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Perioperative factors influencing patient outcome after liver transplantation

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Abstract We have previously shown that the development of multiple organ dysfunction syndrome (MODS) after liver transplantation significantly reduced patient survival. Therefore, the question arises of which are the most prominent perioperative donor and recipient factors leading to MODS after transplantation. In total, 634 patients with 700 liver transplants were analyzed. Donor factors included age, increase in transaminases, sex mismatch, requirement for catecholamines, intensive care time, histology, and macroscopic graft appearence. Recipient factors included Child classification, preoperative gastrointestinal (GI) bleeding, mechanical ventilation, hemodialysis, and requirement for catecholamines. MODS was defined by more than two severe organ dysfunctions. The cumulative 2 to 9-year patient survival was 90.9% in patients developing less than 3 severe organ dysfunctions following transplantation. Survival decreased to 60.3% in patients with MODS. Neither any of the donor factors nor the duration of cold ischemia (CIT) was associated with an increase in MODS or decrease in survival. On the other hand, duration of warm ischemia, amount of blood loss, requirement for red packed blood cells, and reoperation had an influence on the development of MODS (40%–56%) and decreased patient survival to 58%–69%. Preoperative therapy with catecholamines, GI bleeding, mechanical ventilation, and hemodialysis were associated with the development of MODS in 54%–88%. Patient survival following MODS decreased to 50%–74%. Initial graft function had a slight influence on the development of MODS, but no influence on the long-term patient survival. In conclusion, patient survival was significantly influenced by the development of postoperative MODS. The most prominent factors in this were recipient and intraoperative ones. No major influence was observed for donor factors, CIT, and initial graft function. Prevention of MODS will further improve the outcome after liver transplantation.

Key words Liver transplantation · Multiple organ dysfunction syndrome · Patient outcome · Donor recipient status

Introduction

Multiple organ dysfunction syndrome (MODS) invariably occurs after liver transplantation in association with poor initial graft function, severe acute and chronic rejection, and serious infections. It is accompanied by increased postoperative morbidity [1–3]. Previous investigations have shown a decrease in long-term patient survival in association with MODS [4]. Marginal donors and poor preoperative patient status have been previ-

ously estimated to be associated with a higher morbidity and mortality after liver transplantation [5, 6]. The discussion on risk factors for poor outcome is still ongoing.

In order to optimize patient and intensive care management, it is desirable to know which risk factors predipose to MODS and decrease patient outcome. Therefore, donor and recipient as well as perioperative factors were analyzed with respect to the incidence of postoperative MODS and survival.

Patients and methods

In all, 634 patients receiving 700 consecutive liver transplants were analyzed. Indications for liver transplantation included alcoholic cirrhosis ($n = 118$), hepatitis B ($n = 108$), hepatitis C ($n = 105$), primary biliary cirrhosis ($n = 66$), primary sclerosing cholangitis ($n = 31$), autoimmune hepatitis ($n = 21$), Budd-Chiari syndrome ($n = 15$), other liver diseases ($n = 133$), and retransplantation ($n = 63$). Surgical procedure, antibiotic and various other prophylactic measures were performed perioperatively as previously reported [7].

Perioperative factors. Donor criteria included age, intensive care time, requirement for catecholamines, hypotension, sex and ABO mismatch, histological investigations of graft biopsies, increase in transaminases, and MEGX test. Recipient criteria included child classification, requirement for mechanical ventilation, hemodialysis, catecholamines, and gastrointestinal (GI) bleeding within 72 h prior to transplantation. Furthermore, duration of cold and warm ischemia time, duration of operative procedure, intraoperative blood loss, requirement for red packed blood cells and fresh frozen plasma, persistant hemorrhage at the end of the operation, and requirement for reoperation were examined. Graft function has been assessed as previously described using increase in transaminases, bile flow, and color [8].

MODS. Organ dysfunctions were graded into mild and severe and included liver, renal, and blood dysfunction, circulatory and respiratory insufficiency, neurological impairment, and GI bleeding. An established, simple scoring system was used [9]. Patients with 3 or more severe organ dysfunctions were classified as having MODS ($n = 141/634$; 22.2%).

Immunosuppression. This was either cyclosporine A (CsA)- or tacrolimus-based. CsA-based immunosuppression was commenced as quadruple therapy in combination with azathioprine or mycophenolate mofetil (MMF), prednisolone, and ATG or ALG, or the IL-2 receptor antagonist BT563 (Biotest, Dreieich, Germany) for the first 7 or 12 postoperative days, respectively, and subsequently continued as triple therapy. Tacrolimus-based immunosuppression was predominantly managed by dual therapy in combination with prednisolone. Some patients received triple or quadruple therapy including MMF or ATG [7].

Statistical analysis. Kaplan Meier estimates, Wilcoxon, chi-square, and Kruskal-Wallis tests, and analysis of variance (one-way ANOVA and multivariate analysis) were used as indicated.

Table 1 Multiple organ dysfunction (MODS) and patient survival ($P \leq 0.01$ for no MODS vs MODS patient survival, cumulative 2- to 9-year patient survival)

Number of organ dysfunctions	Patient survival (*n*)	Patient survival (%)
No MODS:		
0–1	114/124	91.9%
< 3	458/493	90.9%
MODS:		
≥ 3	85/141	60.3%
≥ 4	21/57	36.8%
Total	533/634	84.1%

Results

Survival. The cumulative 2 to 9-year patient survival was 84.1% (533/634 patients). Patient survival was significantly influenced by the development of MODS. Patients with fewer than 3 organ dysfunctions (no MODS) survived in 90.9%, while in MODS patients, survival decreased to 60.3% (Table 1).

