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ORIGINAL ARTICLE

Elevated gamma-glutamyltransferase is associated with mortality in lung transplantation for cystic fibrosis

Alexander Wree,[1] Lars P. Bechmann,[1] Nevitha Kumarasamy,[1] Urte Sommerwerck,[2] Christoph Jochum,[1] Heinz Jakob,[3] Hideo A. Baba,[4] Guido Gerken,[1] Markus Kamler[3] and Ali Canbay[1]

1 Department of Gastroenterology and Hepatology, University Hospital Essen, Essen, Germany
2 Ruhrlandklinik, Department of Respiratory Medicine, Tüschener Weg, Essen, Germany
3 Department of Thoracic and Cardiovascular Surgery, West German Heart Center Essen, University Hospital Essen, Essen, Germany
4 Institute for Pathology and Neuropathology, University Hospital Essen, Essen, Germany

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Correspondence
Ali Canbay MD, Professor of Medicine, Department of Gastroenterology and Hepatology, University Hospital Essen, Hufelandstrasse 55, 45122 Essen, Germany.
Tel.: +49 201 723 84713;
fax: +49 201 723 5719;
e-mail: ali.canbay@uni-due.de

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Summary

Cystic fibrosis (CF) is a life-threatening autosomal recessive hereditary disease, affecting multiple organs. In end stage disease, lung transplantation improves the quality of life and prolongs survival. CF liver disease (CFLD) as co-morbidity develops in 8–17% of CF patients. We aimed to investigate the impact of liver injury on prognosis following lung transplantation. Thirty-one patients with CF who underwent double lung transplantation (DLTx) from 1999 to 2009 were included. Post-transplant survival, liver serum parameters as well as INR, creatinine and the MELD-Score were determined preoperatively, 1 day and 4 weeks postoperatively. Prognostic impact of liver function on outcome was analysed. Mean patient age was 25 (15–38) and post-transplant 1 year-survival was 74%, 3 years 71% and 5 years 68%. Patients were grouped according to post-transplant survival, those deceased within the first year as group I (n = 8) and patients who survived longer as group II (n = 23). Group I exhibited significantly elevated gamma-glutamyltransferase (GGT), bilirubin and reduced platelets postoperatively. Low platelet count, increased bilirubin and GGT were associated with mortality after DLTx. Prospective studies are needed to determine a potential use and clinical implications for liver function tests in patients with CF before lung transplantation.

Introduction

Cystic fibrosis is the most common life-threatening autosomal recessive hereditary disease among Caucasians. CF is caused by mutations in an epithelial chloride channel encoded by the cystic fibrosis transmembrane conductance regulator (CFTR) gene and approximately one in 3500 newborns is affected [1,2]. CF impairs multiple organ systems, including the lung, pancreas, liver, intestine, gallbladder, sweat glands and male reproductive tract [2]. CF liver disease (CFLD) develops in 8–17% of CF patients and manifests as portal hypertension and abnormalities in liver function [3]. In the liver, loss of the CFTR protein leads to abnormal Cl^-, HCO_3^- and H_2O transport in the cholangiocytes causing thickening of bile and decreased bile flow. A progression to liver fibrosis and even liver cirrhosis in cystic fibrosis (CFLC) with portal hypertension can be observed in 3–5% of all CF patients [3,4].

Although CF impacts the function of multiple organ systems, respiratory failure remains the most frequent impairment and cause of death [5]. With the development of new therapies, important strides have been made in improving the quality and duration of life. Thus, the median life expectancy of CF patients nowadays has increased from 27 to 38 years of age over the last two decades [6]. However, when conventional therapies fail, lung transplantation remains the only option to improve

the quality of life and prolong survival [5]. Over the last 12 years, approximately 16% of all lung transplantations were performed in patients with end-stage CF [7,8]. The overall survival rate in patients who have undergone lung transplantation has improved over time, but remains still lower than those of other solid-organ transplants. Actual survival rates in all lung-transplants are approximately 78% at 1 year, 63% at 3 years and 51% at 5 years [7]. CF patients tend to have a more favourable long-term survival than patients with chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis after lung transplantation, most likely because of their younger age and a lack of co morbidities [7].

