ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

ISSN 1425-9524
© Ann Transplant, 2014; 19: 503-512
DOI: 10.12659/AOT.890977

Received: 2014.05.06
Accepted: 2014.07.04
Published: 2014.10.10

Preoperative Interleukin-22 Values Add Valuable Information for Outcome Prediction Following Orthotopic Liver Transplantation: A Preliminary Study

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Source of support: This work was supported by a personal grant to T.M.B. by the Clinic of Anaesthesiology, Intensive Care Medicine and Pain Therapy

Background: Recent findings support the idea that interleukin (IL)-22 serum levels are related to disease severity in end-stage liver disease. Existing scoring systems – Model for End-Stage Liver Disease (MELD), Survival Outcomes Following Liver Transplantation (SOFT) and Pre-allocation-SOFT (P-SOFT) – are well-established in appraising survival rates with or without liver transplantation. We tested the hypothesis that IL-22 serum levels at transplantation date correlate with survival and potentially have value as a predictive factor for survival.

Material/Methods: MELD, SOFT, and P-SOFT scores were calculated to estimate post-transplantation survival. Serum levels of IL-22, IL-6, IL-10, C-reactive protein (CRP), and procalcitonin (PCT) were collected prior to transplantation in 41 patients. Outcomes were assessed at 3 months, 1 year, and 3 years after transplantation.

Results: IL-22 significantly correlated with MELD, P-SOFT, and SOFT scores (Rs 0.35, 0.63, 0.56 respectively, $p<0.05$) and with the discrimination in post-transplantation survival. IL-6 showed a heterogeneous pattern (Rs 0.40, 0.63, 0.57, respectively, $p<0.05$); CRP and PCT did not correlate. We therefore added IL-22 serum values to existing scoring systems in a generalized linear model (GLM), resulting in a significantly improved outcome prediction in 58% of the cases for both the P-SOFT ($p<0.01$) and SOFT scores ($p<0.001$).

Conclusions: Further studies are needed to address the concept that IL-22 serum values at the time of transplantation provide valuable information about survival rates following orthotopic liver transplantation.

Keywords: End Stage Liver Disease • Liver Transplantation • Patient Outcome Assessment

Abbreviations: **ALD** – alcoholic liver disease; **Cc** – correlation coefficient; **CD** – cluster of differentiation; **CRP** – C-reactive protein; **ELISA** – enzyme-linked immunosorbent assay; **GLM** – generalized linear model; **HBV** – Hepatitis B virus infection; **HCV** – Hepatitis C virus infection; **HCC** – hepatocellular carcinoma; **ICU** – Intensive Care Unit; **IL** – interleukin; **LOS** – length of stay; **MELD** – Model for End-Stage Liver Disease; **NASH** – nonalcoholic steatohepatitis; **OLT** – orthotopic liver transplantation; **PCT** – procalcitonin; **P-SOFT** – pre-allocation survival outcome following liver transplantation; **Rs** – Spearman correlation coefficient; **SOFT** – survival outcome following liver transplantation; **Th** – T-helper cells

Full-text PDF: http://www.annalsoftransplantation.com/abstract/index/idArt/890977

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Background

In the most common causes of chronic liver failure – alcoholic liver disease (ALD) [1] and viral infections of the liver (Hepatitis B and C, HBV and HCV) [2,3] – disease progression is mainly mediated by lymphocytes within the liver. Liver biopsies show an enrichment of innate immunity cells associated with increased levels of pro- and anti-inflammatory cytokines [4–9]. It has been demonstrated that Th17-CD4 T cells are of particular importance for chronic liver failure [10].

In this study, we focused on IL-22, IL-6, and IL-10, which are cytokines known to be involved in the inflammatory response of chronic liver disease.

Interleukin 22 (IL-22) is one of the cytokines expressed by Th17 cells. Recent data have shown that IL-22 levels are increased in chronic hepatic failure [7,9,11–13]; moreover, data point to the importance of IL-22 in the induction of immune tolerance in liver transplant recipients [14]. The main biological role of IL-22 is to increase innate immunity and to enhance cell regeneration in several tissues (lung, intestine, and liver) [11,12,15–17]. However, considering the role of IL-22 in chronic liver inflammation and especially its role in disease progression in Hepatitis B, its complete function remains controversial [12]. Xiang et al. reported that IL-22 was negatively correlated to the histological activity index [18], suggesting a protective effect of IL-22, while Park et al. [7] demonstrated a positive correlation with severity of liver inflammation. Jiang et al. showed a significantly higher IL-22 expression in Edmondson Grade III-IV HCC patients versus Grade I–II, confirmed by both real-time polymerase chain reaction and immunohistochemistry [19]. Furthermore, Kronenberger et al. demonstrated that elevated serum levels of IL-22 correlate with mortality in advanced chronic ALD-, HBV-, and HCV-induced liver cirrhosis with and without HCC [13].

