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Analysis of differences in outcome of two European liver transplant centers

Balázs Nemes,[1] Wojtek Polak,[2] Gábor Ther,[1] Herman Hendriks,[2] László Kóbori,[1] Robert J. Porte,[2] Enikõ Sárváry,[1] Koert P. de Jong,[2] Attila Doros,[1] Zsuzsa Gerlei,[1] Aad P van den Berg,[2] Imre Fehérvári,[1] Dénes Görög,[1] Paul M. Peeters,[2] Jenõ Járay[1] and Maarten J. H. Slooff[2]

1 Department of Transplantation and Surgical Clinic, Semmelweis University, Budapest, Hungary
2 Department of Hepatobiliary Surgery and Liver Transplantation, University Medical Center Groningen, Groningen, The Netherlands

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Correspondence
Dr Balázs Nemes, Department of Transplantation and Surgery, Semmelweis University, Baross u. 23., Budapest, H-1087, Hungary. Tel.: +36 1 2676000; fax: +36 1 3170964; e-mail: nemes@trans.sote.hu

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Summary

Authors analyzed the differences in the outcome of two European liver transplant centers differing in case volume and experience. The first was the Transplantation and Surgical Clinic, Semmelweis University, Budapest, Hungary (SEB) and the second the University Medical Center Groningen, Groningen, The Netherlands (UMCG). We investigated if such differences could be explained. The 1-, 3- and 5-year patient survival in the UMCG was 86%, 80%, and 77% compared with 65%, 56%, and 55% in SEB. Graft survival at the same time points was 79%, 71%, and 66% in the UMCG and 62%, 55%, and 53% in SEB. Significant differences were present regarding the donor and recipient age, diagnosis mix, disease severity and operation variables, perioperative transfusion rate, vascular complications, postoperative infection rate, and need for renal replacement. To determine factors correlating with survival, a separate uni- and multivariate analysis was performed in each center individually, between study parameters and patient survival. In both centers, perioperative red blood cell (RBC) transfusion rate was a significant predictor for patient survival. The difference in blood loss can be explained by different operation techniques and shorter operation time in SEB, with consequently less time spent on hemostasis. It was jointly concluded that measures to reduce blood loss by adapting the operation technique might lead to improved survival and reduced morbidity.

Introduction

It is an established fact that centers performing liver transplantations have different outcomes in terms of patient and graft survival and morbidity. Such differences are most often related to center volume [1–3]. However, conflicting evidence does exist regarding this relation of center volume and outcome in liver transplantation. Edwards *et al.* [1] observed a higher mortality in centers performing 20 or fewer liver transplantations (OLT) per year. However, the relevance of the 20 OLTs, as cut-off point was debated [4]. McMillan *et al.* [5] reported no statistical differences in patient survival between a small-volume center, performing 122 OLTs in 7 years, and the patient survival of the national register. Seiler *et al.* [6] also published a comparable patient survival in 60 patients over 6 years. The effect of center volume on outcome seems to decrease when experience is gained over time [7]. Liver transplantation is a technically and logistically very complex procedure performed for a variety of diseases in often different types of patients. Thus far, no studies are published analyzing why differences in center volume and experience lead to different outcomes. In order to clarify the effect of center volume and experience on outcome after liver transplantation, a study was performed in two distinct liver transplantation centers in

Europe. The first center (SEB; Transplantation and Surgical Clinic, Semmelweis University, Budapest, Hungary) is a young center, started in 1995, with a limited experience and numbers [8], while the other center UMCG (Department of Hepatobiliary Surgery and Liver Transplantation, University Medical Center Groningen, Groningen, The Netherlands) is one of the oldest ones in Europe, started in 1979, with consequently higher numbers and experience [9,10]. The aim of this study was to investigate whether there were differences in outcome in terms of patient and graft survival and morbidity and to identify the causes of such differences in order to take measures to improve the outcome.