Most lung-transplant programmes will consider a patient with portal hypertension for lung transplantation, as long as hepatocellular function is intact, which usually implies fairly normal liver-function tests.

Therefore, the aim of the present study was to evaluate the impact of liver function on the outcome in patients with CF without known CFLC, who underwent double-lung transplantation (DLTx) at the University of Essen from 1999 to 2009.

Patients and methods

Study population

In the presented study, 31 patients (14 female/17 male) were included, who suffered from end stage CF and were treated with DLTx from 1999 to 2009. Demographic data, clinical course as well as laboratory parameters were retrospectively analysed. Preoperative workup of lung transplant recipients was performed in line with local standard operating procedures, which remained unchanged over the observation period and included functional and imaging tests of lung and heart, extensive laboratory tests, and examination of several specialists to exclude infectious foci. None of the patients had a known pre-existing CF related liver disease.

Data collection

Patients' data included date of birth, gender, time to transplantation, high urgency status, operation day and postoperative development. Results of laboratory investigations were collected on the day of DLTx preoperatively, 1 day and 4 weeks after first DLTx. In four patients, who were retransplanted within a median of 26 months, only the course of the first transplantation was used for data analysis, as these patients fall into a different category with different risks and complications. A complete blood count including haemoglobin level, red cell count, mean red cell volume, mean red cell haemoglobin, white cell and platelet count was performed. To characterize the liver function, international normalized ratio (INR), prothrombin time, transaminases (ALT, AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, cholesterine, albumin and total serum protein were assessed. Further c-reactive protein (CRP), creatinine, urea, uric acid, amylase and lipase were included. Preoperative serological tests were performed for viral hepatitis (HAV, HBV, HCV), adenovirus, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and Parvovirus B19 antibodies. All serum derived parameters listed were determined by standard tests in the central laboratory unit of the University Hospital Essen. Detailed laboratory values and follow-up data including cause of death for individual patients are shown in Table S1.

MELD-Score was calculated for each patient as follows [9]:

$$\begin{aligned} &10 \times 0.957\ \mathrm{Ln}(\text{serum creatinine}[\text{mg/dl}]) \\ &\quad + 0.378\ \mathrm{Ln}(\text{total bilirubin}[\text{mg/dl}]) \\ &\quad + 1.12\ \mathrm{Ln}(\mathrm{INR}) + 0.643 \end{aligned}$$

Dataanalysis

Data are expressed as mean ± SD or as median and range/quartiles for continuous variables and as absolute number or percentage for categorical variables. Mann–Whitney *U*-test and Wilcoxon-test was used to compare medians, Kaplan–Meier-Analysis and Log Rank test were performed for *post hoc* survival analysis. Significance was assumed at 5%, two-sided significance level. Data were analysed using a Statistical Package from Social Sciences [SPSS 17 (SPSS Inc., Chicago; USA)].

Results

General characteristics and time to transplantation

Table 1 summarizes the characteristics of 31 patients (14f/17m) without apparent clinical signs of CFLC. The median age was 25 years (15–38 years). All patients received DLTx, after a median listing time of 224 days (15–808 days). Of 31 patients, 23 were finally listed high urgency (HU) before the first DLTx performed with a median duration of 69 days (11–266 days) on HU listing. A second transplantation was necessary in four patients within a median of 26 months after the first transplantation (11–45 months) because of organ failure. As complications and risks of retransplantations highly deviate from those of primary transplantations, only the clinical course of the first transplantation for each patient was included in the given data. The median listing time before second DLTx was 90 days (85–150 days). Two patients were listed HU for the second DLTx (median 102 days).

Table 1. Study participants' characteristics, listing times and survival.

