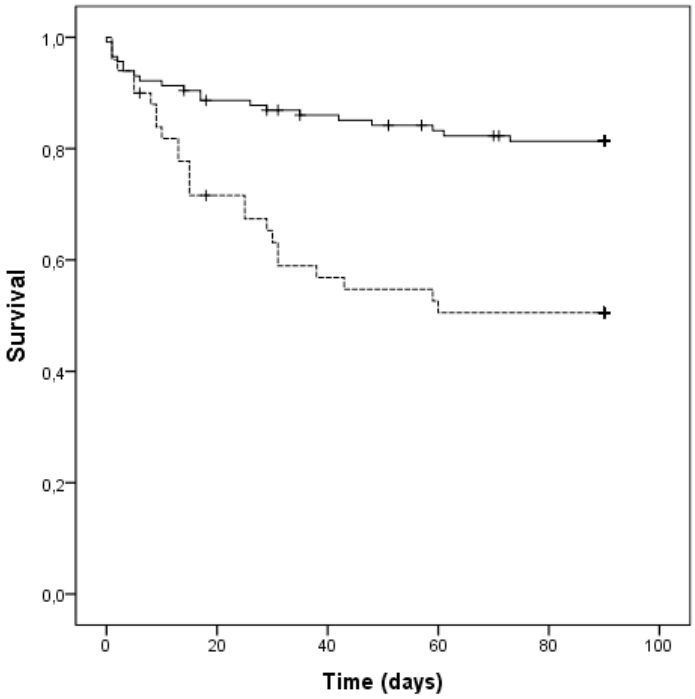
The presence of SIRS discriminated the thirty-day survival.
——— No presence of SIRS (mortality 12%)
------- Presence of SIRS (mortality 43%)

Figure 8 Ninety-day survival according to the MELD score



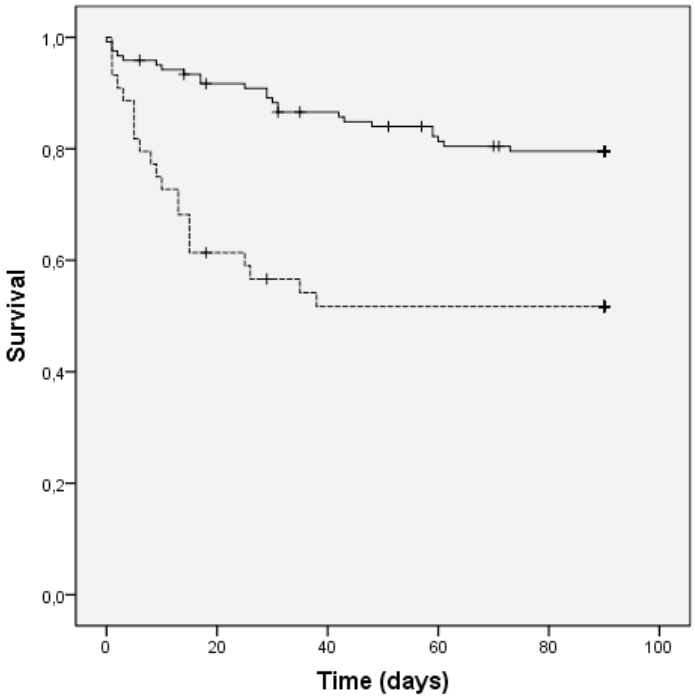
MELD score >23 discriminated the ninety-day survival.
——— MELD score ≤23 (11% mortality)
------- MELD score >23 (56% mortality)

Figure 9 Ninety-day survival according to the CRP level



CRP level >31 mg/l discriminated the ninety-day survival.
——— CRP ≤31mg/l (18% mortality)
------- CRP >31mg/l (48% mortality)

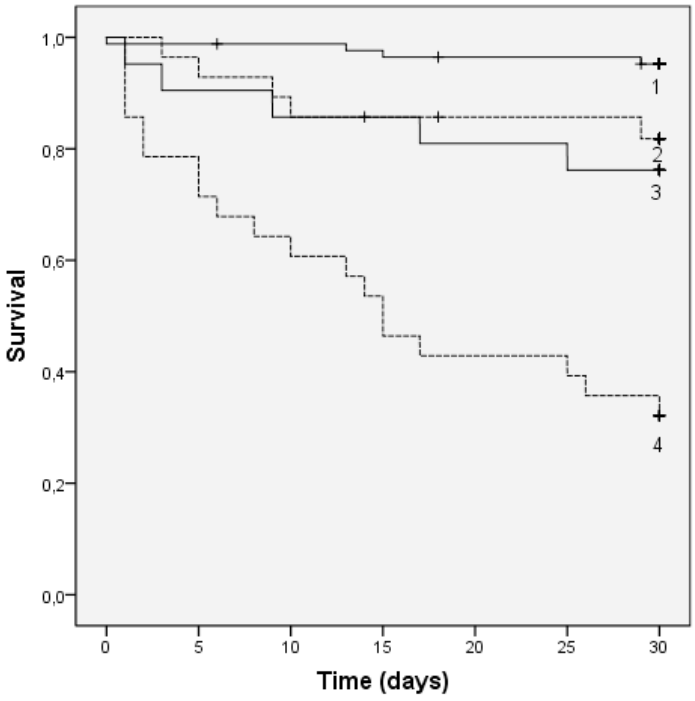
Figure 10 Ninety-day survival according to the presence of SIRS



The presence of SIRS discriminated the ninety-day survival.
——— No presence of SIRS (20% mortality)
------- Presence of SIRS (48% mortality)