Patients and methods

Study population

In order to create homogenous groups, only primary, full size, adult liver transplantations (>16 years of age), performed between 1995 and 2002, were included. Combined organ transplantations (liver and kidney, liver and lung) and pediatric cases were excluded. During the 8-year study period, 333 patients had an OLT in the UMCG, 251 adults and 88 children. Among the 251 adults, four patients received a kidney and liver, four patients received partial liver grafts, and two patients received a combined liver and lung transplantation. Consequently, 241 adult, full-size liver transplant patients were included in the study for the UMCG. During the same period, 134 patients underwent on OLT in SEB, 126 adults and eight children. Among the 126 adults, two patients received a liver and kidney; there were neither partial liver transplantations nor combined lung and liver transplantations performed: the study group of SEB thus consisted of 124 adult patients.

Patients were selected according to local selection protocols of the two centers, which were published previously [9,11,12]. For the purpose of this study, the following recipient parameters were recorded: the Child–Pugh score [13,14], whether the patient had pre-OLT upper abdominal surgery, the urgency code of the patient at the time of OLT and whether the patient had complications related to the liver disease. Encephalopathy and spontaneous bacterial peritonitis were classified according to the definition given by Blei [15]. Hepatorenal syndrome (HRS) in both centers was defined, as the creatinin clearance was <90 ml/min and/or sings of sodium and water retention.

In both centers, ABO identical or compatible grafts from, hemodynamically stable, brain death, and heart beating donors with normal or near normal liver function tests were used. In both centers, organ retrieval was performed according to the technique described by Starzl *et al.* [16]. For *in situ* perfusion of the liver, either histidine–tryptophan–ketoglutarate solution (HTK) or University of Wisconsin solution (UW; adenosine) was used.

Anesthesiological management

In the UMCG, total i.v. anesthesia (using sufentanil, midazolam, and vercuronium) with volume-controlled ventilation was provided [17]. In SEB, the induction was performed with etomidate, fentanyl or alfentanyl and atracurium and maintained with fentanyl, isoflurane, atracurium and dopamine [18–20]. Both centers used aprotinine for reduction of fibrinolysis as described by Porte *et al.* [21]. In SEB, aprotinine was used as a standard in the beginning. From 1999, it is used on demand, in selected cases. Pulmonary artery catheter was used in both center for hemodynamical monitoring, consisting of central venous pressure (CVP), mean arterial pressure (MAP), cardiac output (CO), and pulmonary capillary wedge pressure. There was a change in SEB after the 64th OLT: a transpulmonary thermodilution (PiCCO, COLD) was used to measure CVP, MAP, CO, intrathoracal blood volume and extravascular lung water. Further, both centers used the regular blood gas analysis. SEB also used the Tonocap (DATEX) for the evaluation of the regional perfusion of the gastric mucosa (PHI) [19]. Thrombelastography was used in both centers intraoperatively to assess the coagulation status [18,20,22]. In the UMCG, RBC replacement was carried out to maintain a hematokrit between 0.25 and 0.30 [17,21], while in SEB it was 0.30. In the UMCG, Cell Saver was used up till 1997 when substantial blood loss was anticipated [17]. In SEB, the Cell Saver was used routinely after 1998. Hydroxyethyl starch (HAES) was used frequently in SEB intra- and postoperatively for volume support because it was necessary because of the more extended blood loss. HAES was only used in UMCG less frequently in cases that needed urgent volume support.

Operative technique

In both centers, electrocautery and argon beam coagulation were used during the recipient hepatectomy. Hemoclips and transfiction sutures or ligatures were used for larger vessels. When appropriate, a running suture for the diaphragmatic attachment was often used after hepatectomy. If necessary Liostipt© and/or Surgicel© or Gelaspon© were used for small, diffuse, surface bleedings. Implantation was performed in both centers by the conventional technique described by Starzl as well as the piggyback technique [23,24]. In the UMCG, all conventional OLTs were performed with a veno-venous bypass (VVB) while in SEB the VVB was used selectively in conventional OLT

cases [18,25]. In both centers, an end to end portal vein reconstruction, with a continuous suture and growth factor, was performed. In cases of complex arterial reconstructions, when the use of donor iliac conduits was needed, both infrarenal and supratruncal approaches were used in the UMCG; while in SEB exclusively infrarenal conduits were used. Reperfusion was either sequential (portal vein followed by the artery) or simultaneous in the UMCG, while in SEB only sequential reperfusion was used. In both centers, duct to duct or hepaticojejunostomies were performed for biliary reconstruction. In the UMCG, always over a stent, while biliary stents were abolished in SEB after 1997. In the UMCG in contrast to SEB, a needle jejunostomy was introduced at the end of the procedure for feeding and return of collected bile production.