Several studies reported a correlation of high serum levels of interleukin 6 (IL-6) in hepatitis, liver cirrhosis, and HCC with a significant increase of severity of illness and poor prognosis for HCC patients [5,20]. During chronic viral infections of the liver, IL-10 has been shown to be of crucial importance in suppression of T cell activity during viral clearance, allowing persistence of viral infections to develop [21–23]. In summary, data indicate that IL-22, IL-6, and IL-10 are cytokines involved in the pathogenesis and disease progression of chronic liver failure.

In clinical practice, several scoring systems exist to predict the patient's individual life expectancy with or without transplantation [24]. In the pre-transplantation period, the MELD score (Model for End-Stage Liver Disease) is a validated tool for measuring the severity of liver disease and the individual risk of mortality by indexing several physiological measures [25–28].

The Survival Outcomes Following Liver Transplantation (SOFT) score has been established in order to predict post-transplantation survival at 3 months [24]. The SOFT Score utilizes 18 risk factors – 13 recipient factors, 4 donor factors, and 1 operative factor – to predict survival following transplantation. A simplified version is the Pre-allocation-SOFT (P-SOFT) score, excluding some factors used in the SOFT score (portal bleeding in the last 48 h prior to transplantation, and donor variables).

However, these scores do not include direct markers of acute inflammation or innate immune response. Immune system activation or preconditioning may significantly impair outcome after transplantation

We tested the hypothesis that serum levels of cytokines at the time of transplantation, particularly IL-22, correlate with survival. To test whether outcome prediction of existing scores might change, we added IL-22 serum levels to these scores using a generalized linear model.

Material and Methods

The study was approved by the local ethics committee of the University Hospital Frankfurt am Main. All patients listed for orthotopic liver transplant and over 18 years of age were eligible to be included in the study. Patients scheduled for re-transplantation were excluded from the study due to pre-existing immunosuppressive drug medication at the time of inclusion in the study.

Blood samples

Blood samples and blood specimens for blood cultures were taken before transplantation after insertion of the arterial cannula. To monitor for acute infection, postoperative blood samples were obtained upon admittance to the ICU and once a day for the next 5 consecutive days. Blood samples were centrifuged and aliquots were stored at –80°C for further investigation.

Scores

MELD, P-SOFT, and SOFT scores were evaluated before transplantation for each patient (Table 1).

Laboratory parameters

Levels of IL-22 were determined by ELISA (R&D Systems, Wiesbaden Nordenstadt, Germany), and IL-6 and IL-10 by Immulite 2000 (Siemens Medical Solutions Diagnostics GmbH, Bad Nauheim, Germany). Measurements of CRP and PCT were performed as routine laboratory markers at the central laboratory of the hospital.

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Table 1. Calculation models for P-SOFT, SOFT and MELD score.

Risk factor	Points allotted
Preallocation score to predict survival outcomes following liver transplantation (P-SOFT)	
• Age >60	4
• BMI >35	2
• One previous transplant	9
• Two previous transplants	14
• Previous abdominal surgery	2
• Albumin <2.0 g/dL	2
• Dialysis prior to transplantation	3
• Intensive care unit pretransplant	6
• Admitted to hospital pretransplant	3
• MELD score >30	4
• Life support pretransplant	9
• Encephalopathy	2
• Portal vein thrombosis	5
• Ascites pretransplant	3
Score to predict survival outcomes following liver transplantation (SOFT)	
• P-SOFT score	Total from above
• Portal bleed 48 h pretransplant	6
• Donor age 10–20 years	–2
• Donor age >60 years	3
• Donor cause of death from cerebral vascular accident	2
• Donor creatinine >1.5 mg/dL	2
• National allocation	2
• Cold ischemia time 0–6 h	–3
Model for End-Stage Liver Disease (MELD)	
• Serum creatinine	
• Total serum bilirubin	
• International normalized ratio (INR)	

Calculation of SOFT and P-SOFT score as published by Rana et al. [24]. The original MELD score is calculated as followed: 10× (0.957× ln(serum creatinine) +0.378× ln(total serum bilirubin) + 1.12× ln(INR) +0.643× (Cause of cirrhosis (0 alcohol, cholestatic, 1 other etiologies) [28]. Currently the MELD score is calculated without of the cause of cirrhosis.

Immunosuppression and antiinfective therapy

During the operation, all patients received 500 mg methylprednisolone as a single dose; the immunosuppressive regimen after transplantation consisted of tacrolimus and mycophenolate mofetil. An anti-infective therapy of cefotaxime and metronidazole was routinely administered for the first 3 days postoperatively.

Outcome

For the medical follow-up after transplantation, patients regularly attended the university hospital. One patient moved to another city, requiring the medical follow-up to be performed at the respective local hospital.