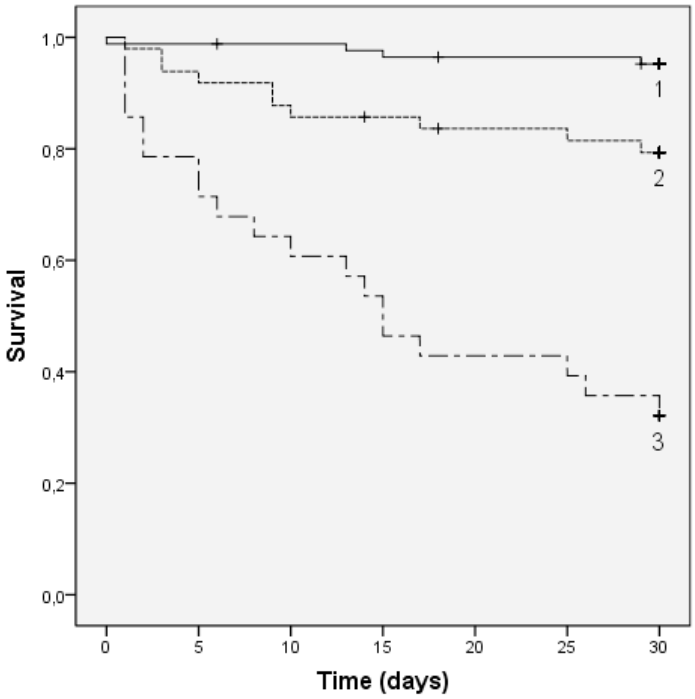
When combining the most predictive variables as evidenced by the logistic regression analyses there were two significant combinations for the short-term mortality (day 30 and 90) to mention. The combination of ACLF and albumin (**'ACLF-Albumin model'**) revealed 4 possible groups for the thirty-day mortality rate to distinguish. Group 1 comprises no ACLF and albumin >2,55g/dL; group 2 is defined as no ACLF and albumin ≤2,55g/dL; group 3 includes the presence of ACLF and albumin >2,55g/dL; group 4 comprises the presence of ACLF and albumin ≤2,55g/dL (figure 11). Considering that group 2 and 3 showed comparable thirty-day mortality rates (18% and 24%) led to the definition of 3 possible groups. Patients summarized among group 1 had a low mortality risk (5%), while the patients of group 2 had an intermediate (20%) and those of group 3 a high (68%) mortality risk (figure 12, table 25).

Figure 11 Thirty-day survival according to the combination of ACLF and albumin



——— (1): no ACLF and albumin >2,55g/dL (5% mortality)
------- (2): no ACLF and albumin ≤2,55g/dL (18% mortality)
——— (3): presence of ACLF and albumin >2,55g/dL (24% mortality)
------- (4): presence of ACLF and albumin ≤2,55g/dL (68% mortality)

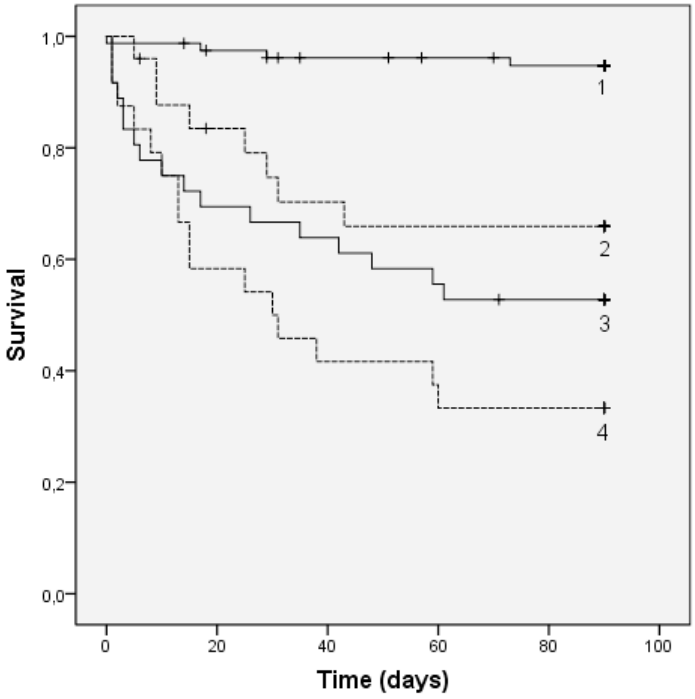
Figure 12 Thirty-day survival according to the combination of ACLF and albumin



——— (1): no ACLF and albumin >2,55g/dL (5% mortality)
------- (2): no ACLF and albumin ≤2,55g/dL or presence of ACLF and albumin >2,55g/dL (20% mortality)
—-— (3): ACLF and albumin ≤2,55g/dL (68% mortality)

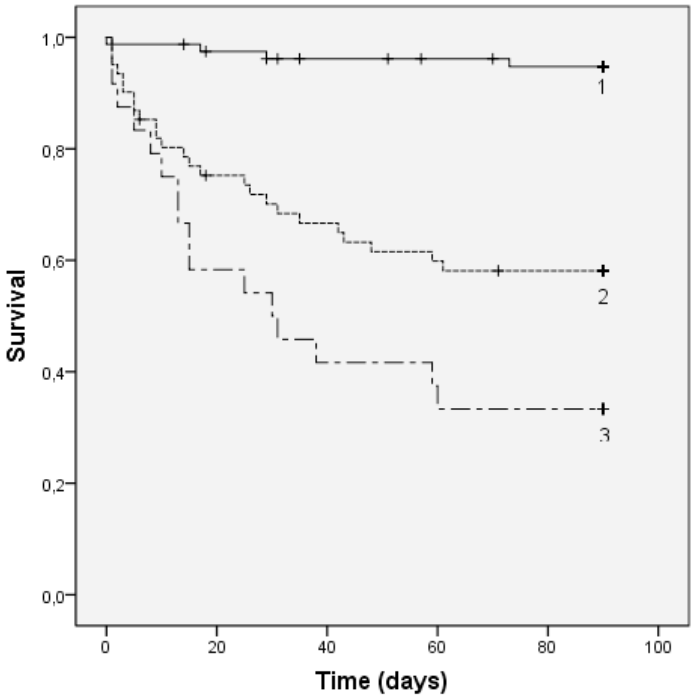
The second significant combination was found to be between MELD score and CRP (**'MELD-CRP model'**) and also allowed stratification into 4 different groups for the ninety-day mortality rate. Group 1 comprises CRP ≤31mg/l and MELD score ≤23; group 2 is defined as CRP >31mg/l and MELD score ≤23; group 3 compromises CRP ≤31mg/l and MELD score >23 and group 4 includes CRP >31mg/l and MELD score >23 (figure 13). The groups 2 and 3 were again combined which led to the definition of 3 possible groups. According to the different groups, patients have a low (5%; group 1), intermediate (41%; group 2) or high (67%; group 3) ninety-day mortality rate (figure 14, table 25).