Donor factors. None of the donor factors investigated was associated with an increased risk for the development of postoperative MODS, and none of these factors influenced the long-term patient survival. Good donors developed MODS in similar frequency (22.7%) to marginal donors (29.1%). Survival in MODS patients decreased to 66.2% and 69.0% for good and marginal donors (Table 2). Patients with no postoperative MODS survived in 91.3% and 91.0% for good and marginal donors, respectively.

Recipient factors. Child C patients developed MODS more often than child A or B patients: 38.6% vs 17.9%. However, survival following MODS was similar in both groups: 70.9% and 66.2%, respectively, while survival was 92.1% and 89.6% in child A/B and child C patients developing no MODS. Patients requiring mechanical ventilation or hemodialysis prior to transplantation developed MODS significantly more often (74.1% and 61.1%), but survival was similar to patients requiring no mechanical ventilation or hemodialysis but developing MODS (75% and 63.6%) and lower than in those patients without MODS (85.7% and 100%). Patients requiring catecholamines developed MODS in 87.5% with a lethal outcome in 42.9% of these patients. Lethality was also high in those patients requiring catecholamines who developed no MODS (50%). Similar observations were made for patients with GI bleeding prior to transplantation (Table 2).

Other perioperative factors. Cold ischemia time had no influence on the deveolpment of MODS and patient

Table 2 Selected perioperative factors leading to MODS (*GI* gastrointestinal)

Donor factors	Good donor ($n = 353$)	Marginal donor ($n = 344$)	Significance
MODS	22.7%	29.1%	NS
Survival in MODS patients	66.2%	71.0%	NS
Survival in no MODS patients	91.3%	91%	NS
Operative factors	≤ 10 EK ($n = 562$)	> 10 EK ($n = 135$)	Significance
MODS	21.7%	43.3%	$P \leq 0.01$
Survival in MODS patients	86.9%	69.0%	$P \leq 0.01$
Survival in no MODS patients	92.5%	84.4%	$P \leq 0.05$
Recipient factors	No GI bleeding ($n = 675$)	GI bleeding ($n = 22$)	Significance
MODS	24.9%	54.5%	$P \leq 0.01$
Survival in MODS patients	70.2%	50.0%	$P \leq 0.01$
Survival in no MODS patients	91.5%	70.0%	$P \leq 0.05$

survival. Duration of warm ischemia correlated with the incidence of MODS (39.4%) and patient survival (57.7%). Similar observations were made for blood loss (incidence of MODS: 44.9%, survival: 68.6%), requirement of red packed blood cells (incidence of MODS: 43.0%, survival: 69%), reoperation (incidence of MODS: 55.6%, survival: 62.5%), and persistent hemorrhage at the end of the transplantation (incidence of MODS: 55.3%, survival: 65.5%; Table 2).

Initial graft function correlated with the incidence of MODS: good 19.8%, moderate 32.5%, and poor 37.5%. However, no decrease in patient survival was observed in association with initial graft function, only in association with the development of MODS.

Discussion

MOD seriously increases postoperative morbidity. Furthermore, it decreases patient survival significantly. Therefore, the detection of risk factors is desirable. Marginal donors and poor initial graft function have been reported to increase postoperative morbidity and mortality [1–3]. However, according to our analysis, none of the donor factors increased the incidenc of MODS significantly, or decreased long-term patient survival. This may mean that other perioperative factors are necessary in addition to decrease long-term patient survival.

Marginal recipients alone had a greater impact on the development of MODS and decrease in patient survival. The most important patient factors included the requirement of catecholamines and GI bleeding within 72 h prior to transplantation. Both factors predisposed to the development of MODS and increased lethality, irrespective of MODS development. Child classification, requirement for mechanical ventilation, and hemodialysis increased the risk for the development of MODS, but survival was more dependent on the presence of MODS than the risk factors per se. Therefore, additional factors may be necessary for the decrease in patient survival.

Duration of cold ischemia has been correlated with patient outcome [10], but in our study no difference in the development of MODS and patient survival was observed. This is in contrast to the duration of warm ischemia, which had a significant impact on the development of MODS and patient survival. Previous investigations also show a significant impact of warm ischemia on initial graft function [11]. In addition similar observations were made for other perioperative factors, including blood loss, requirement for red packed blood cells, persistent bleeding, and reoperation. However, the most prominent impact on lethality was also the development of MODS and not the factors per se.

Poor initial graft function has been reported to be associated with high morbidity and mortality [10]. Morbidity was increased in our patients, as reflected by the increase in the development of MODS. However, no differences in long-term patient survival were observed, in accordance with previous observations [12]. Therefore, the use of marginal donors seems justified.

An increase in postoperative severe organ dysfunctions clearly decreased long-term patient survival. Recipient and other perioperative factors had a significant impact on the development of MODS. However, few factors alone (catecholamines, GI bleeding) were directly responsible for a significant decrease in patient survival with and without the development of MODS. Therefore, a combination of several factors will be most detrimental. The current practice to choose good donors and liver grafts and keep the duration of cold ischemia short in severely compromised recipients with several of these risk factors may reflect the relative good survival in these patients. Nevertheless, further postoperative factors may contribute to organ dysfunction, which should be analyzed in the future.

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