Postoperative management

Initially, in both centers, selective bowel decontamination (SBD), together with parenteral antibiotics, was used for infection prevention [26,27]. However, SEB discontinued the use of SBD in 1997 and the UMCG in 2000. Parenteral antibiotics (amoxycillin + ciprofloxacin) were continued for 24 h in the UMCG [28] and 96 h in SEB [29], based on an earlier experience in SEB [30]. Herpes viral prophylaxis with acyclovir (200 mg q.i.d.) was used longer in SEB (12 weeks) compared with the UMCG (4 weeks). In case of a CMV-positive donor liver in a CMV-negative recipient, a pre-emptive treatment with oral ganciclovir was used from Day 10 for 14 weeks in the UMCG, while Cytotec© i.v (till from 2002), then per oral ganciclovir was used in SEB. Ganciclovir dosages depended on creatinin clearance. Rejection prevention was basically different between the centers. Tailored immunosuppression was used in the UMCG. For liver diseases of possible autoimmune origin (like AIH, PBC, and PSC), a triple immunosuppressive schema was used containing cyclosporine, azathioprine, and low-dose prednisolon in the UMCG. For all other patients, a double therapy was introduced containing tacrolimus or cyclosporine and low-dose steroid. In patients with impaired renal function, IL-2 antibodies (basiliximab) were used for induction therapy instead of calcineurin inhibitors until the creatinin clearance was above 50 ml/min [31]. A fixed scheme was used for all patients in the SEB [18] containing cyclosporine, azathioprine – later mycophenolate-mophetile – and methylprednisolon while tacrolimus was used only occasionally and as secondary choice in case of proven hepatitis C recurrence [32]. Also, it appeared that cyclosporine levels were kept higher in SEB during the first 6 months: the target level was 300–400 μg/ml in the SEB and up to 250 μg/ml in UMCG for the 1–2 weeks, diminishing to 200 μg/ml in SEB and to 100–150 μg/ml in UMCG by the second month. In both centers, a liver biopsy was the gold standard for the diagnosis of rejection. However, in the UMCG protocol, as well as on demand, biopsies were taken [33] while in SEB only on-demand biopsies were taken [34]. In both centers, the Banff criteria were applied for histological grading of rejections [35]. Treatment of rejection depended in both centers on the grading of rejection and clinical signs. In general, grade I acute rejection was only treated in case of liver function tests abnormalities. Grade II and III rejections were always treated. Treatment of these acute rejections consisted of steroid boluses of 1 g per 24 h during three consecutive days. Steroid resistant rejections, proven by biopsies, were treated with ATG in the UMCG while with ATG or OKT3 in the SEB.

Liver and kidney function were monitored on a daily basis with a decreasing frequency over time on both centers. Kidney failure after liver transplantation was defined if any type of renal replacement therapy was needed. Only slight differences in postoperative surveillance were present between the centers [36]. Doppler ultrasonography was carried out on prefixed time points in both centers and on demand when liver function deteriorated.

In the framework of this study, the following outcome parameters and definition of study parameters were used for both centers.

Outcome parameters

Patient survival was defined as the time period between the first transplantation and patient death or the end date of the study (December 2002). Graft survival was defined as the time period between the first transplantation and graft loss caused either by patient death or graft failure needing a reOLT or by the end date of the study period. Complications were assessed as the number of patients with complications and the median number of complications/patient. The same was recorded for reinterventions. A reintervention was defined as any surgical, endoscopic, or invasive radiological intervention during the study period. The incidence of infectious, bleeding, vascular, and biliary complications was assessed within the first year after OLT. The definitions of these complications are published elsewhere and were the same in both centers [29–31,37,38].

Study variables

Donor variables analyzed were age and duration (days) of stay on the intensive care. The following recipient variables were taken into account: diagnosis, age, gender, and condition of the patient as measured by Child–Pugh

scores and classes, whether patients had previous operations or not, whether complications of liver disease were present or not and urgency at the time of transplantation. The following perioperative variables were scored: the type of the operation (piggyback versus conventional), whether the VVB was used or not, whether a biliary drain was used or not, the type of the preservation solution, the transfusion rate of RBC and FFP units, and the amount (ml) of thrombocyte transfusion as well as the amount of autologous blood (ml) given during the operation, stay on the intensive care unit (days), and the intubation period (days). Operation time was defined from the incision till the closure of abdomen, the cold ischemic time (CIT) from start of the cold perfusion in the donor till the liver is removed from ice for transplantation. The warm ischemic time (WIT) was the time between the liver is removed from ice till reperfusion via portal vein or arterial (if sequential) or portal and arterial (if simultaneous reperfusion).