Figure 13 Ninety-day survival according to the combination of CRP and MELD score



——— (1): CRP ≤31mg/l and MELD ≤23 (5% mortality)
------- (2): CRP >31mg/l and MELD ≤23 (32% mortality)
——— (3): CRP ≤31mg/l and MELD >23 (47% mortality)
------- (4): CRP >31mg/l and MELD >23 (64% mortality)

Figure 14 Ninety-day survival according to the combination of CRP and MELD score

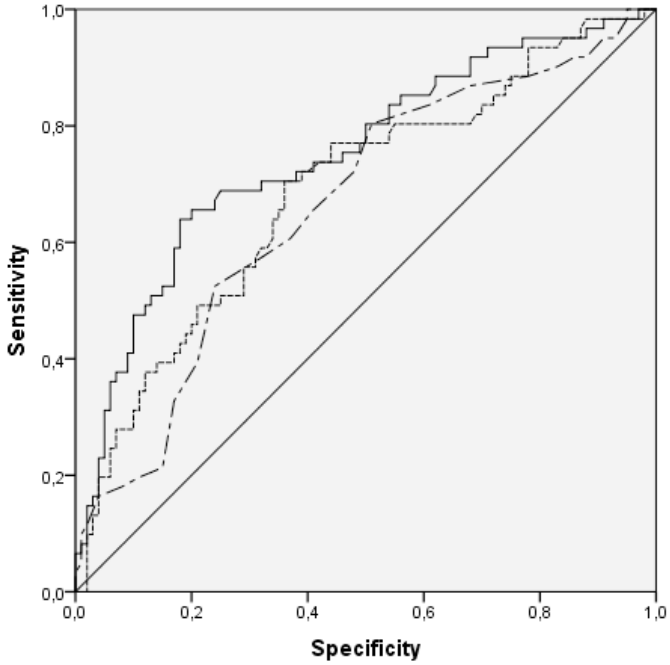


——— (1): CRP ≤31mg/l and MELD ≤23 (5% mortality)
------- (2): CRP >31mg/l and MELD ≤23 or
CRP ≤31mg/l and MELD >23 (41% mortality)
—-— (3): CRP >31mg/l and MELD >23 (67% mortality)

3.3.2.2 Long-term mortality at 1 year

The diagnostic accuracy for the mortality at 1 year in descending order was best performed by the MELD score (AUROC: 0,748) followed by CRP (AUROC: 0,686) and albumin (AUROC: 0,668). The platelet count (AUROC: 0,570) and MPV (AUROC: 0,483) did not show significant diagnostic accuracy (figure 15). The best diagnostic cut-off values calculated by the Youden's index are displayed in table 22. As evidenced by the Youden's index the best predictive value of albumin, the MELD score and CRP for the mortality at 1 year were 2,55g/dL, 23 points and 31mg/l.

Figure 15 ROC-curve of the mortality at 1 year



------- (CRP); ——— (MELD); —-—(ALB);

Table 21 Diagnostic accuracy and best cut-off values for the mortality at 1 year

Mortality (at 1 year		
Variable	AUROC	Cut-off value
MELD*	0,748	23 points
CRP*	0,686	31mg/l
Albumin*	0,668	2,55g/dL
MPV	0,483	-
Platelet count	0,570	-

AUROC=Area Under the Receiver Operating Characteristics
* The cut-off value was calculated for variables with a notable diagnostic accuracy.

According to the different cut-off values, new categorical variables for albumin, CRP and the MELD scores were defined. The limit values of the newly defined variables were equal to those for the short-term mortality. All redefined variables are displayed in table 22.

Table 22 Redefined categorical variables for the mortality at 1 year

Group	Range of values
CRP1	0 - 31mg/l
CRP2	>31mg/l
ALB1	0 - 2,55g/dl
ALB2	> 2,55g/dl
MELD1	0 - 23 points
MELD2	> 23 points

The newly defined categorical variables CRP 1/2, ALB 1/2, MELD 1/2 and ACLF 0/1 were again entered in multivariate and univariate logistic regression analyses. The results are presented in table 23. As evidenced by logistic regression analysis the mortality at 1 year was best predicted by MELD 1/2 (p<0,001) and CRP 1/2 (p=0,002). By comparing the Nagelkerke R^2 the explained variance was 0,249 in MELD 1/2 and 0,106 in CRP 1/2.

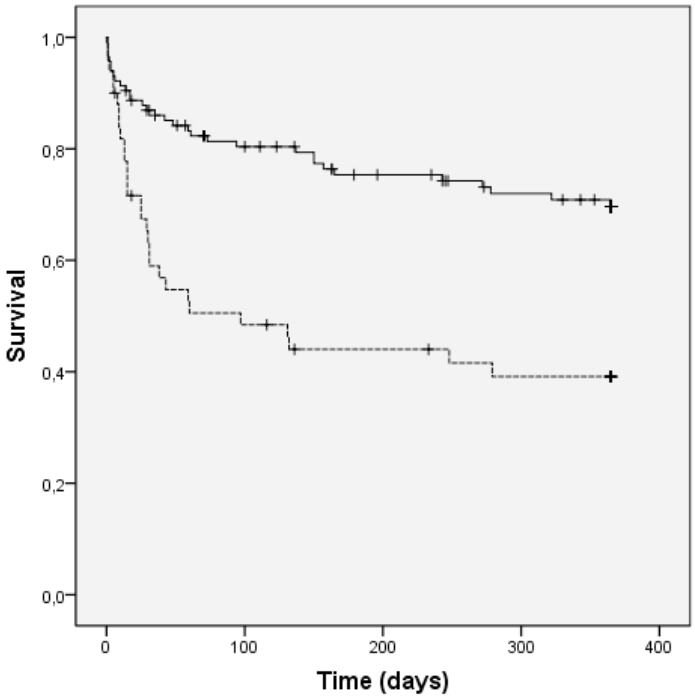
Table 23 Multivariate and univariate logistic regression analysis of mortality at 1 year

	Mortality (1 year) variable	B	p-value	OR	95% CI	
Multivariate	MELD 1/2	2,246	0	9,45	3,892-22,945	
	CRP 1/2	1,432	0,002	4,188	1,682-10,425	
						R^2 Nagelkerke
Univariate	MELD 1/2	1,996	0	7,357	3,598-15,041	0,249
	CRP 1/2	1,276	0	3,582	1,789-7,17	0,106

OR, Odds ratio; CI, Confidence interval; B, regression coefficient;

