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d-LIVER

ICT-enabled, cellular artificial liver system incorporating personalized patient management and support

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OBJECTIVE: ICT-2011.5.1

D1.3: Specification of essential clinical parameters predicting individual outcome – An interim analysis

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1. Executive Summary

End stage liver disease (ESLD) is associated with poor outcome (1). Liver transplantation is considered to be a viable therapy for patients with end-stage liver disease but due to an increasing incidence of liver disease and the chronic shortage of donor organs, the length of time patients spend waiting for a liver transplant is increasing (2). Not all patients will benefit from liver transplantation (3, 4) and there is therefore a need for scoring systems which can help to accurately estimate an individual's need for transplantation and the expected long term outcome. The scores commonly used at present have significant limitations; the Child-Pugh score includes subjective parameters (grade of ascites and encephalopathy) while the MELD score includes serum creatinine, which reflects renal function rather than being a direct measure of liver function (5, 6). There is therefore a requirement for more objective scoring systems to estimate patient mortality and severe morbidity. In addition, new methods need to be explored to support or replace liver function at the point of need.

Within d-LIVER task 1.3, variables which could be useful to indicate enrolment of patients to the d-LIVER system or the initiation of bio-artificial liver (BAL) therapy will be investigated. A prospective observational study was started at the Charité University Hospital enrolling patients with chronic liver failure to collect the conventional clinical and laboratory parameters as well as data on maximal enzymatic liver function capacity (LiMAx test), the clearance potential of the liver (indocyanine green retention test) and non-invasive measurement of liver stiffness (transient elastography).

This deliverable aims to specify essential clinical parameters for the prediction of the individual outcome of patients with end stage liver disease based on an interim analysis of study data.

2. Introduction

This document provides preliminary data from a prospective clinical trial. Beyond that the background section should serve the reader, with and without medical background, to gain a deeper understanding of the complex situation of chronic liver failure patients. These days new and more objective scoring systems estimating morbidity and mortality of chronic liver failure patients are desired to render simpler and more transparent allocation of donor organs.

Section 3 will give the reader a short introduction and overview of the disease pattern of chronic liver failure and therapeutic options. Moreover currently used scoring systems are described highlighting their strengths and weaknesses.

Section 4 outlines the aim of the study while Section 5 covers the protocol of the clinical trial undertaken at the Charité University Hospital. Section 6 provides preliminary results and prediction of individual outcome. Section 7 gives a discussion of the results while Section 8 provides some conclusions.

Note that Sections 5, 6 and 7 are confidential, and are available only for the project members and the reviewers.

3. Background and current concepts in liver allocation

Since the first successful liver transplantation in 1967, more than 170,000 liver transplantations have been performed worldwide(7). Liver transplantation has become the therapy of choice for most forms of ESLD(8). Survival rates after liver transplantation have increased dramatically since the first procedures, due to improvements in immunosuppressive drugs, surgical techniques, organ preservation and peri-operative care (9, 10). Most of these improvements occurred during the first 35 years of liver transplantation with few additional improvements over the last decade. A “chronic” shortage of donor organs is partly responsible for the increased use of so-called marginal organs (organs of declined quality e.g. organs from old donors, donors with infectious diseases) and the waiting time for organ transplantation is getting longer with MELD scores of patients on transplant lists increasing as a result (11, 12). Thus there is a greater demand for new methods to support or replace liver function at the point of need. Moreover, the currently used scoring system for organ distribution – the MELD Score (Model of End Stage Liver Disease) - is not free of limitations. Thus modifications such as MELD-Na and UKELD have been proposed and the development of new methods to optimize organ allocation is the subject of current research.

3.1. Prediction of outcome

The prognosis of patients with cirrhosis of the liver is generally poor and associated with high rates of morbidity and mortality (1). Scoring systems have been developed which estimate the risk of death due to decompensation and liver failure allowing stratification of patients for liver transplantation. However, these scores are based on standard biochemical tests and clinical signs of liver insufficiency. In particular scoring systems such as Child Turcotte Pugh Score (CTPS) or MELD score reflect symptoms and complications of ESLD, rather than being a direct representation of liver function (5, 6). Thus little is known about the association of actual liver function and the prognosis of patients with liver cirrhosis.

3.1.1. Scoring systems in clinical practice

Child Turcotte Pugh Score / CTP classes

This scoring system was originally developed to predict survival among cirrhotic patients after portosystemic shunt operation for portal hypertension (6, 13). Until 2002 entrance criteria for admission to the waiting list for transplantation were based on this score.

Based on 5 parameters (3 laboratory parameters and 2 clinical parameters) the Child Turcotte Pugh Score (CTP Score) categorizes patients into 3 classes according to the sum of the individual findings. Rates of morbidity and mortality (one year survival) differ between groups (Group A – low risk; Group B - intermediate risk; Group C – high risk).