Statistical analysis

The statistical analysis was performed with Sigma Plot 11.0 (Systat Software, Inc, San Jose, CA) and Matlab 2008a with the Statistical Toolbox (Mathworks, Inc, Natick, MA). Correlations between values were modelled with a multilinear robust regression model using a bisquare weighting function, accounting for possible outliers. Accordingly, Rho (Rs) and p values were calculated with the Spearman method. Survival rates were plotted using the Kaplan-Meier estimate of the cumulative distribution function and tested by log rank test. C statistics were calculated as the area under the curve of the appropriate receiver operating characteristic curve. Corresponding confidence intervals were calculated via bootstrap statistics. P values below 0,05 are considered significant throughout this article.

Generalized linear model (GLM)

The potential improvement of the existing scoring systems MELD, SOFT and P-SOFT was modelled by adding the most promising cytokine – IL-22. To this end, a generative nested model approach was used (i.e., a GLM model of the Poisson distribution of the survival time), enabling 3 tests to be performed on the data. First, it was tested whether IL-22 provides an increased explanatory effect on the survival time. Second, the differential effect of IL-22 inclusion on the survival time prediction was modelled and isolated. Finally, a leave-one-out cross-validation assessed the individual importance of including IL-22 when predicting survival time of a new patient not included in the study [29]. This last step is absolutely essential to assess the relevance and generalizability of the reported findings given the relatively small sample size of this study.

Results

We included 41 patients (30 males, 11 females) in this study from November 2005 to November 2007 (Table 2).

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Table 2. Demographic data and underlying disease of study population, outcome data are depicted for one year survival.

	All	1 year	
		Alive	Deceased
n	41	27	14
Gender			
Male	30	19	11
Female	11	8	3
Age (years)	57	55	58
Interquartile range	47–64	53–62	46–66
Scores			
APACHE II	16	14	16
Interquartile range	13–19	12–17	14–23
MELD (mean ±SD)	23.2±8.8	19.9±6.9	29.4±9.3
P-SOFT (mean ±SD)	10.7±8.0	8.1±6.0	15.6±9.5
SOFT (mean ±SD)	12.8±8.0	10.0±5.7	18.1±9.4
LOS ICU (d)	5	5	8
Interquartile range	2–10	2–6	2–34
LOS hospital (d)	28	23	37
Interquartile range	19–41	19–35	23–55
Day alive (d)	106	>1year	98
Interquartile range	38–212		34–136
Underlying disease:			
Cirrh. kryptogenic	2		
Cirrh. HBV	2		2
Cirrh. HBV + HCC	3		1
Cirrh. HBV + HCV	1		
Cirrh. HCV	7		3
Cirrh. HCV + HCC	8		1
Cirrh. NASH	1		1
Cirrh. ethyltoxic	8		2
Cirrh. ethyltoxic + HCC	5		1
Cirrh. sclerosing cholangitis			1
Acute liver failure	1		1
Intrahep. carcinoma bile duct	1		1

APACHE II – Acute Physiology + Age + Chronic Health score II at admission to ICU; P-SOFT – Predict Survival Outcome Following Liver Transplantation; SOFT – Survival Outcome Following Liver Transplantation; LOS – length of stay; Cirrh – Cirrhosis; HBV – Hepatitis B virus infection; HCC – hepatocellular carcinoma; HCV – hepatitis C virus infection; NASH – nonalcoholic steatohepatitis.

The most common indication for transplantation was hepatitis C cirrhosis (36.5%), of which 53% of patients also presented with HCC. The second group of patients had ALD (31.7%), of whom 38,5% also had HCC. In 12% of patients, the indication for transplantation was hepatitis C-induced liver cirrhosis (Table 2).

Predicted and actual survival – MELD, SOFT, and P-SOFT scores

High scores in all 3 scoring systems – MELD, SOFT, and P-SOFT – correlated negatively with survival in the study population (MELD: Rs=–0.44, p<0.01; SOFT: Rs=–0.45, p<0.01; P-SOFT: Rs=–0.42, p<0,01).