Statistics

The data were evaluated by SPSS 12.0. Survival data were computed by the Kaplan–Meier method and differences in survival assessed by the log-rank test. Differences of the study variables between the centers were assessed by the Student *t*-test or Mann–Whitney *U*-test (for continuous variables) or chi-squared test (if categorical variables). To analyze the impact of the study variables within each center, differences in categorical variables were analyzed with Kaplan–Meier statistics. For continuous variables median values were assessed in groups of patients having survived and patients who had died after transplantation (independent Student *t*-test). Continuous variables were tested in patients surviving the transplantation and those who died first with the Levene's test for equality of variances for homogeneicity and subsequently with the two-tailed independent sample student *t*-test or Mann–Whitney *U*-test. To identify, risk factors for survival variables having a statistical influence on patient/graft survival after univariate analysis were entered by a stepwise backward manner into a multivariate analysis (Cox regression analysis). The level of significance was set at 0.05.

Results

Patient and graft survival in the two centers are significantly different as shown in Fig. 1. One-, 3- and 5-year patient survival in the UMCG was, respectively, 86%, 80%, and 77% compared with 65%, 56% and 55% in SEB ($P = 0.001$). Graft Survival at the same time points was, respectively, 79%, 71%, and 66% in the UMCG

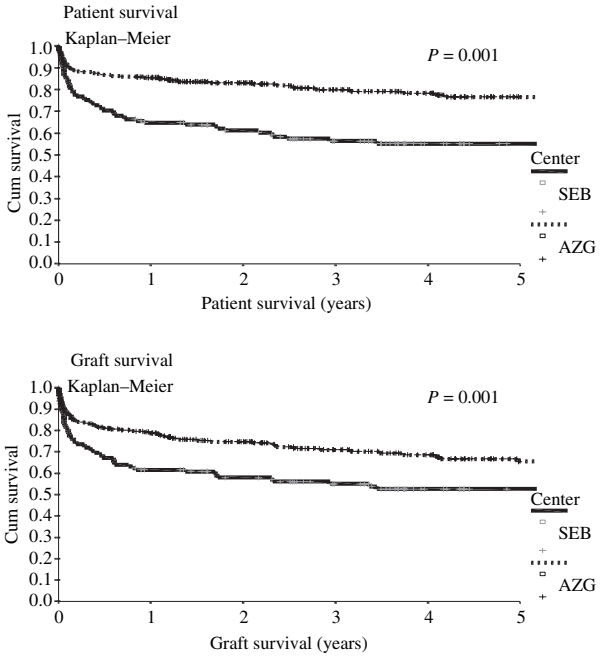

Figure 1 Patient and graft survival.

compared with 62%, 55%, and 53% in SEB ($P = 0.0001$). In the UMCG 51 (21%), patients died after OLT compared with 53 (43%) patients in SEB ($P = 0.0001$). In Table 1, the distribution of deaths over time is shown. In SEB (26 of 124, 21%) compared with the UMCG (27 of 241, 11%) ($P = 0.012$) a higher number of patients died during the first 2 months after OLT. The same was true for the remaining first year after OLT; an additional nine patients (4%) died in the UMCG compared with 17 (14%) in SEB ($P = 0.036$). After 1 year, no differences in mortality was observed between both centers. The causes of death in the UMCG were: 13 multiorgan failure (MOF) (48%), five cardio- and cerebrovascular (18%), four tumor (15%) three graft insufficiency (11%) and two hemorrhage (7.4%). Causes of death for SEB were 17 MOF (66%), three cardio- and cerebrovascular (12%), three tumor (12%), one graft insufficiency (4)%, two hemorrhage (8)%. The focus of MOF was different in

Table 1. Distribution of deaths over time.