Calculation: Each measure is scored 1-3 according to the severity of impairment, indicating 3 as the most severe derangement (*table 1*).

Table 1: CTP scoring system.

Measure	1 point	2 points	3 points
Total bilirubin (µmol/l)	< 34	34 - 50	> 50
Serum Albumin (g/l)	> 35	28 - 35	< 28
INR	< 1.7	1.71 – 2.30	> 2.30
Ascites	None	Mild	Severe
Hepatic Encephalopathy	None	Grade I – II	Grade III - IV

Interpretation: Patients with chronic liver disease are classified into Class A to C.

5-6 points → Class A patients have a 3-year survival of 73%

7-9 points → Class B patients have a 3-year survival of 59%

10-15 points → Class C patients have a 3-year survival of 46% (14)

The major limitation of the CTP score is that it includes the stratification of ascites and encephalopathy, which are relatively subjective findings.

MELD

The allocation of deceased donor livers for transplantation in Europe and the United States is now based on the severity of illness as determined by MELD(6, 15). The score is derived from a linear regression model based on

- serum bilirubin,
- serum creatinine
- international normalized ratio (INR).

It is calculated according to the following formula:

$$\{MELD = 3.78(\ln Bil) + 11.2(\ln INR) + 9.57(\ln Cr) + 6.43\}$$

Figure 1: Formula for Calculation of MELD

(Bil = Bilirubin (mg/dL), INR= International Normalised Ratio, Cr = Creatinine (mg/dL))

The United Network for Organ Sharing (UNOS) has made modifications to the score. For example, if the patient has been dialyzed twice within the last 7 days, the value for serum creatinine used, should be 4.0mg/dL (16).

In interpreting the MELD Score in hospitalized patients, the 3-month mortality is approximately:

- 40 or more → 71.3% mortality
- 30–39 →52.6% mortality
- 20–29 → 19.6% mortality
- 10–19 → 6.0% mortality
- <9 →1.9% mortality (15)

MELD score does not reflect the urgency of transplantation for example in hepatocellular cancer (HCC). In the case of HCC, the need for LT is not life-threatening liver failure, but the progression of cancer to a point where a high probability of cure is no longer possible. For these instances there is an established modified system, called exceptional MELD. The exceptional MELD is not based on lab values, but has a fixed initial value and can be upgraded at 90-day intervals. An exceptional MELD score of 20 or 24 points is assigned to patients with stage T1 or T2 hepatocellular carcinoma (HCC), respectively(17). However, this strategy is based on scarce data and the optimal score for these patients remains uncertain.

MELD Na and United Kingdom model for End-Stage Liver Disease (UKELD)

MELD-Na was created using nationwide waiting list registration data from the United Network for Organ Sharing (18, 19). In 2005 and 2006, Mayo Clinic developed and validated a multivariable survival model to predict mortality at 90 days after registration. The predictor variable was the Model for End-Stage Liver Disease (MELD) score with the addition of the serum sodium concentration. In addition to the MELD score, the serum sodium concentration has been recognized as an important prognostic factor in patients with liver cirrhosis(20). For example, hyponatremia has been associated with the hepatorenal syndrome, ascites and death from liver disease.

In the UK transplant centres use the so-called UKELD score to evaluate the risk of mortality without transplantation. The score is derived from patient INR, serum creatinine, serum bilirubin and serum sodium (figure 2). With a UKELD score of 49 patients have approximately a 9% chance of dying within the next year while a UKELD score of 60 is predictive of a 50% 1-year survival (20).

$$\{UKELD = 5.395(\ln INR) + 1.485(\ln Cr) + 3.13(\ln Bil) - 81.565(\ln Na) + 435\}$$

Figure 2: Formula for Calculation of UKELD

(Bil = Bilirubin (µmol/L), INR = International Normalised Ratio, Cr = Creatinine (µmol/L), Na = Sodium (mmol/L)).

4. Aim of the study

The aim of this prospective study is to evaluate the prognostic value of liver tests and established scores regarding transplant-free survival and mortality. Beyond that, this study aims to determine new scoring systems which include measures of liver function.

5. Patients and Methods

This Section is confidential and so is not included in this version of the document.

6. Results

This Section is confidential and so is not included in this version of the document.

7. Discussion

This Section is confidential and so is not included in this version of the document.

8. Conclusions

Analysis of preliminary data confirms the potential of established markers to predict outcome in patients with ESLD. Liver specific tests that evaluate actual liver function show good tendencies in discriminating transplant free survivors versus non-survivors. However further patient recruitment is needed to provide a predictive model for enrolment into d-LIVER and for initiation of bio-artificial liver support therapy sessions.

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