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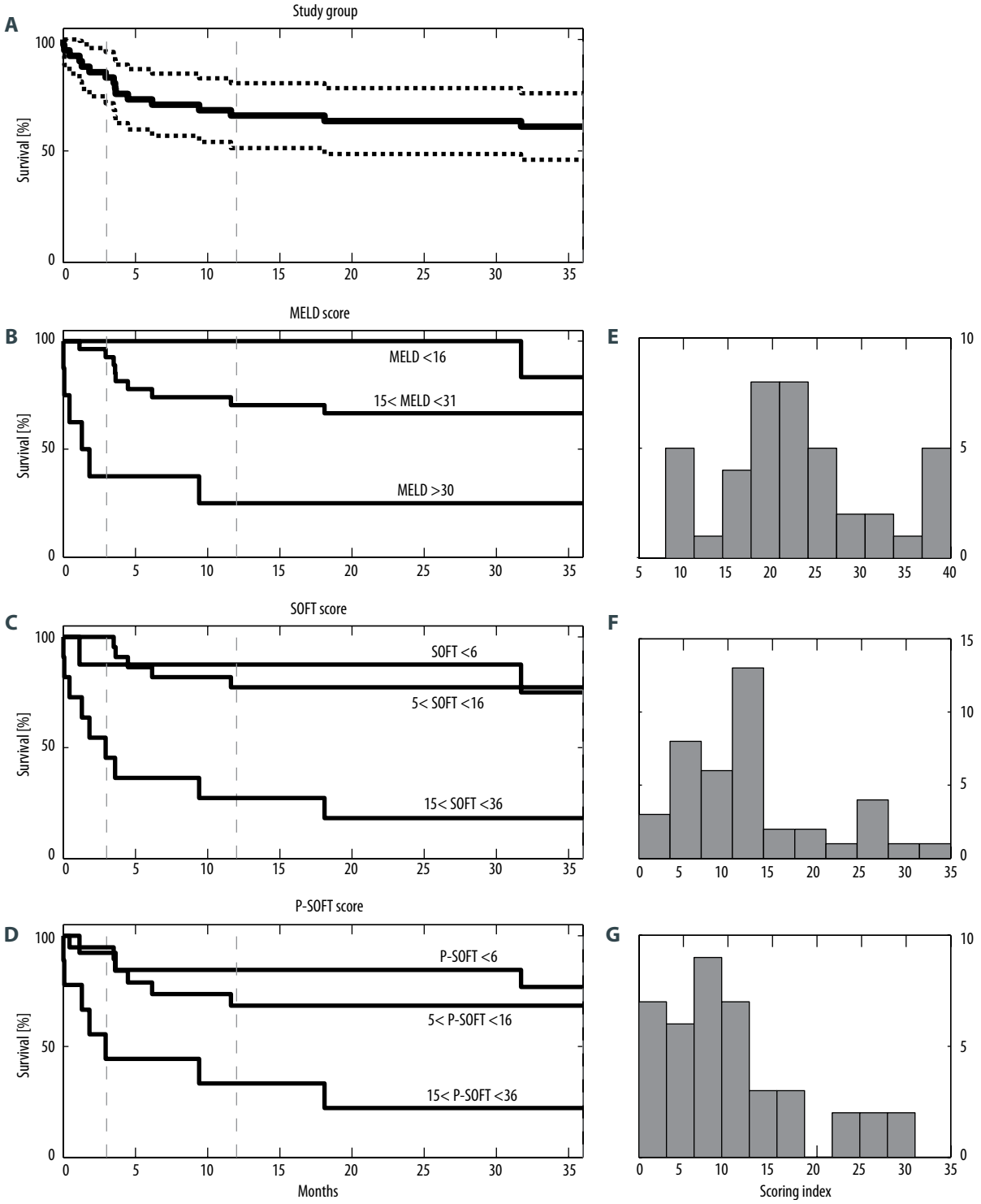

Figure 1. Kaplan-Meier survival rates of the entire study population, MELD, SOFT, and P-SOFT scores. The left column (**A–D**) depicts the Kaplan-Meier survival rates. On the right side, (**E–G**) corresponding histograms show the underlying distribution of scoring numbers. (**A**): Survival rate of study population and corresponding 95% confidence intervals of the Kaplan-Meier curve; (**B/E**): Survival rate with respect to MELD score; Log rank significantly different after 3 months and 1 and 3 years; (**C/F**): Survival rate with respect to SOFT score; Log rank test significantly different between categories <16, >15 at all 3 time points (3 months and 1 and 3 years); (**D/G**): Survival rate with respect to P-SOFT score; Log rank test significantly different between categories <16, >15 at all 3 time points (3 months and 1 and 3 years)