Distribution of death	UMCG (241) (%)	SEB (124) (%)	*P*
1–2 months	27 (11)	26 (21)	0.012
2–6 months	6 (2.5)	10 (8)	0.014
6–12 months	3 (1)	7 (6)	0.036
>12 months	15 (6)	10 (8)	NS

NOTE: continuous variables are presented as median (range) and categorical variables as number (percentage).

Table 2. Postoperative complications.

	UMCG (241)	SEB (124)	*P*
Primary nonfunction (PNF)	4 (2)	6 (5)	0.08
Postoperative bleeding	38 (16)	41 (33)	0.0009
Vascular complications (all)	14 (6)	15 (12)	0.035
Biliary complications (all)	68 (28)	23 (18)	0.043
Infectious complications	90 (37)	60 (48)	0.046
Kidney failure after liver transplantation	39 (16)	40 (32)	0.0009
Acute rejection	125 (52)	46 (37)	0.007
Chronic rejection	16 (7)	6 (5)	0.47
Cytomegalovirus infection	81 (34)	25 (20)	0.007
Patients with complications	144 (60)	76 (61)	0.89
No. of complication/patient	1 (0–6)	2 (0–7)	0.005
Patients with reintervention	108 (45)	60 (48)	0.51
No. of reintervention/patients	1 (0–11)	1 (0–8)	0.52

NOTE: continuous variables are presented as median (range) and categorical variables as number (percentage).

both centers. It was abdominal 61%, in UMCG and 58% in SEB (NS), pulmonal 48% in UMCG and 30% in SEB, while biliary 9% in UMCG and 44% in SEB ($P = 0.007$). Regarding postoperative morbidity, significant differences were observed between both centers (Table 2). Postoperative bleeding rate, number of vascular complications, and rate of kidney failure were significantly higher in SEB compared with UMCG.

Acute rejections and CMV infections were all significantly higher in the UMCG than in SEB.

In order to explain these differences, patient and donor demographics and operative variables were compared between both centers in Table 3. Patients in the UMCG were significantly older than patients in SEB. Between both centers, significant differences existed concerning the diagnosis of liver diseases. The proportion of patients with parenchymal liver disease was higher in SEB compared with UMCG ($P = 0.006$). This was mainly caused by a higher proportion of patients with posthepatitis C cirrhosis in SEB. The proportion of patients with cholestatic ($P = 0.05$) and metabolic diseases ($P = 0.003$) was significantly higher in the UMCG than in SEB, whereas in SEB more patients were transplanted with tumors as primary indication for transplantation ($P = 0.004$). The majority of these tumors were primary ($n = 2$) or secondary malignancies ($n = 3$). Regarding the disease severity, it appeared that the Child–Pugh score was not different between both centers. In the UMCG, a significantly higher proportion of patients had previous abdominal operations compared with SEB ($P = 0.006$) and more patients were transplanted on higher than normal urgency grades (Eurotransplant Urgency Code 2 or High Urgent Code) compared with SEB ($P = 0.02$). Donors for patients in the UMCG were significantly older than for SEB patients ($P = 0.0009$) and had stayed 1 day (median) longer on the intensive care unit ($P = 0.0009$). All operative variables but WIT was significantly different between both centers. HTK was in more than half of the transplantations the preservation solution in SEB while in the UMCG only a minority of the grafts was preserved in HTK. The most applied operation technique in the UMCG was the piggyback technique while in SEB the conventional OLT was the dominant technique. When the conventional technique was used, the VVB was used always in the UMCG while in SEB in only 38 (47%) of the conventional cases. Biliary drains were only used in about a quarter of the patients in SEB while in the UMCG 71% of the patients were provided with a biliary drain. The transfusion rate (RBC/FFP/thrombocytes) was significantly higher in SEB compared with UMCG. Both median CIT and duration of the operations were shorter in SEB compared with UMCG.

In order to see which factors in each individual centers were determinants for survival, the impact on survival of the described study variables was also analyzed for both centers separately. Only variables with a significant difference in the univariate analysis were included in a stepwise multivariate analysis. For the UMCG: recipient age, acute hepatic failure versus cholestatic diseases, WIT, RBC, FFP-, and thrombocyte transfusion and for SEB: donor age, recipient previous upper abdominal operation, and intraoperative blood transfusion. In both centers, perioperative RBC transfusion rate had a significant influence on patient survival. In the UMCG recipient age and in SEB previous upper abdominal operations appeared also to have significant impact on patient survival as well (Table 4).