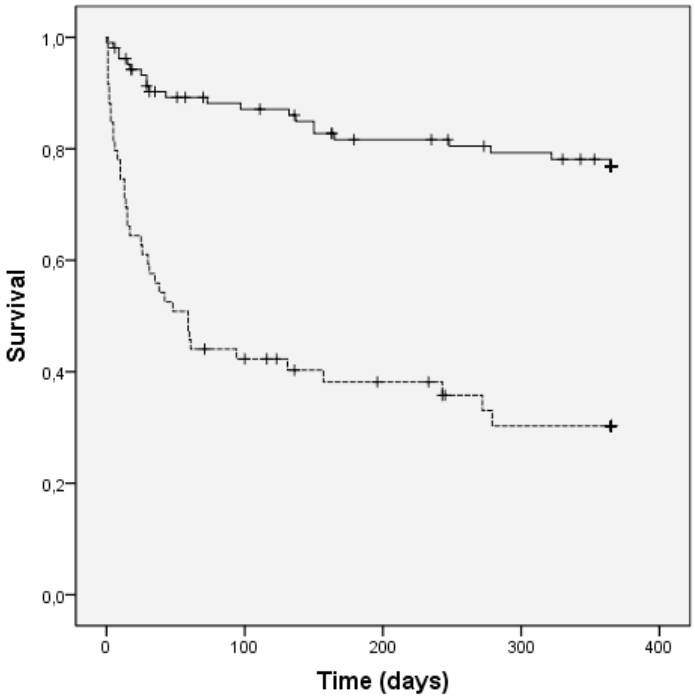
The best predictive variables MELD 1/2 and CRP 1/2 were entered in Kaplan Meier curves. The survival after 1 year was considerably discriminated by CRP values >31mg/l. One-year mortality for patients with a baseline CRP ≤31mg/l was 28% and 58% for patients with a baseline CRP >31mg/l (figure 16). The one-year mortality rate was 21% in the study group of patients with a baseline MELD score of ≤23 points and 66% in patients with a baseline MELD score of >23 points (figure 17).

Figure 16 One-year survival according to the CRP level



CRP >31mg/l points discriminated the one-year survival.
—— CRP ≤31mg/l (28% mortality)
------- CRP >31mg/l (58% mortality)

Figure 17 One-year survival according to the MELD score

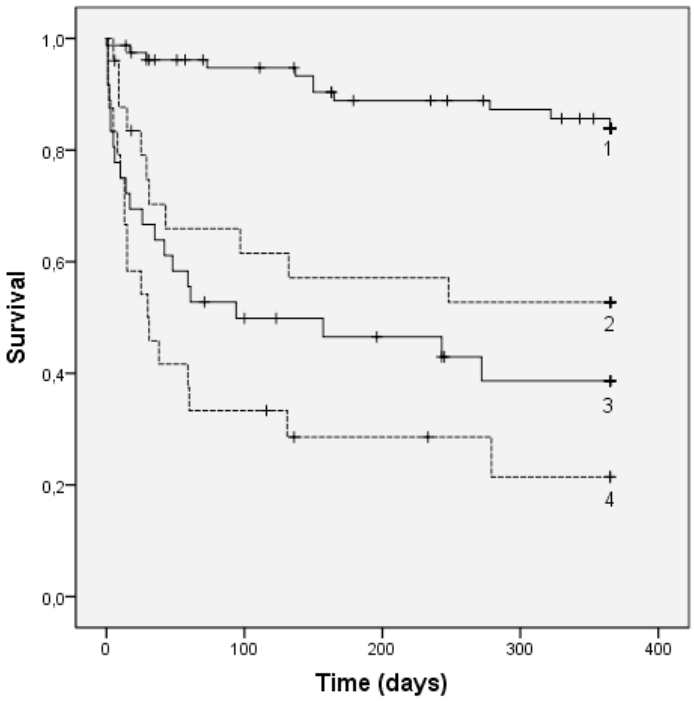


MELD score >23 points discriminated the one-year survival.
—— MELD score ≤23 (21% mortality)
------- MELD score >23 (66% mortality)

When combining the most predictive variables as evidenced by the logistic regression analyses there were 2 significant combinations for the long-term mortality (1 year) to mention. The first significant combination was found to be between MELD score and CRP (**'MELD-CRP model'**). Group 1 comprises CRP ≤31mg/l and MELD ≤23; group 2 is defined as CRP >31mg/l and MELD ≤23; group 3 comprises CRP ≤31mg/l and MELD >23 and group 4 is defined as CRP >31mg/l and MELD >23 (figure 18). Group 2 (44% mortality) and 3 (58% mortality) were combined which led to the definition of 3 possible groups with a low (14%), intermediate (52%) and high (75%) one-year mortality rate for group 1, group 2 and group 3 (figure 19, table 25). The second combination with statistical significance was seen in ACLF and CRP (**'ACLF-CRP model'**). There are again 4 groups to mention. Group 1 comprises CRP ≤31mg/l and no ACLF; group 2 is defined as CRP >31mg/l and no ACLF; group 3 comprises CRP ≤31mg/l and the presence of ACLF and group 4 is defined as CRP >31mg/l and the presence of ACLF (figure 20). Group 3 (63% mortality) and 4 (78% mortality) were combined which led to the definition of 3 possible

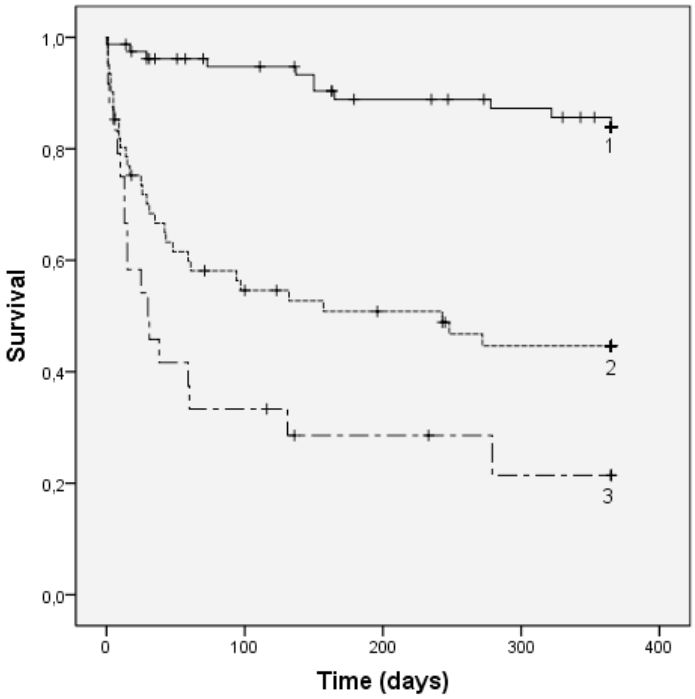
groups with a low (17%; group 1), intermediate (41%; group 2) or high (70%; group 3) one-year mortality rate (figure 21, table 25). Among the combinations for the long-term mortality rate (1 year), the combination of MELD score and CRP on the one hand and ACLF and CRP on the other hand showed comparable results.