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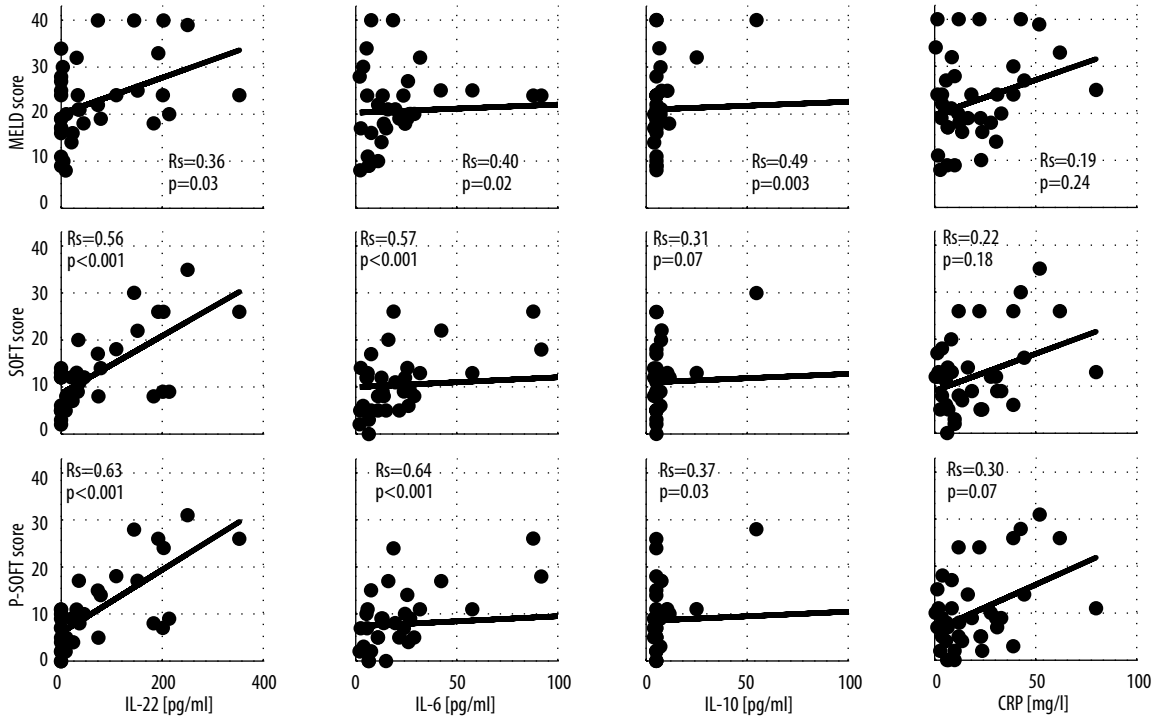

Figure 2. Spearman correlation between MELD, SOFT, P-SOFT score, and IL-22, IL-6. IL-10, CRP, and PCT. Correlation (Spearman) between MELD score (first line) and IL-22 (first column), IL-6 (second column), IL-10 (third column), CRP (fourth column); corresponding correlations to SOFT score (second line) and P-SOFT score (third line). For IL-6, 3 outliers are not depicted within the scale (>1000 pg/ml); 2 outliers for IL-10 are not depicted within the scale (>1000 pg/ml). IL: Interleukin; CRP: C-reactive protein.

To accommodate the differences in progression of end-stage liver disease at the time of inclusion, patients were assigned to 1 group in each of the 3 scoring systems. MELD >30 predicted a 1-year expected survival of 25%, MELD 15–30 predicted a 1-year expected survival of 70,4%, and MELD <15 predicted that all 7 patients survived 1 year (log rank test at 3 months, 1 year, and 3 years; p<0,001; Figure 1B). SOFT (P-SOFT) scores 6–15 indicated a 1-year post-transplantation survival rate of 72% (65%) and scores above 15 predicted survival after 1 year of 25% (35%) (log rank test at 3 months, 1 year, and 3 years; p<0,05; Figure 1C, 1D). Sub-classification in categories below 6 and 6–15 did not show a significant difference in survival for the SOFT (P-SOFT) score.

C statistics were evaluated to 0.74 [CI: 0.51–0.89] for the MELD score, 0.71 [CI: 0.49–0.88] for the SOFT score, and 0.70 [CI: 0.46–0.87] for the P-SOFT score.

Cytokines

IL-22 levels in the serum correlated significantly with MELD, SOFT, and P-SOFT scores, exhibiting a potentially meaningful pattern with high variability (Rs 0.36, 0.56, 0.63 respectively; Figure 2). IL-6 correlated to the 3 scores, with comparable Rho values as well. IL-10 and PCT were shown to correlate significantly with MELD and P-SOFT scores only (Figure 2) and CRP serum levels correlated with none of the 3 scoring systems (Figure 2).

Cytokines and survival

Similar to the Kaplan-Meier survival plots of the scoring systems, we assigned the respective plasma values of the patients to 2 categories each. The categories were separated by a threshold of 100 pg/ml for IL-22, 5 pg/ml for IL-6 and IL-10, 50 mg/l for CRP, and 0.5 ng/ml for PCT.