Table 3. Recipient and donor demographics and operation variables.

	UMCG (241)	SEB (124)	*P*
Recipient gender male/female (ratio)	137/104 (57/43)	61/63 (49/51)	0.16
Recipient age	47 (17–68)	42 (16–62)	0.013
Diagnosis			
Fulminant hepatic failure	17 (7)	8 (6)	0.60
Parenchymal	123 (51)	82 (66)	0.006
Cholestatic diseases	66 (29)	23 (18)	0.05
Metabolic diseases	27 (12)	3 (3)	0.003
Tumors as primary indication	1 (0,04)	6 (5)	0.004
Miscellaneous	7 (3)	3 (2)	0.78
Disease severity			
Child–Pugh score	9 (5–15)	9 (5–14)	0.62
Disease-related complications	125 (52)	67 (54)	0.80
Previous abdominal operations	84 (35)	26 (21)	0.006
Number and % HU patients	35 (15)	8 (6)	0.02
Donor			
Donor age (years)	45 (7–72)	38 (12–63)	0.0009
Donor stay on intensive care unit (days)	2 (1–27)	1 (0–8)	0.0009
Operation variables			
Preservation fluid UW/HTK	231/10 (96/4)	55/69 (44/56)	0.0009
Operation: piggyback/conventional	149/92 (62/38)	43/80 (35/65)	0.0009
Use of veno-venous bypass in conventional OLTs	90 (98)	38 (47)	0.0009
Biliary drain used	170 (71)	35 (28)	0.0009
Blood transfusion [units of red blood cells (RBC)]	5 (0–100)	12 (2–50)	0.001
FFP transfusion (ml)	1350 (0–12825)	3400 (300–9800)	0.0009
Thrombocyte transfusion (ml)	92 (0–600)	200 (20–800)	0.0009
Cold ischemic time (min)	575 (203–990)	489 (299–1097)	0.0009
Warm ischemic time (min)	54 (20–129)	55 (27–107)	0.55
Total operation time (min)	570 (285–1080)	450 (313–1030)	0.001

NOTE: continuous variables are presented as median (range) and categorical variables as number (percentage). HU = high urgency; UW = University Wisconsin solution; HTK = histidine-tryptophan-ketoglutarate solution.

Table 4. Multivariate (Cox regression) analysis of study parameters in relation to survival.

Variables	ß (±SE)	*P*
UMCG		
Peroperative blood transfusion (units of RBC)	1.05 (1.02 ± 1.07)	0.0009
Recipient age (years)	1.04 (1.01 ± 1.06)	0.006
SEB		
Donor age (years)	1.05 (1.02 ± 1.09)	0.001
Peroperative blood transfusion (units of RBC)	1.05 (1.01 ± 1.09)	0.006
Previous upper abdominal operation	0.45 (0.22 ± 0.92)	0.03

Discussion

This is the first open comparison between the outcomes of two liver transplant centers reported in the literature. Comparing the results of the two centers performing such a complex procedure as liver transplantation is a hazardous undertaking. Indications, surgical techniques, immunosuppressive protocols, infection prevention, and postoperative surveillance depend on local protocols and medical culture. Comparing the outcome of two centers might serve as an instrument to improve procedures and the outcome in both centers. Patients transplanted in the UMCG showed a significant higher patient survival compared with patients transplanted in SEB. In Table 1, it is shown that, in SEB compared with the UMCG, a significantly higher number of patients died in the early phase after transplantation. This suggests that the lower patient survival might be related to the different operative techniques and perioperative care in both centers. Analyzing the difference in recipient, donor and operation characteristics (Table 3) revealed several differences between the centers. In order to investigate whether these differences were relevant, the relation between the study variables and patient survival was analyzed per center in a uni- and multivariate manner (Table 4). In both centers, peroperative transfusion rate

(RBC/FFP/thrombocytes) is a predictor for patient survival. In the UMCG, it appeared that also recipient age was a significant predictive factor for patient survival and in SEB the fact whether the patients had previous operations. These latter two factors, however, are given facts and cannot be influenced at the time of the actual transplantation procedure.