Figure 18 One-year survival according to the combination of CRP and MELD score



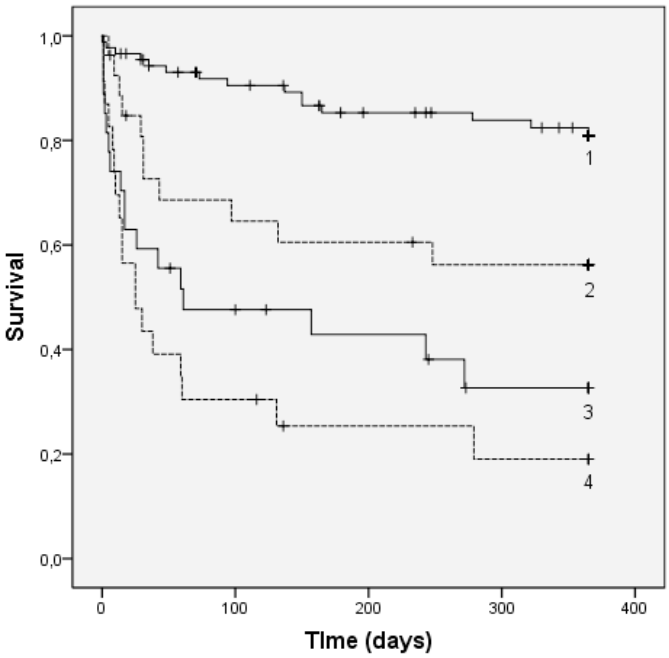
——— (1): CRP ≤31mg/l and MELD ≤23 (14% mortality)
------- (2): CRP >31mg/l and MELD ≤23 (44% mortality)
——— (3): CRP ≤31mg/l and MELD >23 (58% mortality)
------- (4): CRP >31mg/l and MELD >23 (75% mortality)

Figure 19 One-year survival according to the combination of CRP and MELD score



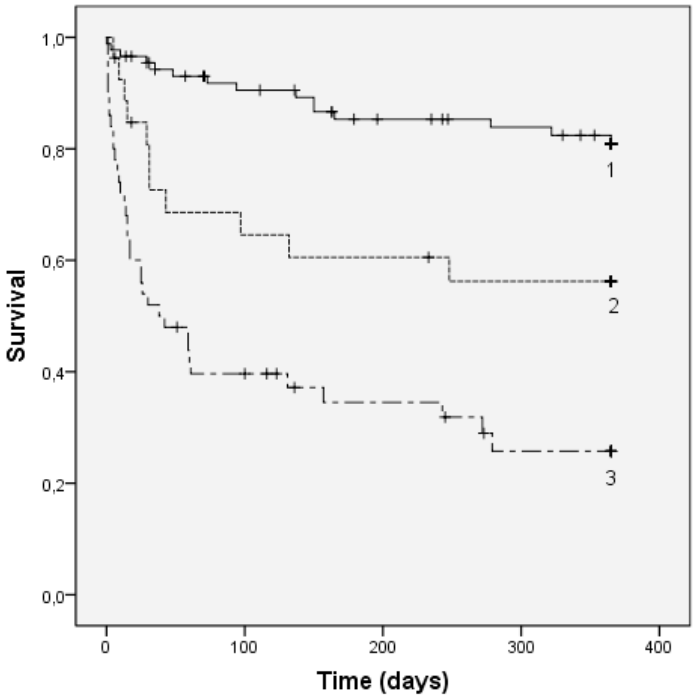
——— (1): CRP ≤31mg/l and MELD ≤23(14% mortality)
------- (2): CRP >31mg/l and MELD ≤23 or
CRP ≤31mg/l and MELD >23 (52% mortality)
—-— (3): CRP >31mg/l and MELD >23 (75% mortality)

Figure 20 One-year survival according to the combination of CRP and presence of ACLF



——— (1): CRP ≤31mg/l and no ACLF (17% mortality)
------- (2): CRP >31mg/l and no ACLF (41% mortality)
——— (3): CRP ≤31mg/l and presence of ACLF (63% mortality)
------- (4): CRP >31mg/l and presence of ACLF (78% mortality)

Figure 21 One-year survival according to the combination of CRP and presence of ACLF



——— (1): CRP ≤31mg/l and no ACLF (17% mortality)
------- (2): CRP >31mg/l and no ACLF (41% mortality)
—-— (3): presence of ACLF (70% mortality)

The classification of patients with decompensated cirrhosis into 3 groups as shown with the 'ACLF-Albumin model', 'MELD-CRP model' and 'ACLF-CRP model' revealed remarkable differences in mortality rates at day 30, day 90 and 1 year (table 25). Groups with low, intermediate and high risk of mortality can be distinguished and moreover, depending on the group, recommendations for further management could be made. Patients numbered among group 1 (low mortality risk) should be discharged, those among group 2 (intermediate mortality risk) admitted to a specialized ward and those among group 3 (high mortality risk) should be admitted to an ICU ward (table 24). When comparing the combinations with the original scores, improvement of the newly created models was shown (table 26). The AUROC of the 'ACLF-Albumin model' revealed improvement in relation to that of the ACLF score alone. The diagnostic accuracy of the 'MELD-CRP model' for the ninety-day mortality also improved when compared with the MELD score alone (AUROC: 0,806 vs. 0,784). Considering the one-year mortality, both the 'MELD-CRP model' vs. MELD score alone (AUROC: 0,766 vs. 0,748) and the 'ACLF-CRP model' vs. ACLF score alone (AUROC: 0,759 vs. 0,715) showed improvement in diagnostic accuracy.

Table 24 Overview of 2-variable models and mortality rates upon different groups

Mortality at day 30	Mortality rate Group 1 (low) discharge	Mortality rate Group 2 (intermediate) ward admission	Mortality rate Group 3 (high) ICU admission
'ACLF-Albumin model'	5%	20%	68%
Mortality at day 90			
'MELD-CRP model'	5%	41%	67%
Mortality at 1 year			
'MELD-CRP model'	14%	52%	75%
'ACLF-CRP model'	17%	41%	70%

MELD, Model of End stage Liver Disease; CRP, C-reactive protein;
ACLF, Acute-on-Chronic-Liver-Failure; ICU, intensive care unit;

Table 25 Comparison of 2-variable models with original scores

2-variable model	AUROC (2-variable model)	AUROC (original score)
Mortality at day 30		
'ACLF-Albumin model'	0,830	0,765 (ACLF score)
Mortality at day 90		
'MELD-CRP model'	0,806	0,784 (MELD score)
Mortality at 1 year		
'MELD-CRP model'	0,766	0,748 (MELD score)
'ACLF-CRP model'	0,759	0,715 (ACLF score)

AUROC, Area Under the Receiver Operating Characteristics
MELD, Model of End stage Liver Disease; CRP, C-reactive protein;
ACLF, Acute-on-Chronic-Liver-Failure; ICU, intensive care unit;