		Median	Min	Max
First lung transplantation				
Gender	14 f/17 m			
Age	[years]	25	15	38
Listing time	[days]	224	15	808
High urgency listing	9 f/14 m			
Time on urgency listing	[days]	69	11	266
Second lung transplantation				
Gender	3 f/1 m			
Listing time	[days]	90	85	150
High urgency listing	1 f/1 m			
Time on urgency listing	[days]	102	89	114
			Number	%
Follow up/survival				
Died in first 3 months			5	16
Died from month 3 to 12			3	10
Died from year 1 to 5			2	7
Survival longer than 5 years			21	67
Total			31	100
Retransplanted			4	13

f: female; m: male.

Post-transplant survival

Patient follow-up ranged from 6 to 3711 days with a median of 1000 days. Five patients died in the first 3 months and another three in the first year after transplantation, these were grouped as early death (group I). The main causes of death in the first year after DLTx were because of systemic bacterial or fungal infections with sepsis and consecutive multi-organ failure. No direct liver related causes of death were reported. The remaining 23 patients were classified as long time survivor (group II; Table 1). Two patients died several years after DLTx because of malnutrition in case of intestinal CF manifestation or because of acute kidney failure. The respective patients-survival rates were 74% after 1 year, 71% after 3 years and 68% after 5 years.

Preoperative blood and serum parameters

Preoperatively patients exhibited slightly reduced haemoglobin levels (median 11.5 g/dl; Table 2), elevated leucocytes (median 13/nl), next to normal coagulation parameters (INR 0.8–1.25), and not significantly elevated transaminases (AST/ALT 7–65 U/l). Normal GGT values were found in the majority of the patients (median GGT 31 U/l), with elevated levels in four Patients (116, 355, 436, 513 U/l). Elevated CRP level (median 5.0 mg/dl, max. 23 mg/dl), normal bilirubin (median 0.3 mg/dl) and creatinine values (median 0.71 mg/dl) were detected (Fig. 1), resulting in MELD scores ranging from 6 to 15 (median 6) (Fig. 2). Serum creatinine was only elevated in one patient (2.14 mg/dl).

Pre- and postoperative reduced platelet levels are associated with early death

Although in normal range, platelet count on the day of transplantation was significantly lower ($P < 0.01$) in

Table 2. Laboratory parameters for early death and long time survivors at first lung DLTx.

		Group I			Group II			
	Norm	Median	Min	Max	Median	Min	Max	*P* value
Laboratory results prior lung transplantation								
Haemoglobin [g/dl]	13.7–17.2	11.6	8.5	14.7	11.5	9.4	15.5	0.65
Platelets [nl]	140–320	239	66	364	350	164	980	**0.01**
AST [U/l]	0–50	21	9	58	18	7	65	0.57
ALT [U/l]	0–50	26	5	64	19	6	54	0.48
INR		1.15	0.95	1.24	0.99	0.88	1.25	0.08
Bilirubin [mg/dl]	0.3–1.2	0.4	0.3	0.6	0.3	0.1	0.8	0.27
Creatinine [mg/dl]	0.9–1.3	0.81	0.50	2.14	0.71	0.50	1.18	0.40
MELD	06–40	8	6	15	6	6	9	**0.03**
Laboratory results 28 days after transplantation								
Haemoglobin [g/dl]	13.7–17.2	9.8	8.8	13.2	9.5	7.6	12.0	0.38
Platelets [nl]	140–320	124	10	221	319	43	718	**0.00**
AST [U/l]	0–50	32	14	459	16	8	65	0.06
ALT [U/l]	0–50	43	22	363	23	7	58	**0.04**
INR		1.12	1.04	2.43	0.99	0.90	1.26	**0.02**
Bilirubin [mg/dl]	0.3–1.2	2.1	0.3	41.0	0.4	0.2	11.5	**0.01**
Creatinine [mg/dl]	0.9–1.3	0.93	0.45	2.03	0.93	0.51	2.32	1.00
MELD	06–40	15	7	24	7	6	18	**0.01**

Group I, patients who died within 1 year after DLTx; Group II, patients who survived more than 1 year after DLTx; tested with Mann–Whitney test. Bold value indicates statistically significant ($P < 0.05$).