Patients with IL-22 levels <100 pg/ml before transplantation had a 1-year survival rate of 77.8% compared with 33.3% if IL-22 had been >100 pg/ml (Figure 3A, 3D) (log rank test for 3 months, 1 year, and 3 years p <0.05). In addition to IL-22, IL-10 and PCT showed significant differences in survival. One-year survival in patients with IL-10 levels >5 pg/ml was 41.7% compared with 82.6% in patients with IL-10 serum levels <5 pg/ml (p<0.05 for 1 and 3 years; Figure 3B, 3E). If PCT levels were <0.5 ng/ml, patients had a 1-year survival of 76.9%, in contrast to 16.7% with PCT levels >0.5 ng/ml (p<0.001 for 1 and 3

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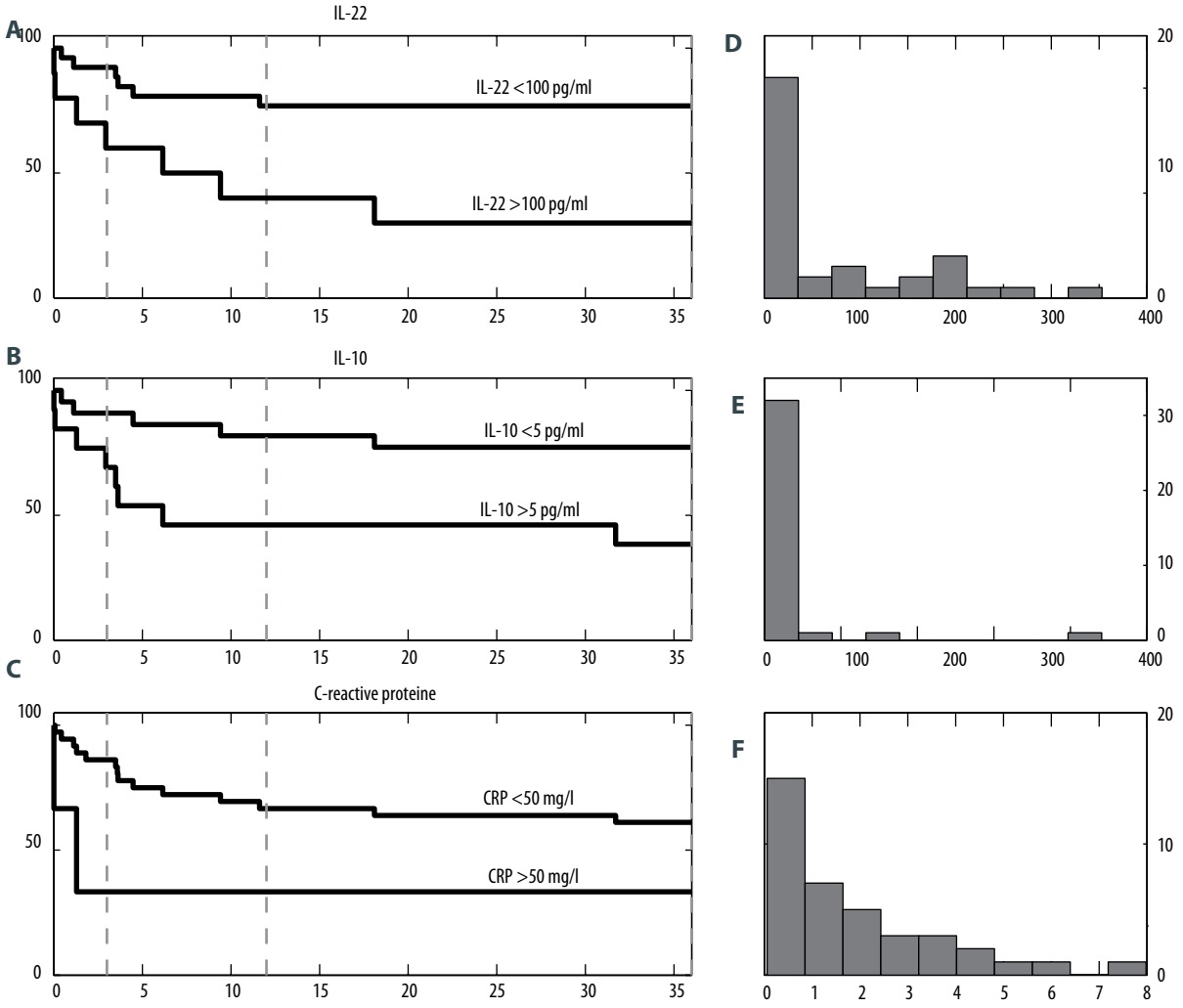

Figure 3. Kaplan-Meier survival rates with respect to IL-22, IL-10, CRP, and PCT, and corresponding histograms. Left column (A-D) Kaplan-Meier survival rates; on the right side (E-H) corresponding histograms. (**A/D**) Survival rate with respect to IL-22 >/< 100 pg/ml, in log rank test the only inflammatory marker significantly different at all three time points (3 months and 1 and 3 years); (**B/E**) Survival rate with respect to IL-10 >/< 5 pg/ml, Log rank significantly different after 1 and 3 years; (**C/F**) Survival rate with respect to CRP >/< 50mg/l, Log rank test without significant differences; IL: Interleukin; CRP: C-reactive protein.

years). The log rank test assigned no significant difference in survival for IL-6 and CRP (CRP Figure 3C, F; IL-6 is not depicted).