4 Discussion

The aim of the present study was to propose a simple risk stratification model for the short-term (day 30 and day 90) and long-term mortality (1 year) in patients hospitalized due to decompensated cirrhosis. A variety of clinical and laboratory parameters were evaluated in combination with well-established scoring systems for liver impairment in order to determine their predictive value for mortality in patients with decompensated cirrhosis. Accurate assessment of the disease severity and prognosis of decompensated cirrhosis is crucial regarding optimal therapeutic management, as well as decision making for organ allocation. Recent studies show that mortality in decompensated cirrhosis is not mainly determined by isolated liver failure but rather by precipitating events and organ failure/s superimposed on liver impairment. (18) Indeed, Moreau et al. reported that patients with single liver failure and no additional organ failures or impairments, defined as 'no Acute-On-Chronic-Liver-Failure (ACLF)', have a considerably better outcome than patients with additional organ failure/s, particularly in the case of renal failure. Moreover, the presence of SIRS (with or without bacterial infection) is considered to have important prognostic relevance. It is associated with increased mortality, portal hypertension complications and HE in cirrhotic patients with or without renal impairment. (122,123,126) On the one hand, SIRS may induce immune dysregulation, which potentially contributes to the development of infections. On the other hand, occurring infections trigger a pro-inflammatory response which may contribute to the development of SIRS. There are different pathophysiological alterations in the course of liver disease presumed to indicate SIRS. Frequently appearing bacterial infections seem to be one of the main causes of SIRS in patients with advanced cirrhosis. Furthermore, the activation of the pro-inflammatory pathway may also be the result of occult bacterial infection, high circulating endotoxins or imbalance between the pro-inflammatory response and reduced anti-inflammatory pathway in immune cells. (123,127) In the course of cirrhosis, the clinical diagnosis of SIRS is often difficult to establish. Subclinical HE may cause an increase in respiratory rate and induce hypocapnia, tachycardia can be covert by beta-blockers or induced by hyperdynamic circulation and hypersplenism can cover leukocytosis or aggravate leukopenia. (122,123,126) In consideration of the importance of SIRS and extrahepatic organ failure/s it becomes necessary to include parameters reflecting these events in prognostic models. The widely used CTP and MELD score neither incorporate parameters representing multi-organ failure nor parameters reflecting SIRS. Therefore, in cirrhotic patients with low CTP and MELD scores presenting organ failure/s and/or SIRS alongside liver impairment, the disease

severity may be underestimated. Organ failure scores such as the Acute Physiology and Chronic Health Evaluation (APACHE) II system and the Sequential Organ Failure Assessment (SOFA) score evaluate the dysfunction of extrahepatic organ systems and it was hypothesized that these could be used to more accurately predict the prognosis of patients with decompensated cirrhosis. (131,132)

In recent studies, surrogate parameters of infection/inflammation in cirrhosis were proposed to have prognostic significance (84–87,128,129). Upon these parameters, there is strong evidence that CRP is an appropriate marker reflecting SIRS and predicts short-term and long-term mortality in patients with cirrhosis. (88,126) As evidenced, in the course of chronic liver disease (CLD) the cytokine interleukin 6 (IL-6) is elevated. CRP is produced in the liver in the acute phase of inflammation in response to IL-6 and it seems that its production is not altered by liver impairment. (126,133,134) Park et al. showed that CRP is still produced in cirrhotic patients with bacterial infections, but the CRP levels were found to be lower than in patients with bacterial infection and no underlying cirrhosis. (135) There is evidence that increased levels of CRP without the presence of SIRS indicates poor prognosis as well. In these patients who do not meet the criteria of SIRS it has been hypothesized that CRP may act as a sensitive marker for hidden systemic inflammation that could not be detected by clinical SIRS criteria. (18,88)

The main results of the study were as follows: albumin levels ≤2,55g/dL, CRP levels >31mg/l, MELD >23 and the presence of ACLF predicted short-term mortality (at day 30 and day 90) whereas CRP levels >31mg/l and MELD >23 predicted long-term mortality (1 year). When combining MELD score or present ACLF with the most predictive variables we obtained four 2-variable models for risk stratification that were accurate mortality predictors; the combination of ACLF and albumin (**'ACLF-Albumin model'**) was best predictive for the thirty-day mortality, while the ninety-day mortality was best predicted by the combination of MELD score and CRP (**'MELD-CRP model'**). For the one-year mortality the combination of MELD score and CRP (**'MELD-CRP model'**) as well as the combination of ACLF and CRP (**'ACLF-CRP model'**) were similarly predictive. The other investigated surrogate markers for infection such as NLR, MPV, platelet, neutrophil, lymphocyte or eosinophil count did not show any relevant predictive results. The newly created 'ACLF-Albumin model' for the mortality at day 30 classifies patients into groups with low, intermediate and high mortality rate (table 25). When comparing the AUROC of the 'ACLF-Albumin model' with that of the ACLF score alone, improvement was seen (0,830 vs. 0,765).

Albumin as a component of the CTP score was found to be a significant predictor of mortality, especially in patients with compensated cirrhosis and in patients with CTP A hepatitis C virus-related cirrhosis. (16,136) Sargenti et al. suggested low albumin levels and more than one organ failure to be predictive for in-hospital mortality in cirrhotic patients with serious infections complicated by ACLF. (73) Considering the high mortality rate among patients with both the presence of ACLF and low albumin levels (68%), compared to an intermediate mortality rate (20%) in patients with solely the presence of ACLF, suggests low albumin levels to be an important hallmark in the disease progression of decompensated cirrhosis. Furthermore, when combining CRP with MELD or ACLF score it was again possible to divide the study population into 3 groups with low, intermediate or high risk of mortality at different endpoints (table 25). The 'MELD-CRP model' for the mortality at day 90 showed improvement when comparing with the MELD score alone (AUROC: 0,806 vs. 0,784). Both the 'MELD-CRP model' vs. MELD score alone (AUROC: 0,766 vs. 0,748) and the 'ACLF-CRP model' vs. ACLF score alone (AUROC: 0,759 vs. 0,715) showed improvement in the diagnostic accuracy. Patients numbered among group 2 (low MELD, high CRP) of the 'MELD-CRP model' have a significant higher mortality rate at day 90 than patients numbered among group 1 (low MELD, low CRP) (4% vs. 41%). Hence, the disease severity among these patients might be underestimated when using the MELD score alone. These risk stratification models incorporating CRP can be integrated in decision making in Emergency room situations for further patient management. Considering the different groups, patients with a low mortality risk may be discharged; those with an intermediate mortality risk admitted to a specialized Department of Internal Medicine and patients classified as having a high mortality rate should be admitted to an ICU. The 'ACLF-CRP model' and 'MELD-CRP model' show comparable mortality rates at 1 year in their 3 different groups, although the 'ACLF-CRP model' incorporates 3 more organ systems (lungs, circulation and central nervous system). An issue to address in future studies is whether the additional information about organ failures displayed by the ACLF grading in the 'ACLF-CRP model' compared to the 'MELD-CRP model' may be more predictive and whether the 'ACLF-CRP model' should be favored.