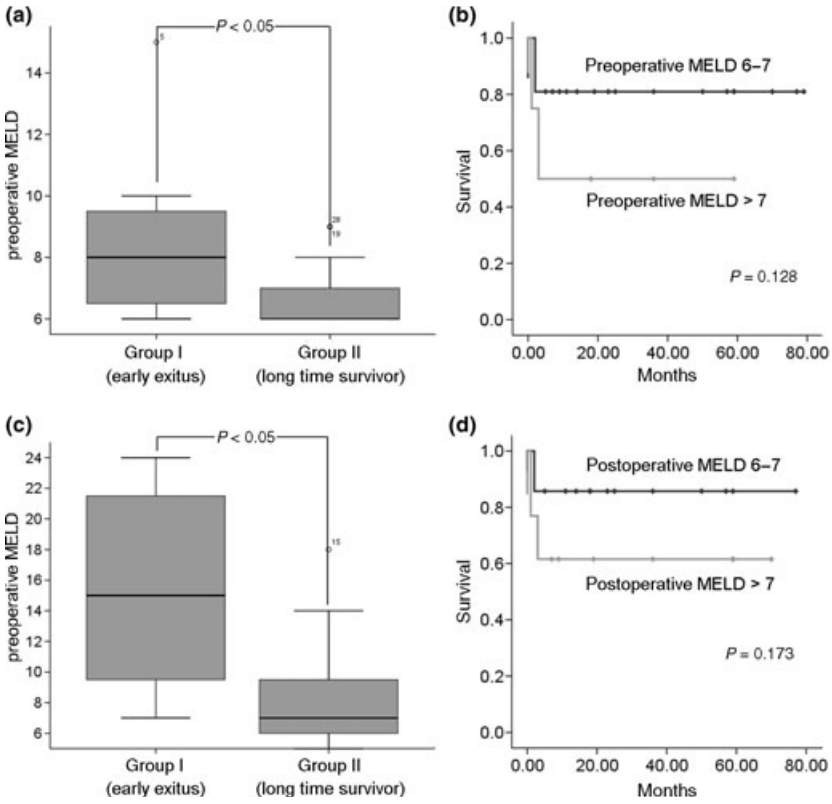

Figure 1 MELD-Score cannot discriminate early deaths versus long-term survivors. (a) Preoperative MELD-Score was higher in group I (early exitus) compared with group II (long time survivor) ($P < 0.05$). (b) Preoperative MELD-Score higher than seven before lung transplantation had a tendency to negative outcome, which was not statistically significant ($P = 0.13$). (c) Postoperatively MELD-Score was elevated, ranging from 7 to 24, and group I showed significantly higher values than group II ($P < 0.05$). (d) Kaplan–Meier analysis of MELD-Score postoperatively did not show significant results, when a threshold of 7 or higher was applied ($P = 0.173$). For calculation of significances Mann–Whitney test and Log-Rank test were applied.

group I (median 239/nl) compared with group II (median 350/nl). Interestingly, postoperative platelet count was significantly lower in group I (median 124/nl) compared with group II (median 318/nl; $P < 0.01$; Table 2). This might be because of an impaired general condition of the patients in group I.

MELD-Score cannot discriminate early deaths versus long-term survivors

MELD-Score was primarily developed as a prognostic tool to estimate the survival after transjugular intrahepatic portosystemic shunt placement in cirrhotic patients [10]. In our cohort of patients, without known pre-existing CF related liver cirrhosis relatively low MELD-Scores were calculated (Table 2). MELD-Score differed significantly between early death and long term survivors, as group I exhibited a significantly higher preoperative and postoperative MELD score than group II ($P < 0.03$; Table 2, Fig. 1). Kaplan–Meier analysis and Log Rank test in pre- and postoperative MELD-Score as overall marker for liver function did not show significant results, when a threshold of 7 or higher was applied ($P = 0.13$; $P = 0.173$; Fig. 1). As a result of the low Scores (median 6), which were not associated with liver-related morbidity or mortality, the MELD lacked clinical impact for this particular setting.