Monitoring for infection

Monitoring for infection included the determination of CRP, PCT, and IL-6 levels. Blood cultures were obtained from each patient before transplantation. In 2 patients, blood cultures drawn before transplantation were positive. Microbiological testing provided evidence of *Staphylococcus epidermidis* and *Enterococcus faecalis* in 1 patient and *Klebsiella pneumoniae* in the other. These patients had high serum values of CRP and IL-6, and in 1 patient PCT without evident clinical signs of infection (e.g., elevated body temperature, and tachycardia). In 1 other patient, preoperative blood cultures tested negative; however, blood cultures drawn after transplantation tested positive for *Enterococcus faecium*. Although no clinical signs of infection were present, IL-6 serum values were high prior to transplantation, creating an outlier in the single-value plots.

Length of ICU/hospital stay, cause of death

No correlation was found between length of stay (LOS) in the ICU or LOS in the hospital and levels of cytokine, CRP, or PCT. The overall 1-year survival rate was 66%; after 3 years, 16 (39%) out of 41 patients had died (Table 3). The main cause

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Table 3. Depicts patients diseased during 3 year observation after orthotopic liver transplantation.

Age	Gender	Underlying disease	Cause of death	LOS ICU	LOS hospital	Day alive
42	Male	Cirrhosis (HCV)	Acute hepatic failure, SIRS shock	1	37	110
65	Male	Cirrhosis (sclerosing cholangitis)	ARDS	2	2	2
68	Male	Cirrhosis (HCV, HCC)	HCV reinfection	3	28	353
66	Male	Cirrhosis (ethyltoxic)	Heart failure	10	59	187
54	Male	Cirrhosis (ethyltoxic)	Heart failure	15	35	550
52	Male	Cirrhosis (ethyltoxic)	Heart failure	13	13	13
66	Male	Intrahepatic carcinoma of the bile duct	Heart failure	0	0	0
36	Male	Cirrhosis (HBV)	Hepatic bleeding after Re-OLT	4	36	286
46	Male	Acute liver failure (HBV)	Intracerebral bleeding	39	39	39
66	Female	Cirrhosis (HCV)	Sepsis, HCV-re-infection	18	60	109
62	Male	Cirrhosis (HBV, HCC)	Sepsis, lung cancer	4	14	964
58	Male	Cirrhosis (HBV, HCC)	Sepsis, MOV	34	34	34
42	Male	Cirrhosis (HCV)	Sepsis, MOV	5	23	89
58	Female	Acute liver failure	Sepsis, MOV	55	55	55
59	Female	Cirrhosis (ethyltoxic)	Sepsis, MOV	1	41	136
47	Male	Cirrhosis (NASH)	Sepsis, MOV	106	106	106

Displayed is the underlying disease before liver transplantation and the cause of death after transplantation. HCV – hepatitis c virus infection; HBV – hepatitis b virus infection; HCC – hepato cellular carcinoma; ARDS – adult respiratory distress syndrome; NASH – nonalcoholic steatohepatitis; Re-OLT – retransplantation; SIRS – systemic inflammatory response syndrome; MOV – multi organ dysfunction syndrome; LOS – length of stay; ICU – intensive care unit.

of death was sepsis in 44% of the patients and 25% of the patients died due to heart failure.

Generalized linear model (GLM)

To test whether IL-22 provides explanatory effect on survival time, its prediction was compared across 2 models using the nested model approach.

The first model (M1) uses 1 of the 3 scoring systems – MELD, SOFT, and P-SOFT – as a predictor. The second model (M2) uses IL-22 in addition to the score's existing parameters. We assessed predictability using a leave-one-out cross-validation. To this end, the data from all but 1 patient's data were used to train model M1 and M2. These 2 models were then used to predict the survival time of the 1 excluded patient. We assessed improvement in predictability in 2 ways. First, we assessed the percentage of patients for whom the inclusion of IL-22 improved the accuracy of prediction. Second, the absolute improvement of the survival time prediction error for every patient across M1 and M2 was assessed using a likelihood ratio test (p-values derived using a chi-squared test).

In the cross-validation, adding IL-22 to the scoring systems of MELD, SOFT, and P-SOFT score improved the prediction of survival rate in 16%, 58%, and 58% of patients, respectively. The likelihood to observe the measured improvement by chance was determined to be $p=0.33$ (MELD), $p<0.01$ (SOFT), and $p<0.001$ (P-SOFT).