Considering that SIRS (with or without infection) is thought to be a major contributing factor to the development of organ failure and disease progression in cirrhosis, the early detection of an ongoing inflammatory process is crucial. (121–123) As aforementioned, there is growing evidence that CRP levels seem to provide evidence for ongoing hidden

inflammation in cirrhotic patients. Consistent with these findings, in our study group only 54% of the patients presenting with high CRP levels (≥31mg/l) upon admission were diagnosed with a bacterial infection. Furthermore, in 62% of the patients with high CRP levels upon admission, no SIRS was diagnosed. This may be caused by the difficulty of determining SIRS in cirrhotic patients or the inflammatory response has not yet become manifest but is already reflected by CRP. In the present study the best cut-off value for CRP was 31mg/l for the mortality at day 90 and 1-year. Cervoni et al. proposed a comparable CRP level of 29mg/l and in the study of Di Martino et al. a CRP level of 32mg/l was found to be predictive for the risk of mortality in patients with decompensated cirrhosis. (88,126) Our findings are consistent with other studies suggesting that the prognostic value of CRP is independent of widely used prognostic criteria, such as MELD or CTP scores. (88,126) Cervoni et al. evaluated the predictive value of CRP as a surrogate marker of SIRS in order to improve prediction of short-term mortality in patients with decompensated cirrhosis on the waiting list for liver transplantation. Accurate prediction of mortality in these patients ensures the sickest patients to be prioritized for liver transplant allocation. Likewise, Cervoni et al. showed that CRP levels ≥29mg/l are appropriate for predicting short-term mortality and better than infection or clinically assessed SIRS in patients with decompensated cirrhosis (CTP score ≥B8). Since high CRP levels were associated with the occurrence of SIRS, but SIRS was not predictive for the short-term mortality in this study group it was hypothesized that CRP may act as a surrogate marker for inflammation. (88) These findings were confirmed and extended by Di Martino et al. who proposed 32mg/l as a predictive cutoff value of CRP. Furthermore, it was shown that in patients with less severe cirrhosis (defined by lower CTP scores) a cut-off value of 10mg/l was already predictive for the short-term mortality. (126) Cervoni et al. proposed a 3-variable model including a high MELD score, extrahepatic comorbidities and a persistent elevation of CRP (>29 mg/l), which showed improvement in predicting the 6-month survival rate when compared with the AUROC of MELD score alone (0,80 vs. 0,67). Di Martino et al. validated the prognostic model in an independent study in which they show that the 3-variable model using a CRP cut-off value of 32mg/l predicted 3-month survival in patients with decompensated liver cirrhosis more accurately than the MELD score alone (0,895 vs. 0,876). (126) These results indicate that combining MELD score with CRP strengthens the predictive capacity of the MELD score, which is critical for proper prioritization of liver allocation. (137) Both of the suggested cut-off values of CRP are comparable with the cut-off shown to be predictive for short-term and long-term mortality

in our study population (29mg/l vs. 32mg/l vs. 31mg/l). In comparison to our study Cervoni et al. established a model using the variation of CRP levels within 15 days and not only the CRP level upon admission. The advantage might be that continuing systemic inflammation with a predictive value for the mortality may be identified, whereas promptly resolved bacterial infections are excluded. On the other hand, requirement of CRP values at an interval of 15 days makes the model more difficult to apply. Similarly to Cervoni et al. and Di Martino et al., we did not detect a correlation between CRP and the MELD score. In Di Martino et al. the 3-varibale model was tested in a study population including patients with both compensated and decompensated cirrhosis. In this scenario the improvement of the prognostic model when compared with the MELD score alone showed no significance. (126) Recently, Cervoni et al. proposed a new 3-variable prognostic model for the 3-month mortality rate. This model includes 'sustained high CRP values (≥29mg/l)', age and MELD score and was found to show significant improvement when compared with the MELD score alone. (138) These results strengthen the growing evidence that the incorporation of CRP in the MELD score may result in a more accurate prediction of short- and long-term mortality. The United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) approved the MELD-Na score in 2014 for patients on liver transplant list with a MELD score higher than 11. The 'MELD-Na' equation, including serum sodium levels, is used for allocation since January 2016 in the United States. (139) This policy change underscores the importance of finding and including parameters in the MELD score that display pathophysiological events predicting disease progression and high mortality rate. Recent studies also show predictive value of other inflammatory and infectious markers such as NLR, MPV, eosinophil count, ferritin, procalcitonin, lipopolysaccharide-binding protein or the mid regional fragment of pro-adrenomedullin (MR-proADM) for bacterial infection and mortality in patients with cirrhosis. Kotecha et al. suggested that a low baseline eosinophil count in critically ill patients with decompensated cirrhosis is predictive for the in-hospital mortality. (84) The soluble urokinase plasminogen activator receptor (suPAR) is another potential predictive parameter in patients with cirrhosis. Elevated suPAR concentrations were associated with poor prognosis in patients with chronic liver disease. (128) The blood NLR was found to be accurately in predicting long-term mortality in patients with stable cirrhosis in a study conducted by Biyik et al.. Notable, a high NLR in patients with low MELD score was predictive for a high risk of mortality among these patients. (86) However, in our study the NLR showed no statistical significance neither for the short-

term nor the long-term mortality. This might be explained by differences of the study cohort. Taking into account that compared to our study only patients with stable cirrhosis and without bacterial infections were included in the study of Biyik et al., the applicability of the NLR might be limited to these patients. Bacterial infections and ongoing systemic response in patients with decompensated cirrhosis might have a strong impact by increasing neutrophil count, even though they might resolve quickly and, in some cases without worsening the prognosis. Reuken et al. suggested that the mid regional fragment of pro-adrenomedullin (MR-proADM) predicts complicated bacterial infections as well as short-term mortality irrespective of bacterial infections and SIRS in patients with decompensated cirrhosis. (129) Concern was raised due to the fact that higher MR-proADM levels seemed to be paralleled with SBP rather than SIRS in this study population. Considering the growing evidence that SIRS (with or without bacterial infection) in cirrhotic patients is a major contributing factor to disease progression, the applicability has to be approved in a more representative study population. (129) Considering the frequent occurrence of pathological bacterial translocation from the gastrointestinal lumen to the mesenteric lymph nodes and into the systemic circulation, detection of bacterial DNA (bacDNA) was suggested for prediction of mortality. Zapater et al. showed that the presence of bacDNA in serum and ascitic fluid is an independent predictor of mortality in patients with cirrhosis and absence of bacterial infections. (140) However, the presence of bacDNA was not found to be an accurate predictor of mortality in patients with decompensated cirrhosis presenting with bacterial infection and/or SIRS. (141) Although these aforementioned potential predictive markers seem to be interesting given their pathophysiological background, they are not routinely available as CRP, albumin and the other laboratory parameters evaluated in this study are.