Postoperative elevated bilirubin and INR are associated with mortality

Elevated bilirubin after any major surgery can be caused by multiple factors and correlates with mortality. Unsurprisingly, bilirubin values were elevated after lung transplantation. While preoperatively bilirubin concentrations ranged from 0.1 to 0.8 mg/dl, postoperative values increased to 0.2–41.0 mg/dl (Table 2). Only one patient in group II exhibited elevated bilirubin values (11.5 mg/dl), concurring with a severe infection (CRP-Values of 29.2 mg/dl; norm: 0–0.5 mg/dl) at that time. Elevated bilirubin values were observed in four of eight group I

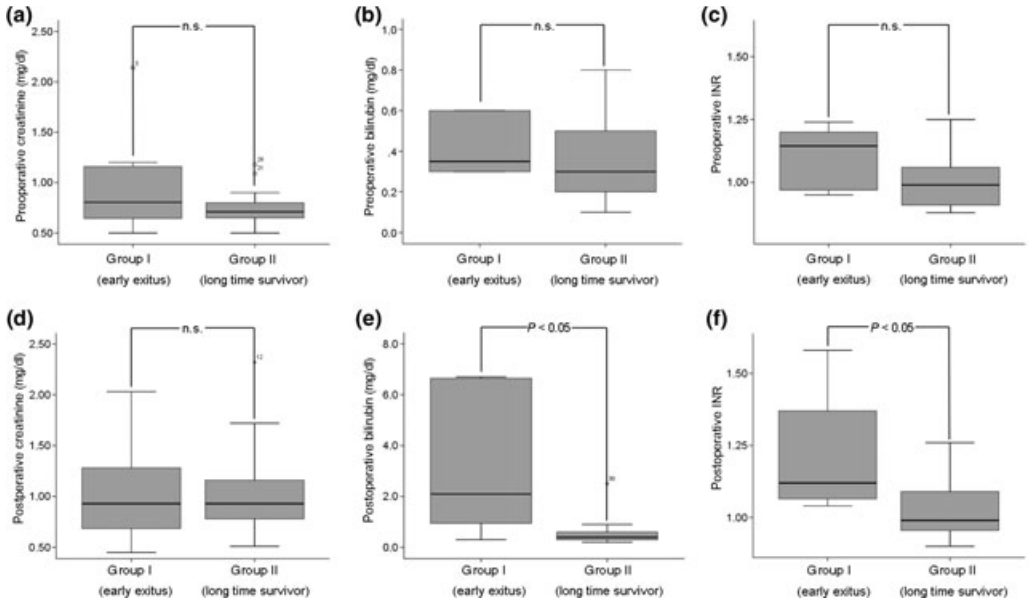

Figure 2 Individual components of MELD-Score preoperatively and postoperatively. (a) Preoperative as well as postoperative (d) creatinine values were not significantly different in group I (early exitus) versus group II (long time survivor). (b) Bilirubin values were elevated after lung transplantation, as values were preoperatively normal ranging from 0.1 to 0.8 mg/dl the postoperative (e) values ranged from 0.2 to 41.0 mg/dl. In group I, patients had postoperatively significantly higher bilirubin values than patients in group II. Note the 10 times higher range in figure 2e. INR abnormalities, which can be multifactorial in CF, such as from nutritional causes, were also significantly higher in group I pre- (c) and postoperatively (f). For calculation of significances Mann–Whitney test was applied.

patients, with a maximum of 41 mg/dl (Fig. 2b and e). INR, most likely because of malabsorption, malnutrition and/or liver impairment was also significantly higher in group I ($P = 0.01$) (Table 2; Fig. 2c and f).