Red blood cell transfusion rate as a measure for per-operative blood loss is an established determinator for patient survival in liver transplantation [17,21,22,31,39–41]. The RBC transfusion rate in SEB was significantly higher compared with the UMCG. It is unlikely that the mentioned difference in transfusion policy between both centers is the only explanation for the observed increased transfusion rate. The significant higher number of FFP and thrombocyte infusions in SEB support the assumption that the observed higher transfusion rate in this center is caused by a higher peroperative blood loss. When the operation-related variables are analyzed, several relevant differences are present (Table 3) In SEB, the proportion of patients operated with the conventional implantation technique is higher compared with the UMCG ($P = 0009$). In the UMCG, more patients are transplanted with the so-called piggyback technique. Several reports are available showing a decreased RBC transfusion rate when the piggyback technique is used for implantation [24,39,42]. Another important contributing difference between both centers for the higher transfusion rate in SEB might have been the fact that in that center a significant proportion of patients had a conventional OLT carried out without a VVB ($P = 0.0009$). One of the reported advantages of the VVB is a reduction in peroperative blood loss [25,39,42–44] and more hemodynamic stability [45]. That higher blood loss in SEB as reflected by the higher RBC/FFP/thrombocyte transfusion rate is important because it explains also the differences in postoperative complications. In SEB, a significantly higher postoperative bleeding rate, infectious complications, and renal insufficiency were reported [46]. Evidence in the literature points toward the increased blood loss as the causative factor for such complications [39–42,47,48]. As support for the observed impact of per-operative blood loss in SEB is the other finding that whether the patients had previous upper abdominal surgery or not had also a significant impact on survival in SEB. In such patients, dissection of adhesions with collaterals resulting from the portal hypertension can add to the amount of blood loss. In SEB, HAES was used intraoperatively [38] and postoperatively as well. The bleeding tendency after OLT is a critical point. The role of HAES in the hemorheology is contradictory [49]. Some reports declare that the administration of 6% HAES (200 kdalton) in clinically relevant doses can even improve the microcirculation [50]. Because of the acute bigger blood loss, the volume of intraoperative HAES infusion was higher than the recommended limit in some cases in SEB during the early phase of OLT program. Another contributing factor to the observed differences in peroperative blood loss is the time taken for meticulous hemostasis. The fact that in SEB the median duration of the operative procedure was 2 h shorter ($P = 0.001$) compared with that in the UMCG is explained by the fact that in the UMCG more time is spent on hemostasis especially during the explantation of the native liver.

Several other differences between the centers might have contributed to the different outcome. In the UMCG, significantly more biliary complications occurred compared with SEB (0.043). This might be related to the use of a biliary drain, which was used more often in the UMCG. Evidence in the literature points toward an increased biliary complication rate when stents are used [51–53]. There is a higher number of biliary complications in UMCG, but their spectrum, origin, and severity were different compared with SEB. In UMCG, the main component of biliary complications (60%) was leakage after the removal of the biliary drain, 6–12 weeks after OLT. In contrary, in SEB, the main component of biliary problems was the necrosis, which was associated to the increased rate of HAT. In the UMCG, significantly more acute rejections were observed compared with SEB ($P = 0.007$). This could be explained by the milder immunosuppression scheme in the UMCG compared with SEB. The higher level of maintenance immunosuppression in SEB, however, might also have contributed to the higher infection rate and renal failure rate in the SEB patients. On the other hand, in the UMCG, more acute rejections occurred which needed to be treated. This could have caused the higher number of CMV infections in the UMCG.

In conclusion, the difference in patient survival between both centers can for the greater part be explained by the difference in peroperative RBC/FFP/thrombocyte transfusion rate, i.e. blood loss. It is conceivable that the difference in blood loss is explained by different operation techniques and style. Adaptation of these factors may lead to a decrease in transfusion rate with subsequent improvement of survival. Other observed differences such as immunosuppressive schemes and the use of biliary stents – although not predictive for survival – can add to the improvements in both centers. As a result of this analysis, measures have been taken in SEB to adapt the perioperative protocols regarding hemostasis, prevention of HAT (low hematocrit and postoperative thrombosis prophylaxis), and infection prevention. Thus far, this has led to an improvement

of 1- and 2-year patient survival of 80% and 76%, respectively, after 2002.

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