As defined in the CANONIC study, ACLF is a syndrome showing a combination of acute decompensation of cirrhosis, organ failure/s and high short-term mortality. It has to be differentiated from acute decompensation of cirrhosis alone. (18) For the assessment of organ failure/s a modified SOFA score, the Chronic LIver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score is used. Due to subscores ranging from 0 to 4 for each of the 6 compromised organ systems, the score is not simple to calculate, especially in the setting of an Emergency room situation in which simple risk stratification is required. The presence of ACLF alone (expressed by grade 1-3) showed statistical significance for the prediction of the mortality at day 30 ($p<0,001$) in our study population.

Interestingly, by contrast with the study from Moreau et al., our results showed no significant difference concerning mortality rates in the ACLF grades 1 to 3. An explanation for this lack of significance in different ACLF grades in our study could be the much greater study population in the study conducted by Moreau et al.. In 2014 the European Association For The Study of the Liver (EASL) published a modified version of the CLIF-SOFA score for the diagnosis and grading of ACLF. The simplified CLIF Consortium Organ Function (CLIF-C OF) score (table 8) comprises 3 subscores (compared to 5 in the CLIF-SOFA score) for each organ system correlating with the risk of dying within 28-days. (118) In further consequence, there were two additional scores developed to assess the prognosis of those patients with the presence of ACLF and those without ACLF. The Chronic LIver Failure - Consortium - ACLF (CLIF-C-ACLF) score provides prognostic information in patients with present ACLF. In patients without ACLF the CLIF-Consortium score for AD patients (CLIF-C ADs) was suggested to apply and shown to be superior to existing scores such as MELD and CTP. (142) The CLIF-C ADs includes age, creatinine, INR, white blood cell count and sodium. The application of 2 different prognostic scores depending on the presence or absence of ACLF, shows the importance of this syndrome in regard to differences in mortality rates. In comparison to our results the white blood cell count was an independent prognostic marker indicating patients with a distinct systemic inflammatory response and poor outcome in the CLIF-C AD score. Furthermore, the sequential measurement of the CLIF-C AD score again after certain time periods showed retention or even improvement of the predictive accuracy. In our study, the models were applied on data acquired upon hospital admission. In order to determine the potential advance of additional measurements, particularly for rapid resolving bacterial infections, validation in prospective cohorts is needed. Considering that our prognostic models only depend on the presence or absence of ACLF, this makes them more applicable for routine use in the setting of emergency situations. Nevertheless, further studies are necessary to exclude a drop of important prognostic information due to this simplification.

The present study has some limitations that should be mentioned. First, the cohort in this study consists of patients with cirrhosis mainly caused by alcohol abuse (89%). Therefore, future studies should assess whether the models described here are also accurate predictors for short- and long-term mortality in patients presenting cirrhosis with different etiologies. Second, the study is retrospective and therefore the data for the evaluation of subjective variables (ascites, HE) of the CTP score as well as the assignment to the different ACLF grades was received from medical records. Although patients with missing data or

uncertainty in completeness or correctness were excluded, the potential of minor variation compared to a prospective study should be underlined. Finally, the diagnostic evaluation for infection was performed individually by the physician in charge and there was no standardized protocol for infection work-up applied. Nevertheless, patients admitted because of acute decompensation of their cirrhosis were seen by a hepatologist as well, leading to the assumption that the standard of care of all patients was the same. The 2-variable models in the present study were developed from a study population presenting with acute decompensated cirrhosis for the purpose of a simple risk stratification upon admission. Confirmation of the scoring systems in cirrhotic patients with planned admissions is needed to evaluate its applicability to all cirrhotic patients.

5 Conclusion

The aim of the present study was to propose a simple risk stratification system for the short-term as well as for the long-term mortality rate in patients with decompensated cirrhosis. Accurate assessment of the disease severity and prognosis of decompensated cirrhosis is crucial for optimizing therapeutic management. Mounting evidence suggests that in patients with decompensated cirrhosis, the mortality rate is dependent on superimposed organ failure/s and the presence of SIRS, rather than isolated liver failure. Well-established and widely used scoring systems to assess liver impairment, such as the MELD or the CTP scores do not include parameters reflecting these events. Hence, it is necessary to establish scoring systems that combine parameters reflecting the severity of liver impairment, superimposed extrahepatic organ failure/s and SIRS.

There are two main conclusions of the present study. First, the newly defined 2-variable models 'ACLF-Albumin model', 'MELD-CRP model' and 'ACLF-CRP model' allow simple risk stratification of patients into groups with low, intermediate and high short-term as well as long-term mortality rate. According to the mortality risk assessment by these models, either discharge, ward admission or ICU admission may be recommended. Second, these models showed improved accuracy when compared with the MELD score or presence of ACLF (any grade) alone. The predictive value of elevated CRP levels (>31mg/l) in patients without overt bacterial infection or SIRS emphasize the hypothesis that CRP might act as a surrogate marker for infection/inflammation even though these events are not yet clinically manifest. Furthermore, the predictive value of the presence of ACLF (any grade) was interpreted as the importance of superimposed organ failure/s alongside single liver impairment. Patients with decompensated cirrhosis have an increased mortality rate; reliable mortality risk assessment is often challenging but remains essential for adequate disease management. Based on routinely available, reproducible and inexpensive laboratory parameters, these simple risk stratification models may be readily applicable in Emergency Room situations assisting in decision making regarding further patient management. Future requirements are external validation in large prospective cohorts of patients with decompensated and compensated cirrhosis to confirm and extend our findings. The findings in this thesis support that establishing scoring systems combining liver impairment with other predictive parameters reflecting SIRS and extrahepatic organ failure is recommended for the adequate assessment of disease severity in patients with decompensated cirrhosis.

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