Preoperative elevated GGT-levels are associated with early death

Usually, cholestatic enzymes (GGT, alkaline phosphatase) are associated with bile duct injury and/or hepatic toxicity. Furthermore, elevated cholestatic enzymes reflect impaired bile flow in the biliary system. Interestingly, in a *post hoc* survival analysis patients with preoperative elevated GGT value died significantly more often after DLTx ($P = 0.01$; Fig. 3). Moreover, patients with elevated bilirubin levels above 2.0 mg/dl exhibited an impaired survival in the first year after transplantation compared with patients with bilirubin level below 2.0 mg/dl.

Preoperative and postoperative leucocyte counts are not different in early deaths versus long-term survivors

Leucocyte counts are used to diagnose bacterial infections with sepsis. Therefore, we tested preoperative and post-

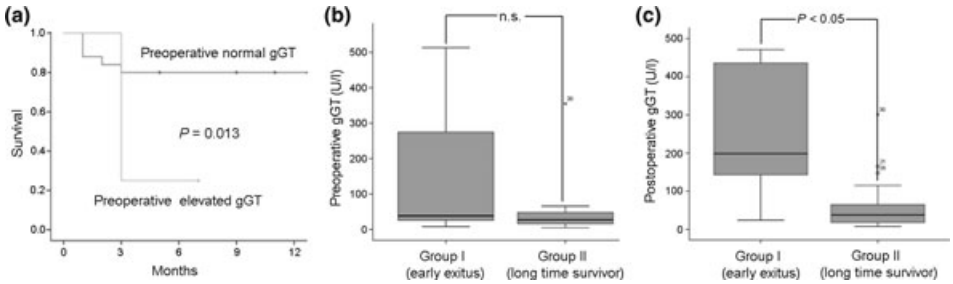

Figure 3 Preoperative elevated γGT-levels are associated with early death. (a) Preoperative elevated gamma glutamyl transferase (GGT) is associated with higher mortality ($P = 0.01$); (b) preoperative GGT was higher in group I (early exitus) than in group II (long time survivor); (c) postoperative GGT was significantly higher in group I compared with group II. For calculation of significances Mann–Whitney test and Log-Rank test were applied.

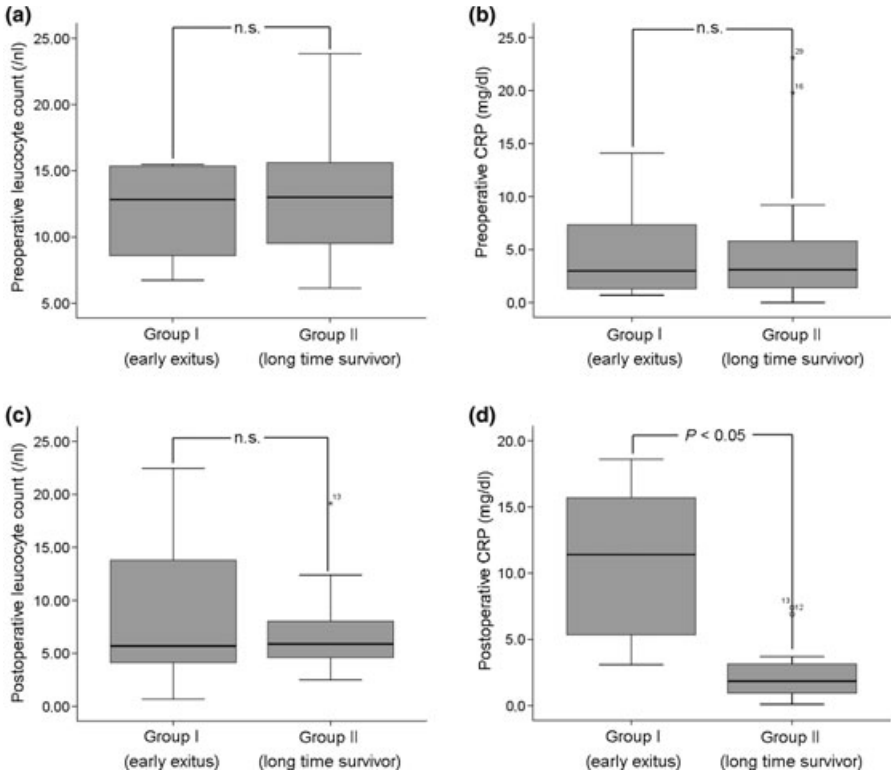

Figure 4 Preoperative and postoperative leucocyte counts and CRP-values. (a,b) Preoperative leucocyte counts and CRP values were not significantly different in group I (early exitus) versus group II (long time survivor); (c) Postoperative leucocyte counts were lower than preoperative because of immunosuppressive therapy in group I and group II; (d) Post transplant CRP-values were significantly higher in group I compared to group II. For calculation of significances Mann–Whitney test was applied.