Discussion

Ongoing inflammation within the liver is of major importance for the progression of liver disease. In an attempt to link inflammatory markers to patient survival, the correlation of 5 preoperative markers to post-transplantation survival was investigated (IL-22, IL-6, IL-10, CRP, and PCT). We found that serum levels of IL-22 just prior to liver transplantation correlate with postoperative survival outcome. Using a generalized linear model, we strongly presume that the serum levels of IL-22 add further value to existing scoring systems appraising the individual survival rate.

Regarding survival, C statistics for the MELD, SOFT, and P-SOFT scores (MELD 0,74 (CI 0,51–0.89); SOFT 0.71 (CI 0.49–0.88); and

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P-SOFT 0.70 (CI 0.46–0.87)) are in good accordance with values published (0.63 (CI 0.62–0.65), 0.69 (CI 0.67–0.70) and 0.70 (CI 0.69–0.71)) [24]. Nevertheless, the 1-year survival rate of 66% (95% CI 41.2–90.5%) is low compared to published data [24,30] presenting 1-year survival rates of up to 80%. Our patient cohort presented with a mean MELD score of 23.2±8.8 points for the study population (46% of patients with a MELD score >30) and a mean MELD score of 29.±49.3 points for the patients deceased after transplantation. A MELD score of >21 points is accompanied by a higher rate of morbidity and mortality [30,31]. Patient survival rates were, without adjustment for disease severity, in the range of the data published by the German data quality system (Aqua Institute) for 2009 (1-year survival rate of 76.6% (95% CI 71–82.1%) [32]. These rates included only patients with a complete 1-year follow-up period after transplantation (79.8% of initial cohort). Thus, the survival rate upon inclusion of all patients is lower than 76.6%. In a worst-case scenario including all patients missed within the first year of follow-up as deceased, a survival rate of 63.1% was reported [32].

Our data demonstrate a significant correlation of the disease severity of chronic hepatic failure prior to transplantation, based on the MELD score, IL-22, IL-10, IL-6, and PCT. The correlation of IL-22 and IL-6 with disease severity is in accordance with data published by Park, Jiang, and Pang et al. for IL-22 [7,19,20]. There was no correlation of IL-22 levels with SIRS or acute sepsis prior to transplantation. Nevertheless, in accordance with published data, the patient with suspected sepsis had increased levels of serum IL-22 [33].

We interpret our data in the context of recent publications, which reported that IL-22 and IL-6 were mainly increased due to the severity of disease and acute or ongoing infection. In addition, IL-22 and IL-6 correlated to the SOFT score items “hospitalization” and “life support prior to transplantation”, whereas PCT and CRP levels had no significant correlation with these items. When testing IL-22, IL-6, IL-10, CRP, and PCT in the log rank test for post-transplantation outcome prediction at 3 months, 1 year, and 3 years after transplantation, only IL-22 showed significant differentiation between survivors and non-survivors at all 3 time points. IL-10 and PCT could significantly distinguish between survivors and non-survivors after 1 and 3 years.

In summary, IL-22 correlates with severity of chronic liver disease (MELD, P-SOFT, “admittance to hospital prior to transplantation”, and “life support prior to transplantation”), with SOFT score, and with discrimination in post-transplantation outcome.

We therefore tested whether including IL-22 expression level in a generalized linear model potentially improves outcome prediction in patients undergoing liver transplantation. We were able to demonstrate in the cross-validation that adding IL-22 to the scoring systems SOFT and P-SOFT results in an improved prediction of survival rate in 58% of patients. In contrast to the SOFT and P-SOFT scores, the MELD score did not show statistical significance regarding the likelihood of observing the measured improvement by chance (p=0.33 (MELD). It is unclear whether the different representations of the acute clinical condition of the patients correspond to MELD, SOFT, and P-SOFT scores.

The main limitation of our proof-of-concept study is the limited study size. A relatively small sample size requires an efficient and robust analysis, as well as rigorous testing of its results with respect to their importance for new and unobserved data. The robustness of our method lies in the fact that we modelled the data using a GLM – modelling strictly positive Poisson-distributed survival times instead of using a standard multivariate analysis that would falsely assume Gaussian-distributed data. Furthermore, to identify the individual contribution of IL-22 to the prediction of survival time, we used a nested model approach that enabled us to identify an improved prediction by the inclusion of IL-22. Most importantly, the generative model approach enabled us to test the generalizability of the results, which is especially important in studies with small sample sizes.

Conclusions

Our data suggest that the use of IL-22 serum levels in a generalized linear modelling approach might improve outcome prediction of the SOFT and P-SOFT scores. Future studies are needed, however, to validate our findings in larger patient collectives.

Statement

The authors have no conflicts of interest to disclose. We declare that no donor organs were obtained from executed prisoners or other institutionalized persons.

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