operative leucocyte counts in group I and group II (Fig. 4). We found, that because of immunosuppressive therapy leucocyte counts were lower after DLTx in both groups (median leucocyte count preoperative 13.0/nl, postoperative 5.8/nl). CRP values, which are also used to diagnose bacterial and fungal infections, were not different in preoperative blood samples. As expected, in postoperative samples CRP values were significantly higher in group I (Fig. 4).

Discussion

To our knowledge, this is the first study addressing the liver as outcome parameter in patients with CF without known CF-related liver cirrhosis who underwent DLTx. In a cohort of 31 patients with median follow-up of 1000 days, we identified preoperatively elevated GGT to be associated with higher mortality after DLTx in patients with CF. In addition, postoperative increased GGT and bilirubin were associated with higher mortality. Although the MELD-Score differed significantly between early deaths and long-term survivors preoperatively as well as postoperatively, overall scores were very low, compared with cirrhotic patients.

Two thousand lung transplantations are performed worldwide every year and 250/year are performed in Germany [11]. Approximately, 16% of all lung transplantation worldwide are performed in patients with end-stage CF [7,8]. In our centre nearly 30 lung transplantations take place every year resulting in a cohort of 31 CF patients over a 10 year time period. Survival rates (74% after 1 year, 71% after 3 years and 68% after 5 years) in our cohort were comparable with recently published rates of the Registry of the International Society for Heart and Lung Transplantation [7]. In general, information concerning long-term operative outcomes in patients with cystic fibrosis is rare. In a retrospective review of 226 CF patients, including 11 patients who received bilateral lung transplantation, Escobar and coworkers found a general operative morbidity of 11% during the first year, which diminished to 2% in the postoperative years 2–4 and 1% in years 5–10, respectively [12]. Morbidity beyond 10 years postoperatively was below 1%. The children receiving lung transplants in this cohort exhibited a mortality of 27% (3 of 11).

CFLD is usually characterized by nonuniform portal tract abnormalities (focal biliary cirrhosis), leading to

portal hypertension with variceal haemorrhage without significant hepatocellular failure [13,14]. The subtle course of CFLD complicates early detection and combinations of diagnostic modalities need to be utilized [15–17]. Although 70% of postmortem specimens have evidence of focal biliary cirrhosis, less than 10% of CF patients develop clinically significant liver disease in congruence with current diagnostic criteria [18–20]. Thus, standard liver function tests and transaminase levels might be misleading in this particular patient cohort. Similarly, in NAFLD patients, despite normal liver function tests, liver fibrosis and hepatocellular injury is present in a majority of patients [21]. Novel, noninvasive biomarkers (i.e. M30 as apoptosis marker and hyaluronic acid, detectable in serum) and diagnostic studies (i.e. transient elastography) might help to identify those individuals with liver impairment without altered transaminase levels before transplantation. It could also be useful to include more sophisticated liver function tests (e.g. indocyanine green clearance test) in the pretransplant examinations of patients with cystic fibrosis to detect advanced liver diseases [22]. A case-control study by Gremse *et al.* [23] showed longer indocyanine green half-life (though not significant) in 19 patients with cystic fibrosis without known CFLD (4.6 ± 2.7 min) compared with 13 healthy controls (3.0 ± 1.0 min) in a lidocaine metabolism trail. Prospective studies are needed to further investigate a role for novel tests in early diagnosis of advanced liver disease in CF.

Some early studies suggested that patients with CFLD had a shorter life expectancy, with a reported mean survival of 4.5 years from diagnosis of liver disease [19]. However, a recent 7-year follow-up study in 42 children with CFLD did not show any differences in deaths or liver transplants when compared to age- and gender-matched controls [24]. However, patients with CFLD had a more severe CF phenotype with worse nutrition parameters and had more often cystic fibrosis-related diabetes [24].

Despite an obvious interrelation of liver function tests and survival in the present study, patients did not die because of liver related deaths as gastrointestinal bleeding, hepatic encephalopathy, coagulopathy, renal failure, hepatopulmonary syndrome or portopulmonary hypertension. The main cause of death was because of multi-organ failure after bacterial or fungal pneumonia induced sepsis. Still it is intriguing, that patients dying at an early time point after DLTx displayed elevated GGT, INR, as well as lower thrombocyte counts. In one patient who died after lung transplantation preoperatively, GGT was elevated, platelets reduced and bilirubin normal, postoperatively this patient developed higher bilirubin values. This suggests that impairment in liver function might be associated with mortality after lung transplantation in selected patients and lung transplantation itself might worsen the liver function in CF patients resulting in higher mortality. In line with our findings a recent publication by Barba *et al.* found a significant impact of elevated GGT and bilirubin values in patients with allogenic haematopoietic stem cell transplantation. Pretransplant elevated GGT and bilirubin were associated with 100-day nonrelapse mortality [25]. In contrast, altered ALT and AST values did not predict mortality. In the general population, although, recent data shows that ALT values are associated with higher mortality [26].

Moreover, bacterial infections are more common in patients with impaired liver function than in the general population [27] and patients with liver cirrhosis have an increased risk to develop sepsis and sepsis related death [28]. In cirrhosis, sepsis is often accompanied by a markedly imbalanced cytokine response (''cytokine storm''), which converts a usually beneficial reaction to counter infections into excessive, damaging inflammation [29]. Recently, the CTFR gene has been shown to regulate a variety of components of the innate immune system in individuals suffering from CF, and mutations in this gene can lead to impaired prevention of infections and severe disease [30].

In our cohort, postoperatively elevated bilirubin was associated with mortality. This fact has been investigated for long in any major surgery and has often multiple factors, sometimes because of multi-organ failure and sometimes because of unknown liver diseases. Two decade-old studies of thoracic surgery patients documented a 25–35% incidence of postoperative hyperbilirubinemia, associated with increased in-hospital morbidity and mortality [31,32]. The predictive power of hyperbilirubinemia is similar to that of respiratory failure whereas the cause of postoperative hyperbilirubinemia remains unknown and is probably multifactorial (e.g. sepsis) [33].

Predictors of survival and nonsurvival after lung-transplantation in patients with cystic fibrosis include several specific pathogens, gastrointestinal complications, bone disease, diabetes mellitus, sinus disease and previous pleural procedures. As the CF population has aged during the last decades, this is an issue of growing importance and has been assorted in detail by Rosenblatt [5]. In our small cohort, these predictors could only be tested exemplarily and we could find increased frequencies neither in group I nor in group II (data not shown).

A basic limitation of our retrospective single centre analysis is the small sample size and a period of 10 years during which transplant protocols have evolved. Moreover, pretransplant liver biopsies were not available to prove advanced liver disease. In summary, we demonstrate an association of increased liver serum parameters and early

mortality after DLTx. Therefore, individuals with CF should be managed by a multidisciplinary team, in consultation with a hepatologist and under close monitoring of liver function as well as novel serological and diagnostic tests. These data may raise awareness on liver parameters in DLTx for CF and may initiate preventative strategies to counter liver related complications in this setting.

Authorship

AW, HJ and MK: research design, acquisition of data, manuscript writing. LPB: data analysis, manuscript writing. NK and CJ: acquisition and analysis of data. US and HAB: acquisition of data. GG: research design and financial support. AC: research design, data analysis, manuscript writing.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Detailed laboratory values and follow-up data for individual patients.

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